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The Official Newspaper of Record for the Hem/Onc Nurse

Review articles emphasizing advances in management based on the most up-to-date studies. Commentaries on implications for oncology nurses.

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RENAL CELL CANCER

PROSTATE CANCER

BREAST CANCER

LYMPHOMA

MYELOMA

MDS

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Sarah L. Scarpace, PharmD, BCOP

New treatment for extravasation page 49

Marianne Bunce-Houston, RN, MS, AOCNS, CRNI

When treating patients with HER2+ breast cancer

No one touches their

HER2-positive status is associated with more aggressive disease and poorer outcomes than HER2-negative breast cancer. Women who received 1 year of Herceptin had a lower risk of HER2+ breast cancer returning.

We applaud you for playing such a critical role in helping patients with HER2+ breast cancer complete the full course of treatment with Herceptin.

Adjuvant indications

Herceptin is indicated for adjuvant treatment of HER2-overexpressing node-positive or node-negative (ER/PR-negative or with one high-risk feature*) breast cancer:

- As part of a treatment regimen containing doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- With docetaxel and carboplatin
- As a single agent following multi-modality anthracycline-based therapy

*High-risk features for patients with ER/PR+ breast cancer include: tumor size >2 cm, age <35 years, and histologic and/or nuclear grade 2/3.

Metastatic indications

Herceptin is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

Boxed WARNINGS and Additional Important Safety Information

Herceptin administration can result in sub-clinical and clinical cardiac failure manifesting as congestive heart failure (CHF) and decreased left ventricular ejection fraction (LVEF). The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin in patients with metastatic breast cancer who develop a clinically significant decrease in left ventricular function.

Patients should undergo monitoring for decreased left ventricular function before Herceptin treatment, and frequently during and after Herceptin treatment. More frequent monitoring should be employed if Herceptin is

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withheld in patients who develop significant left ventricular cardiac dysfunction. In one adjuvant clinical trial, cardiac ischemia or infarction occurred in the Herceptin-containing regimens.

Serious infusion reactions and pulmonary toxicity have occurred; fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.

Exacerbation of chemotherapy-induced neutropenia has also occurred. Herceptin can cause oligohydramnios and fetal harm when administered to a pregnant woman. The most common adverse reactions associated with Herceptin use were fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia.

Please see brief summary of full Prescribing Information, including **Boxed WARNINGS** and additional important safety information, on the following pages.

www.herceptin.com

Herceptin®
trastuzumab
Targeted on HER2, Focused on Living

9568900 01/09

HERCEPTIN® (trastuzumab)

Brief Summary For full Prescribing Information, see package insert.

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

Cardiomyopathy

Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF and decreased LVEF. The incidence and severity of left ventricular cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Herceptin. Discontinue Herceptin treatment in patients receiving adjuvant therapy and strongly consider discontinuation of Herceptin treatment in patients with metastatic breast cancer for clinically significant decrease in left ventricular function. [*see Warnings and Precautions and Dosage and Administration*]

Infusion Reactions; Pulmonary Toxicity

Herceptin administration can result in serious infusion reactions and pulmonary toxicity. Fatal infusion reactions have been reported. In most cases, symptoms occurred during or within 24 hours of administration of Herceptin. Herceptin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinue Herceptin for infusion reactions manifesting as anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. [*see Warnings and Precautions*]

INDICATIONS AND USAGE Adjuvant Breast Cancer Herceptin is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature [*see Clinical Studies*]) breast cancer • As part of a treatment regimen consisting of doxorubicin, Cyclophosphamide, and either paclitaxel or docetaxel • With docetaxel and carboplatin • As a single agent following multi-modality anthracycline based therapy. **Metastatic Breast Cancer** Herceptin is indicated: • In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer • As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease. **CONTRAINDICATIONS** None. **WARNINGS AND PRECAUTIONS Cardiomyopathy** Herceptin can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death [*see Boxed Warning: Cardiomyopathy*]. Herceptin can also cause asymptomatic decline in left ventricular ejection fraction (LVEF). There is a 4–6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving Herceptin as a single agent or in combination therapy compared with those not receiving Herceptin. The highest absolute incidence occurs when Herceptin is administered with an anthracycline. Withhold Herceptin for ≥16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥10% absolute decrease in LVEF from pre-treatment values. [*see Dosage and Administration*] The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied. *Cardiac Monitoring* Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended: • Baseline LVEF measurement immediately prior to initiation of Herceptin • LVEF measurements every 3 months during and upon completion of Herceptin • Repeat LVEF measurement at 4 week intervals if Herceptin is withheld for significant left ventricular cardiac dysfunction [*see Dosage and Administration*] • LVEF measurements every 6 months for at least 2 years following completion of Herceptin as a component of adjuvant therapy. In Study 1, 16% (136/844) of patients discontinued Herceptin due to clinical evidence of myocardial dysfunction or significant decline in LVEF. In Study 3, the number of patients who discontinued Herceptin due to cardiac toxicity was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued Herceptin due to cardiac toxicity. Among 32 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy and all other patients were receiving cardiac medication at last follow-up. Approximately half of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) on continuing medical management at the time of last follow-up. Incidence of congestive heart failure is presented in Table 1. The safety of continuation or resumption of Herceptin in patients with Herceptin-induced left ventricular cardiac dysfunction has not been studied.

Table 1 Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence of CHF	
Study	Regimen	Herceptin	Control
1 & 2[a]	AC[b]→Paclitaxel+ Herceptin	2% (32/1677)	0.4% (7/1600)
3	Chemo→Herceptin monotherapy	2% (30/1678)	0.3% (5/1708)
4	AC[b]→Docetaxel+ Herceptin	2% (20/1068)	0.3% (3/1050)
4	Docetaxel+Carbo+ Herceptin	0.4% (4/1056)	0.3% (3/1050))

[a] Includes 1 patient with fatal cardiomyopathy.
[b] Anthracycline (doxorubicin) and cyclophosphamide.

Table 2 Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I-IV		NYHA III-IV	
Study	Event	Herceptin	Control	Herceptin	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a]Congestive heart failure or significant asymptomatic decrease in LVEF. [b]Anthracycline (doxorubicin or epirubicin) and cyclophosphamide. [c]Includes 1 patient with fatal cardiomyopathy.

Infusion Reactions Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [*see Adverse Reactions*]. In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction. Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications. **Exacerbation of Chemotherapy-Induced Neutropenia** In randomized, controlled clinical trials in women with metastatic breast cancer, the per-patient incidences of NCI CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was not significantly increased. [*see Adverse Reactions*]. **Pulmonary Toxicity** Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and Precautions*]. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity. **HER2 Testing** Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy. These include HercepTest™ and Pathway® HER-2/neu (IHC assays) and PathVysion® and HER2 FISH pharmDx™ (FISH assays). Users should refer to the package inserts of specific assay kits for information on the validation and performance of each assay. Limitations in assay precision (particularly for the IHC method) and in the direct linkage between assay result and overexpression of the Herceptin target (for the FISH method) make it inadvisable to rely on a single method to rule out potential Herceptin benefit. A negative FISH result does not rule out HER2 overexpression and potential benefit from Herceptin. Treatment outcomes for metastatic breast cancer (Study 5) as a function of IHC and FISH testing are provided in Table 9. Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) as a function of IHC and FISH testing are provided in Table 7. *HER2 Protein Overexpression Detection Methods* HER2 protein overexpression can be established by measuring HER2 protein using an IHC method. HercepTest®, one test approved for this use, was assessed for concordance with the Clinical Trial Assay (CTA), using tumor specimens collected and stored independently from those obtained in Herceptin clinical studies in women with metastatic breast cancer. Data are provided in the package insert for HercepTest®. *HER2 Gene Amplification Detection Method* The presence of HER2 protein overexpression and gene amplification are highly correlated, therefore the use of FISH to detect gene amplification may be employed for selection of patients appropriate for Herceptin therapy. PathVysion®, one test approved for this use, was evaluated in an exploratory, retrospective assessment of available CTA 2+ or 3+ tumor specimens collected as part of patient screening for clinical studies in metastatic breast cancer (Studies 5 and 6). Data are provided in the package insert for PathVysion®. **Embryo-Fetal Toxicity (Pregnancy Category D)** Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk of oligohydramnios during the second and third trimesters. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus. [*see Use in Specific Populations*]. **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the label: • Cardiomyopathy [*see Warnings and Precautions*] • Infusion reactions [*see Warnings and Precautions*] • Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions*] • Pulmonary toxicity [*see Warnings and Precautions*] The most common adverse reactions in patients receiving Herceptin are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and Administration*]. **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Adjuvant Breast Cancer Studies* The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer. The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3 Adverse Reactions for Study 3, All Grades[a]:

MedDRA *(v. 7.1)* Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n= 1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[b]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Nasopharyngitis	135 (8%)	43 (3%)
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritus	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Asthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

[a] The incidence of Grade 3/4 adverse reactions was <1% in both arms for each listed term. [b] Higher level grouping term.

The data from Studies 1 and 2 were obtained from 3206 patients enrolled, of which 1635 patients received Herceptin; the median treatment duration was 50 weeks. The median age was 49.0 years (range: 24-80); 84% of patients were White, and 7% were Black, 4% were Hispanic, and 4% were Asian. In Study 1, only Grade 3–5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2-5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (31% vs. 28%), fatigue (28% vs. 22%), infection (22% vs. 14%), hot flashes (17% vs. 15%), anemia (13% vs. 7%), dyspnea (12% vs. 4%), rash/desquamation (11% vs. 7%), neutropenia (7% vs. 5%), headache (6% vs. 4%), and insomnia (3.7% vs. 1.5%). The majority of these events were Grade 2 in severity. In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3–5 non-hematologic toxicities, selected Grade 2–5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1–5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. The following non-cardiac adverse reactions of Grade 2–5 occurred at an incidence of at least 2% greater among patients randomized to Herceptin plus chemotherapy as compared to chemotherapy alone: arthralgia (11% vs. 8.4%), myalgia (10% vs. 8%), nail changes (9% vs. 7%), and dyspnea (2.5% vs. 0.1%). The majority of these events were Grade 2 in severity. Safety data from Study 4 reflect exposure to Herceptin as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n = 1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm. *Metastatic Breast Cancer Studies* The data below reflect exposure to Herceptin in one randomized, open-label study, Study 5, of chemotherapy with (n=235) or without (n=234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n=222) in patients with metastatic breast cancer. Data in Table 5 are based on Studies 5 and 6. Among the 464 patients treated in Study 5, the median age was 52 years (range: 25–77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 58% and 9%, respectively. Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28–86 years), 100% had breast cancer, 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of Herceptin followed by 2 mg/kg weekly. The percentages of patients who received Herceptin treatment for ≥ 6 months and ≥ 12 months were 31% and 16%, respectively.

Table 4 Per-Patient Incidence of Adverse Reactions Occurring in ≥ 5% of Patients in Uncontrolled Studies or at Increased Incidence in the Herceptin Arm (Studies 5 and 6) (Percent of Patients)

	Single Agent[a] n = 352	Herceptin + Paclitaxel n = 91	Paclitaxel Alone n = 95	Herceptin + AC[b] n = 143	AC[b] Alone n = 135
Body as a Whole					
Pain	47	61	62	57	42
Asthenia	42	62	57	54	55
Fever	36	49	23	56	34
Chills	32	41	4	35	11
Headache	26	36	28	44	31
Abdominal pain	22	34	22	23	18
Back pain	22	34	30	27	15
Infection	20	47	27	47	31
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	77
Diarrhea	25	45	29	45	26
Vomiting	23	37	28	53	49
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	26
Heme & Lymphatic					
Anemia	4	14	9	36	26
Leukopenia	3	24	17	52	34
Metabolic					
Peripheral edema	10	22	20	20	17
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	15
Dizziness	13	22	24	24	18
Paresthesia	9	48	39	17	11
Depression	6	12	13	20	12
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	29
Dyspnea	22	27	26	42	25
Rhinitis	14	22	5	22	16
Pharyngitis	12	22	14	30	18
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	17
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	< 1
Urogenital					
Urinary tract infection	5	18	14	13	7

[a]Data for Herceptin single agent were from 4 studies, including 213 patients from Study 6. [b]Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

The following subsections provide additional detail regarding adverse reactions observed in clinical

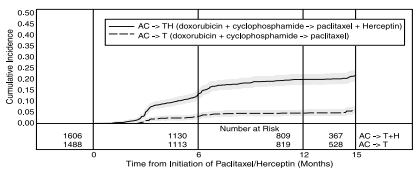
trials of adjuvant breast, metastatic breast cancer, or post-marketing experience. *Cardiomyopathy* Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF < 50% or ≥15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 5, Figures 1 and 2).

Table 5[a] Per-patient Incidence of New Onset Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥ 10% decrease	≥ 16% decrease	<20% and ≥ 10%	≥ 20%
Studies 1 & 2[b]					
AC→TH (n=1606)	22.8% (366)	18.3% (294)	11.7% (188)	33.4% (536)	9.2% (148)
AC→T (n=1488)	9.1% (136)	5.4% (81)	2.2% (33)	18.3% (272)	2.4% (36)
Study 3					
Herceptin (n=1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n=1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4[c]					
TCH (n=1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC→TH (n=1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC→T (n=1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

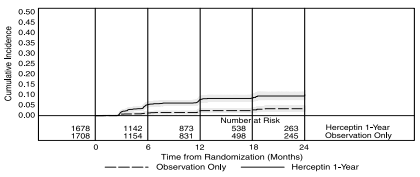
[a]For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization. [b]Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH). [c]Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC→T) or docetaxel plus Herceptin (AC→TH); docetaxel and carboplatin plus Herceptin (TCH).

Figure 1 Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



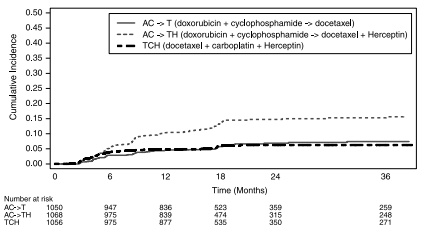
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

Figure 2 Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

Figure 3 Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines. *Infusion Reactions* During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in <1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported. *Anemia* In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was <1%. *Neutropenia* In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5 % [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. *Infection* The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract. In Study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC grade 3-4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms. In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. *Pulmonary Toxicity* Adjuvant Breast Cancer: Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4% vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]). Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone. In Study 3, there were 4 cases of interstitial pneumonitis in Herceptin-treated patients compared to none in the control arm. Metastatic Breast Cancer: Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions*. *Thrombosis/Embolism* In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]). *Diarrhea* Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]), and of Grade 1–4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer. *Glomerulopathy* In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure. **Immunogenicity** As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer. The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading. **USE IN SPECIFIC POPULATIONS Pregnancy Teratogenic Effects: Category D [*see Warnings and Precautions*]** Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk for oligohydramnios during the second and third trimester. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus. In the post-marketing setting, oligohydramnios was reported in women who received Herceptin during pregnancy, either alone or in combination with chemotherapy. In half of these women, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin was resumed after the amniotic fluid index improved, and oligohydramnios recurred. Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents; however, the effects of additional IV hydration with Herceptin treatment are not known. Reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab have revealed no evidence of harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of trastuzumab during the early (Days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed in monkeys. [*See Nonclinical Toxicology*] Because animal reproduction studies are not always predictive of human response, Herceptin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable serum levels of trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Herceptin in pediatric patients has not been established. **Geriatric Use** Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment. **OVERDOSAGE** There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested. **PATIENT COUNSELING INFORMATION** • Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning: Cardiomyopathy*]. • Advise women with reproductive potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [*see Pregnancy*]. • Encourage pregnant women who are using Herceptin to enroll in the Cancer and Childbirth Registry [*see Pregnancy*].

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Renal Cell Carcinoma: Review and Recent Advances

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Renal cell carcinoma (RCC) is a rare disease, with approximately 39,000 new cases diagnosed in 2007, accounting for about 2% of all malignancies in the United States.[1] The incidence of RCC has been increasing by 2% per year for the past 65 years but the reason for this is unknown.[1] In 2007, 12,000 deaths were expected from RCC, and 5-year survival was approximately 40%.[1] Ninety percent of cases are of clear cell histology.

RCC commonly metastasizes to liver, lung, bone, brain, and the adrenal glands. Although prognosis is influenced by tumor grade and stage, poor performance status, high lactate dehydrogenase, low hemoglobin, and high corrected serum calcium are indicators for a poor prognosis.[2]

The "classic" presentation of RCC is a symptom triad of flank pain, hematuria, and a palpable abdominal mass; however, about 50% of cases are found incidentally on a radiograph in patients with nonspecific symptoms, including fatigue, weight loss, and anemia.[2] Risk factors include smoking, obesity, hypertension, and acquired cystic kidney disease from chronic kidney disease.[1,2]

Table. Dosing and Adverse Events of Targeted Therapies Used in RCC

Drug	Dosing	Most common AEs[a]	Most common grade 3/4 AEs[b]
Sunitinib	50 mg PO daily for 4 weeks, then 2-week break without regard to food	LFT elevations; elevated SCr; myelosuppression; lymphopenia; elevated amylase/lipase; hypophosphatemia; diarrhea; fatigue; nausea; stomatitis; vomiting; rash; hand-foot syndrome	Lipase elevations; lymphopenia; neutropenia; elevated uric acid; hypertension; fatigue; hand-foot syndrome; diarrhea
Sorafenib	400 mg (two 200-mg tablets) PO twice daily on an empty stomach	Diarrhea; fatigue; rash; alopecia; hand-foot syndrome; nausea	Hand-foot syndrome; fatigue
Temsirolimus	25 mg IV weekly	Asthenia; rash; pain; nausea; anorexia; dyspnea; infection; hyperlipidemia; hypercholesterolemia; peripheral edema; hyperglycemia; fever; abdominal pain	Anemia; asthenia; pain; hyperglycemia; dyspnea
Bevacizumab + IFN-2a	10 mg/kg IV every 2 weeks, 9 million units subcutaneously three times a week	Fatigue; asthenia; bleeding; anorexia; hypertension; headache; diarrhea; flu-like symptoms	Fatigue; asthenia; proteinuria
Everolimus	10 mg PO daily	Stomatitis; rash; fatigue; hyperglycemia; hypercholesterolemia; hypertriglyceridemia; lymphopenia; increased SCr and LFTs; hypophosphatemia; myelosuppression	Lymphopenia; anemia; hyperglycemia

AE indicates adverse events; IFN, interferon; LFT, liver function tests; RCC, renal cell carcinoma; SCr, serum creatinine.
[a]>20% of patients; [b]>5% of patients.
Sources: References 3-5, 7, 10.

Overview of drug therapy

Drug therapy is primarily reserved for stage IV and relapsed/recurrent RCC. Stages I to III of RCC are surgically resected, and the use of adjuvant drug therapy is not recommended in clinical practice guidelines.[1] External-beam radiation therapy or arterial embolization are reserved for patients who are not surgical candidates.[1] The Table provides a summary of the dosing and adverse events of the drug therapies discussed.

Since the US Food and Drug Administration (FDA) approval of sorafenib in 2005, sunitinib in 2006, and temsirolimus in 2007, the role of interferon alfa and high-dose interleukin-2 is more interesting as a historical treatment option for advanced/metastatic RCC. Interferon alfa is not FDA approved for RCC but yields response rates of approximately 14%, with short durability of response, ranging from 6 months to 2 years.[2] The drug is also poorly tolerated, causing marked fatigue and severe depression.

High-dose interleukin-2 yields better response rates (21%) with greater durability of response (median duration, 54 months) than interferon alfa but is administered on telemetry floors because of the risk of capillary leak syndrome.[2] The drug is also contraindicated in patients with significant cerebrovascular disease, cardiac disease, pulmonary disease, renal disease (serum creatinine >1.5 mg/dL), hepatic disease, abnormal thallium stress test, or abnormal pulmonary function test, which limits the number of patients who are medically well enough to qualify for treatment. A small group of patients are also known to be cured by high-dose interleukin-2, but there is no known way to predict patients who may respond to therapy.[2]

Sunitinib, 50 mg once daily for 4 weeks with 2 weeks off, with or without food, has shown a doubling in median progression-free survival (PFS) compared with active treatment with interferon alfa (11 months vs 5 months, $P < .001$) in a phase 3 trial of 662 previously untreated patients with metastatic RCC.[3] The most common adverse events (>20% of patients) associated with treatment included liver function test elevations, elevated serum creatinine, myelosuppression, lymphopenia, elevated amylase and lipase, hypophosphatemia, diarrhea, fatigue, nausea, stomatitis, vomiting, hypertension, hand-foot syndrome, and rash. The most common grade 3/4 adverse events (>5% of patients) included lipase elevations, lymphopenia, neutropenia, elevated uric acid, hypertension, fatigue, hand-foot syndrome, and diarrhea.[3]

Sorafenib, 400 mg (two 200-mg tablets) twice daily on an empty stomach, was shown to double PFS to 167 days compared with 84 days with placebo in a phase 3 trial of 769 advanced RCC patients who were resistant to prior therapies (not including sunitinib).[4] The most common side effects (>20% of patients) reported with sorafenib include diarrhea, fatigue, rash, hand-foot syndrome, alopecia, and nausea; the most common grade 3/4 toxicities (>5% of patients and statistically different compared with placebo) included hand-foot syndrome and fatigue.[4]

Both sorafenib and sunitinib were studied in patients who had good performance status, were Memorial Sloan-Kettering Cancer Center (MSKCC) low-intermediate risk, and, for more than 95%, had been treated with nephrectomy.

Temsirolimus was studied in a phase 3 trial of 626 previously untreated patients with advanced RCC who were MSKCC poor-risk, only two of three of whom had been treated with nephrectomy.[5] Median overall survival (OS) was significantly improved for patients who were treated with temsirolimus, 25 mg intravenous (IV) weekly (10.9 months), compared with those treated with interferon alfa, 3 million to 18 million units (depending on tolerability) subcutaneous three times a week (7.3 months) (hazard ratio [HR] for death = 0.73; $P = .008$).[5]

Patients treated with both temsirolimus and interferon alfa did not live longer than those treated with interferon alfa alone (median OS = 8.4 months;

HR = 0.96; *P* = .70).[5] The most common side effects (> 20%) in the temsirolimus alone arm included asthenia, rash, anemia, nausea, anorexia, pain, dyspnea, hyperlipidemia and hypercholesterolemia, infection, peripheral edema, hyperglycemia, fever, and abdominal pain.[5] The most common grade 3/4 adverse events in the temsirolimus alone group (>5%) included anemia, asthenia, hyperglycemia, dyspnea, and pain.[5]

Recent advances: General treatment

More than 100 studies on kidney cancers were presented at the 2008 Annual Meeting of the American Society of Clinical Oncology (ASCO), representing a wide array of drug therapy options for the disease. Novel therapies included pazopanib, cediranib, erlotinib, ixabepilone, meloxicam, gefitinib, bevacizumab, and everolimus, as well as vaccine therapies.

Two studies that presented outcome data for bevacizumab and everolimus, a mammalian target of rapamycin (mTOR) inhibitor, were randomized trials in which 649 patients with advanced RCC were randomized to interferon alfa-2a, 9 million units subcutaneously three times a week, with either bevacizumab, 10 mg/kg IV every 2 weeks, or placebo, which was stopped early after the sorafenib and sunitinib data became available.[6,7] Median PFS at the time of unblinding was almost doubled in patients treated with combination therapy compared with single-agent interferon alfa (10.2 months vs 5.4 months; *P* = .0001).[7]

The updated results of AVOREN presented at the 2008 ASCO meeting demonstrate that combination therapy with bevacizumab plus interferon alfa-2a yields significantly better median PFS than interferon alfa-2a alone regardless of various risk categories, including those with mixed clear cell and nonclear cell histology.[7] Furthermore, a subgroup analysis of the 131 patients who received reduced doses of interferon alfa-2a in combination with bevacizumab had comparable median PFS (12.4 months) as those who received full-dose therapy.[8,9]

RECORD-1, a randomized, phase 3 trial that evaluated best supportive care plus either oral everolimus 10 mg daily or placebo in 410 patients with advanced RCC who had progressed on prior sunitinib, sorafenib, or both, was first presented at the 2008 ASCO meeting.[10] The study was stopped early at the second interim analysis after significant improvements in median PFS were observed for the active treatment arm (4.0 months [95% confidence interval (CI), 3.7-5.5 months] vs 1.9 months [95% CI, 1.8-1.9 months]).[10] Stomatitis, rash, and fatigue were the most commonly reported adverse events.[10] This trial was the first to establish a therapy for patients who failed prior therapy with a vascular epithelial growth factor receptor (VEGFR)-tyrosine kinase inhibitor (TKI).[8] Based on the results of this trial, everolimus was approved in March for the treatment of advanced RCC after failure of treatment with sunitinib or sorafenib.

Discussion of these findings at the 2008 ASCO meeting led to a proposal that sunitinib or bevacizumab with interferon alfa be considered as first-line treatment of good-intermediate risk advanced RCC, and temsirolimus or sunitinib as first-line treatment for patients with poor-risk disease.[8] Sorafenib was suggested as second-line therapy for those who previously failed cytokine therapy, and everolimus, for those who failed prior VEGFR-TKI therapy. No data or recommendations were offered for those who failed treatment with an mTOR inhibitor.[8]

Recent advances: Special populations

The subtleties of applying clinical trial data to real patients frequently involve consideration of patient characteristics. Several trials presented at the 2008 ASCO Annual Meeting and the 2008 ASCO Genitourinary Symposium investigated the nuances of drug treatment in special populations, such as those with impaired renal function or older adults with brain metastases.[11-13]

In a retrospective analysis of 32 patients with metastatic RCC who were treated with sorafenib, 14 patients with creatinine clearance (CrCl) <60

mL/min were more likely than their 18 counterparts with CrCl >60 mL/min to experience side effects, such as rash (86% vs 56%), diarrhea (57% vs 33%), and dose interruptions (57% vs 28%) or dose reductions (43% vs 22%).[11] Although these adverse events were increased in patients with impaired renal function, there were no differences in response rates or median PFS.[12] This would suggest that patients with impaired renal function could start therapy at equivalent doses as those with normal renal function, but that they must be more closely monitored for adverse events.

The risk of hemorrhage is a concern for patients who receive anti-VEGFR therapy, particularly those with brain metastases. Similar efficacy and toxicity were reported in a retrospective analysis of 3997 metastatic RCC patients enrolled in an expanded access program for sunitinib regardless of whether brain metastases were present.[12]

Of the 298 patients with brain metastases, 6% required dose reduction for an adverse event, and only one patient had a treatment-related cerebral hemorrhage (which was grade 1/2).[12] Among patients with brain metastases, 11% had a partial response and 51% had stable disease, similar to the results reported in the literature.[12] Although this report did not find a significant increase in hemorrhagic events, it would be worthwhile to wait for additional experience to accrue before accepting the safety of this agent in this particular population.

Finally, many practitioners are hesitant to prescribe full-dose therapy for older adult (age > 65 years) patients for fear of an increased risk of adverse events. A subset analysis of the Advanced Renal Cell Carcinoma Sorafenib (ARCCS) expanded access program in North America found similar rates of adverse events in 1135 older patients, including hand-foot syndrome, rash, fatigue, hypertension, diarrhea, nausea, and anorexia, as well as similar response rates as their 1469 younger

counterparts when given the standard dose of sorafenib.[13] In this instance, the dose of sorafenib should not be reduced on the basis of age alone.

Recent advances: Toxicities

The study of special populations is of interest for two reasons: first, to ascertain whether certain groups of patients respond differently than other groups and second, to see whether certain groups of patients are more prone to various toxicities. In the absence of population-specific data, some investigators have attempted to better describe both the incidence of certain adverse events in general and in patients who may reasonably be presumed to be predisposed to the toxicity—specifically the cardiotoxicity associated with sunitinib, the risk of hand-foot syndrome with sorafenib, skin toxicities with sunitinib, endocrine complications from temsirolimus and sorafenib, and the long-term adverse effects of TKIs.[14-19]

In a retrospective single-institution study of 45 patients treated with sunitinib, seven patients (15%) experienced symptomatic grade 3/4 left ventricular dysfunction (LVD); three of five for whom data were available had persistent LVD despite treatment with standard congestive heart failure (CHF) therapy.[14] This figure is rather alarming when compared with the 21% overall incidence of LVD reported in the literature.[15] The effect was seen even in patients who had normal heart function at the initiation of therapy. Significant predictors of LVD include a history of CHF (P = .002), coronary artery disease (P = .05), and a low body mass index (P = .03).[14] Patients who start sunitinib should be closely monitored for symptoms of CHF.

Skin toxicities are a common side effect of therapies that target the epidermal growth factor receptor pathway. An analysis of 4883 patients found that those who received sorafenib for RCC (n = 3252) experienced more hand-foot syndrome overall than patients treated

with the drug for non-RCC indications (n = 545).[15] The relative risk for all grades of hand-foot syndrome in patients treated for RCC compared with non-RCC was 1.52 (95% CI, 1.32-1.75; *P* <.001); however, there was no significant increase in more severe (high grades) hand-foot syndrome.[15] The cause of the disparity in this analysis is not known, but it might be worth further investigation because the mechanism of toxicity may suggest a difference in mechanism of action for therapeutic effect in different disease states. The incidence of skin toxicities may also be higher in actual practice than reported in the literature. The 40 patients enrolled in clinical trials or the expanded access programs for sunitinib reported 46 dermatologic adverse events.[16] Although the rates of skin toxicities with sunitinib are reported to be 10%, the rate was found to be much higher in this analysis: 30% of patients experienced hair depigmentation, 27% hand-foot syndrome, 22% acral syndrome, 15% scrotal erythema, and 12% mucositis.[16] These rates are likely more reflective of actual practice and warrant greater emphasis during patient counseling and assessment.

"The incidence of skin toxicities may also be higher in actual practice than reported in the literature."

Complete blood cell count and electrolyte monitoring are routine in standard oncology practice. For patients treated with temsirolimus, sorafenib, or sunitinib, endocrine panels must also be monitored. A subset analysis of the registration trial for temsirolimus indicates that hyperglycemia occurs in patients treated with this agent regardless of a prior history of diabetes. This agent also increases total cholesterol but not other lipids.[17] In patients treated with temsirolimus, 16% of patients without diabetes experienced hyperglycemia compared with 3% of those treated with interferon alfa, and all patients with diabetes experienced hyperglycemia while on temsirolimus compared with 36% of those on interferon alfa.[17]

Hypothyroidism attributed to sunitinib has been reported, but the incidence of hypothyroidism with sorafenib was not previously characterized. A prospective single-institution study of 38 patients treated with sorafenib found that seven of 23 patients with normal baseline thyroid-stimulating hormone (TSH) levels experienced elevations in TSH while being treated, two of 15 patients with abnormal baseline TSH levels experienced elevated TSH, and two others experienced thyroiditis.[18] Although these rates are lower than that reported in the literature for sunitinib, they are high enough to warrant monitoring of TSH during therapy.[18]

Finally, because these newer therapies have been routinely available only for the past few years, the long-term rates of adverse events are not well-described. In a small retrospective review of 16 patients who received either sunitinib, sorafenib, or axitinib for at least 16 months (median, 24.4 months), 77% of patients experienced their worst toxicity within the first 12 months of treatment, compared with 23% who experienced it after 12 months.[19] The median time to worst toxicity was 5.5 months (range, 0.6-28.3 months), and the rates of hypothyroidism, anemia, and neutropenia were relatively similar within 12 months of treatment as after 12 months of treatment.[19] Thrombocytopenia and fatigue did seem to be numerically more likely to occur in the first 12 months of therapy (56% vs 25% for thrombocytopenia, 56% vs 13% for fatigue), but the small number of patients in the analysis preclude drawing a stronger conclusion from the results.[20] The issue of long-term therapy certainly warrants additional follow-up with larger numbers of patients.

Summary

Targeted therapies are now the mainstay of drug options for advanced and

Continued on page 41

drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance). As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia: In FRAGMIN clinical trials supporting non-cancer indications, platelet counts of <100,000/mm³ and <50,000/mm³ occurred in <1% and <1% of patients, respectively. In the clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated for up to 6 months in the FRAGMIN treatment arm, platelet counts of <100,000/mm³ occurred in 13.6% of patients, including 6.5% who also had platelet counts less than 50,000/mm³. In the same clinical trial, thrombocytopenia was reported as an adverse event in 10.9% of patients in the FRAGMIN arm and 8.1% of patients in the OAC arm. FRAGMIN dose was decreased or interrupted in patients whose platelet counts fell below 100,000/mm³. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Miscellaneous: Each multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should be used with caution in pregnant women and only if clearly needed. If anticoagulation with FRAGMIN is needed during pregnancy, preservative-free formulations should be used, where possible (see **PRECAUTIONS, Pregnancy Category B, Nonteratogenic Effects**).

PRECAUTIONS

General: FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing. FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding. If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions: FRAGMIN should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see **PRECAUTIONS, Laboratory Tests**). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see **DOSAGE AND ADMINISTRATION**).

Laboratory Tests: Periodic routine complete blood counts, including platelet count, blood chemistry, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (i.e., APTT) is needed. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are relatively insensitive measures of FRAGMIN activity and, therefore, unsuitable for monitoring the anticoagulant effect of FRAGMIN. Anti-Factor Xa may be used to monitor the anticoagulant effect of FRAGMIN, such as in patients with severe renal impairment or if abnormal coagulation parameters or bleeding should occur during FRAGMIN therapy.

Drug/Laboratory Test Interactions: Elevations of Serum Transaminases: In FRAGMIN clinical trials supporting non-cancer indications where hepatic transaminases were measured, asymptomatic increases in transaminase levels (SGOT/AST and SGPT/ALT) greater than three times the upper limit of normal of the laboratory reference range were seen in 4.7% and 4.2%, respectively, of patients during treatment with FRAGMIN. In the FRAGMIN clinical trial of patients with cancer and acute symptomatic venous thromboembolism treated with FRAGMIN for up to 6 months, asymptomatic increases in transaminase levels, AST and ALT, greater than three times the upper limit of normal of the laboratory reference range were reported in 8.9% and 9.5% of patients, respectively. The frequencies of Grades 3 and 4 increases in AST and ALT, as classified by the National Cancer Institute, Common Toxicity Criteria (NCI-CTC) Scoring System, were 3% and 3.8%, respectively. Grades 2, 3 & 4 combined have been reported in 12% and 14% of patients, respectively.

Carcinogenicity, Mutagenesis, Impairment of Fertility: Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the ***in vitro*** Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the ***in vivo*** mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU/kg (7080 IU/m²) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B. Teratogenic Effects: Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU/kg (14,160 IU/m²) in pregnant rats and 4800 IU/kg (40,800 IU/m²) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99–404 mg/kg/day). The 9.5 mL and the 3.8 mL multiple-dose vials of FRAGMIN contain 14 mg/mL of benzyl alcohol.

Nursing Mothers: Limited data are available for excretion of dalteparin in human milk. One study in 15 lactating women receiving prophylactic doses of dalteparin detected small amounts of anti-Xa activity in breast milk, equivalent to a milk/plasma ratio of <0.025-0.224. As oral absorption of LMWH is extremely low, the clinical implications, if any, of this small amount of anticoagulant activity on the nursing infant are unknown. Caution should be exercised when FRAGMIN is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of the total number of patients in clinical studies of FRAGMIN, 5516 patients were 65 years of age or older and 2237 were 75 or older. No overall differences in effectiveness were observed between these subjects and younger subjects. Some studies suggest that the risk of bleeding increases with age. Postmarketing surveillance and literature reports have not revealed additional differences in the safety of FRAGMIN between elderly and younger patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised, particularly in geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function (see also **CLINICAL PHARMACOLOGY** and **General** and **Drug Interactions** subsections of **PRECAUTIONS**).

ADVERSE REACTIONS

Hemorrhage: The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin. In a trial comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a trial comparing FRAGMIN 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Unstable Angina and Non-Q-Wave Myocardial Infarction: Table 8 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 8: Major Bleeding Events in Unstable Angina and Non-Q-Wave Myocardial Infarction

Indication	Dosing Regimen		
Unstable Angina and Non-Q-Wave MI	**FRAGMIN** 120 IU/kg/12 hr. s.c.[1] n(%)	**Heparin** i.v. and s.c.[2] n(%)	**Placebo** every 12 hr s.c. n(%)
Major Bleeding Events[3,4]	15/1497 (1.0)	7/731 (1.0)	4/760 (0.5)

[1]Treatment was administered for 5 to 8 days.
[2]Heparin i.v. infusion for at least 48 hours, APTT 1.5 to 2 times control, then 12,500 U s.c. every 12 hours for 5 to 8 days.
[3]Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.
[4]Bleeding events were considered major if: 1) accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) a transfusion was required; 3) bleeding led to interruption of treatment or death; or 4) intracranial bleeding.

Hip Replacement Surgery: Table 9 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN (preoperative dosing regimen), warfarin sodium, or heparin in two hip replacement surgery clinical trials.

Table 9: Bleeding Events Following Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	**FRAGMIN**[2] 5000 IU once daily s.c. n(%)	**Warfarin** Sodium[1] oral n(%)	**FRAGMIN**[4] 5000 IU once daily s.c. n(%)	**Heparin** 5000 U three times a day s.c. n(%)
Major Bleeding Events[3]	7/274 (2.6)	1/279 (0.4)	0	3/69 (4.3)
Other Bleeding Events[5]				
Hematuria	8/274 (2.9)	5/279 (1.8)	0	0
Wound Hematoma	6/274 (2.2)	0	0	0
Injection Site Hematoma	3/274 (1.1)	NA	2/69 (2.9)	7/69 (10.1)

[1]Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
[2]Includes three treated patients who did not undergo a surgical procedure.
[3]A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.
[4]Includes two treated patients who did not undergo a surgical procedure.
[5]Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications. In the third hip replacement surgery clinical trial, the incidence of major bleeding events was similar in all three treatment groups: 3.6% (18/496) for patients who started FRAGMIN before surgery; 2.5% (12/487) for patients who started FRAGMIN after surgery; and 3.1% (15/489) for patients treated with warfarin sodium.

Abdominal Surgery: Table 10 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 10: Bleeding Events Following Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
Abdominal Surgery	**FRAGMIN** 2500 IU once daily s.c. n(%)	**Heparin** 5000 U twice daily s.c. n(%)	**FRAGMIN** 5000 IU once daily s.c. n(%)	**Heparin** 5000 U twice daily s.c. n(%)	**FRAGMIN** 2500 IU once daily s.c. n(%)	**Placebo** once daily s.c. n(%)	**FRAGMIN** 2500 IU once daily s.c. n(%)	**FRAGMIN** 5000 IU once daily s.c. n(%)
Postoperative Transfusions	26/459 (5.7)	36/454 (7.9)	81/508 (15.9)	63/498 (12.7)	14/182 (7.7)	13/182 (7.1)	89/1025 (8.7)	125/1033 (12.1)
Wound Hematoma	16/467 (3.4)	18/467 (3.9)	12/508 (2.4)	6/498 (1.2)	2/79 (2.5)	2/77 (2.6)	1/1030 (0.1)	4/1039 (0.4)
Reoperation Due to Bleeding	2/392 (0.5)	3/392 (0.8)	4/508 (0.8)	2/498 (0.4)	1/79 (1.3)	1/78 (1.3)	2/1030 (0.2)	13/1038 (1.3)
Injection Site Hematoma	1/466 (0.2)	5/464 (1.1)	36/506 (7.1)	47/493 (9.5)	8/172 (4.7)	2/174 (1.1)	36/1026 (3.5)	57/1035 (5.5)

Medical Patients with Severely Restricted Mobility During Acute Illness: Table 11 summarizes major bleeding events that occurred in a clinical trial of medical patients with severely restricted mobility during acute illness.

Table 11: Bleeding Events in Medical Patients with Severely Restricted Mobility During Acute Illness

Indication	Dosing Regimen	
Medical Patients with Severely Restricted Mobility	**FRAGMIN** 5000 IU once daily s.c. n(%)	**Placebo** once daily s.c. n(%)
Major Bleeding Events[1] at Day 14	8/1848 (0.4)	0/1833 (0)
Major Bleeding Events[1] at Day 21	9/1848 (0.5)	3/1833 (0.2)

[1]A bleeding event was considered major if: 1) it was accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) intraocular, spinal/epidural, intracranial, or retroperitoneal bleeding; 3) required transfusion of ≥2 units of blood products; 4) required significant medical or surgical intervention; or 5) led to death.

Three of the major bleeding events that occurred by Day 21 were fatal, all due to gastrointestinal hemorrhage (two patients in the group treated with FRAGMIN and one in the group receiving placebo). Two deaths occurred after Day 21: one patient in the placebo group died from a subarachnoid hemorrhage that started on Day 55, and one patient died on day 71 (two months after receiving the last dose of FRAGMIN) from a subdural hematoma.

Patients with Cancer and Acute Symptomatic Venous Thromboembolism

Table 12 summarizes the number of patients with bleeding events that occurred in the clinical trial of patients with cancer and acute symptomatic venous thromboembolism. A bleeding event was considered major if it: 1) was accompanied by a decrease in hemoglobin of ≥2 g/dL in connection with clinical symptoms; 2) occurred at a critical site (intraocular, spinal/epidural, intracranial, retroperitoneal, or pericardial bleeding); 3) required transfusion of ≥2 units of blood products; or 4) led to death. Minor bleeding was classified as clinically overt bleeding that did not meet criteria for major bleeding. At the end of the six-month study, a total of 46 (13.6%) patients in the FRAGMIN arm and 62 (18.5%) patients in the OAC arm experienced any bleeding event. One bleeding event (hemoptysis in a patient in the FRAGMIN arm at Day 71) was fatal.

Table 12: Bleeding Events (Major and Any) (As treated population)[1]

Study period	FRAGMIN 200 IU/kg (max. 18,000 IU) s.c. once daily x 1 month, then 150 IU/kg (max 18,000 IU) s.c. once daily x 5 months			OAC FRAGMIN 200 IU/kg (max 18,000 IU) s.c. once daily x 5-7 days and OAC for 6 months (target INR 2-3)		
	Number at risk	Patients with Major Bleeding n(%)	Patients with Any Bleeding n(%)	Number at Risk	Patients with Major Bleeding n(%)	Patients with Any Bleeding n(%)
Total during study	338	19 (5.6)	46 (13.6)	335	12 (3.6)	62 (18.5)
Week 1	338	4 (1.2)	15 (4.4)	335	4 (1.2)	12 (3.6)
Weeks 2-4	332	9 (2.7)	17 (5.1)	321	1 (0.3)	12 (3.7)
Weeks 5-28	297	9 (3.0)	26 (8.8)	267	8 (3.0)	40 (15.0)

[1]Patients with multiple bleeding episodes within any time interval were counted only once in that interval. However, patients with multiple bleeding episodes that occurred at different time intervals were counted once in each interval in which the event occurred.

Thrombocytopenia: See WARNINGS: Thrombocytopenia.

Other: Allergic Reactions: Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bulleous eruption) have occurred rarely. A few cases of anaphylactoid reactions have been reported. Local Reactions: Pain at the injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU once daily vs 11.8% of patients treated with heparin 5000 U twice daily in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU once daily vs 13% of patients treated with heparin 5000 U three times a day.

Ongoing Safety Surveillance: Since first international market introduction in 1985, there have been more than 15 reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. The majority of patients had postoperative indwelling epidural catheters placed for analgesia or received additional drugs affecting hemostasis. In some cases the hematoma resulted in long-term or permanent paralysis (partial or complete). Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Post-Marketing Experience: Skin necrosis has occurred rarely. There have been isolated cases of alopecia reported that improved on drug discontinuation.

OVERDOSAGE

Symptoms/Treatment: An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%). Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation techniques and treatment of anaphylactic shock are readily available. For additional information, consult the labeling of Protamine Sulfate Injection, USP, products. A single subcutaneous dose of 100,000 IU/kg of FRAGMIN to mice caused a mortality of 8% (1/12) whereas 50,000 IU/kg was a non-lethal dose. The observed sign was hematoma at the site of injection.

Rx only

U.S. Patent 4,303,651

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Prostate Cancer 2008

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The natural history of prostate cancer may be prolonged over decades, thus treatment advances have not occurred as rapidly as in other common solid tumors, including breast, lung, and colon cancers. However, in 2008, significant advances were made in the understanding of previously published data on finasteride in the prevention of prostate cancer. Additionally, safety issues with androgen ablation, a long-standing approach to the management of prostate cancer, were reported and a review of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database revealed androgen ablation is not appropriate for most patients with newly diagnosed prostate cancer. Finally, newer therapies are being evaluated in patients with both androgen-sensitive and -insensitive disease. This article discusses these advances with the latest studies described at each step along the natural progression of the disease.

Prevention

The best way to treat cancer is through prevention; thus efforts to develop new preventive strategies and to understand recently reported data on older strategies were a focus in 2008. The Prostate Cancer Prevention Trial (PCPT), which enrolled 19,000 men aged 55 years or older, revealed that finasteride reduced the relative risk of a diagnosis of prostate cancer by about 25%.[1] Although these findings, reported in 1993, were significant, the trial also revealed an increased risk of rapidly growing high-grade cancers in men taking this medication. Because of these concerns, this agent has not been widely used in clinical practice for prevention of prostate cancer.

Five years later, reanalysis of tissue obtained from the original study revealed that the risks were overestimated and clear benefits existed for the use of finasteride.[2-4] For the original analysis of data, both the tumor grade and Gleason grade were derived from a biopsy of a small section of the prostate. However, to adequately assess Gleason grade, the entire prostate must be examined after surgical removal. Therefore, in 2007, researchers graded the entire prostate that was surgically removed in 500 PCPT participants to determine the Gleason grade in these specimens. Data were then mathematically modeled to extend those results to the entire PCPT cohort.[2,3] Both analyses concluded that the rates of high-grade disease were lower in the finasteride arm compared with the placebo arm (Figure 1). According to the model, 8.2% of men in the placebo arm would have been diagnosed with high-grade prostate cancer compared with 6% in the finasteride arm, contradicting the early concerns that finasteride use resulted in high-grade prostate cancer.[3]

A third new report from PCPT data reexamined the biopsy scores from each participant found to have prostate cancer. Using the Epstein criteria (clinical stage, extent of tumor, and prostate-specific antigen [PSA] density) to determine clinical significance, the researchers found 75% of cancers in the placebo group met the criteria for clinical significance—possible cases where finasteride could have prevented prostate cancer.[4] These new results have renewed interest in finasteride, and other agents in this class, to potentially reduce the risk of prostate cancer. Appropriate candidates for finasteride, such as African-American men and those with a family history of disease, should be evaluated for therapy and counseled on the risks and benefits of finasteride.

"The best way to treat cancer is through prevention."

The recently released American Society of Clinical Oncology-American Urological Association Clinical Practice Guidelines recommend that asymptomatic men with a 3.0 ng/mL level who are regularly screened with PSA or are anticipating undergoing annual PSA screening for early detection of prostate cancer may benefit from a discussion of both the benefits of 5-alpha reductase inhibitors (ARIs) for 7 years for the prevention of prostate cancer and the potential risks (including the possibility of high-grade prostate cancer). Men who are taking 5-ARIs for benign conditions may benefit from a similar discussion.[5]

While the news about finasteride excited the prevention world, disappointing news was reported in 2008 for the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The independent Data and Safety Monitoring Committee for the trial met on September 15, 2008, to review SELECT study data and found that selenium and vitamin E, taken alone or together for an average of 5 years, did not prevent prostate cancer.[6] In fact, there was a nonsignificant increased risk of prostate cancer in the vitamin E group ($P = .06$) and type 2 diabetes mellitus in the selenium group (relative risk, 1.07; 99% confidence interval [CI], 0.94-1.22; $P = .16$), but not in the selenium plus vitamin E group.[6] While there is still much to be learned from these data, neither selenium nor vitamin E at the doses and formulations used were shown to prevent prostate cancer.

Before discussing prevention options, patients at risk must be identified. Until recently, identification of patients at risk was limited to factors such as age, race, and family history. Recent genomewide analyses have identified variants in five chromosomal regions that are significantly associated with prostate cancer. Previously, single-nucleotide polymorphisms in each of five chromosomal regions were shown to have only a moderate association with prostate cancer. However, data published in 2008 revealed that variants in three independent regions—8q24, 17q12, and 17q24.3—in combination with family history, accounted for 46% of prostate cancer cases in a Swedish population.[7] The identified association did not predict for aggressiveness of disease; therefore, the assumption is that the genetic variants act at an early stage. These data are the first step in understanding the genetic association of prostate cancer and require further evaluation in assessing risk in individual men.

Androgen-deprivation therapy

Androgen-deprivation therapy (ADT), including gonadotropin-releasing hormone agonists, such as leuprolide and goserelin, and the antiandrogens flutamide and bicalutamide, are important in the management of prostate cancer. Often used as palliative treatment for advanced prostate cancer and in patients with early disease at high risk of progression, these agents have also been used as first-line treatment for patients with T1 or T2 prostate cancer. Clinical outcomes associated with this use are not definitive.

In a retrospective analysis of the population-based SEER database and linked Medicare files, 19,271 men aged 66 years or older were evaluated for survival based on the management of localized (T1 or T2) prostate cancer.[8] These patients were diagnosed between 1992 and 2002, and the data were evaluated for PSA and overall survival based on use of primary ADT (PADT) versus conservative management. In this population, 41% (7867) of patients received PADT (median age 77 years), while the remaining 11,404 received conservative management. The authors found that the PADT group had a lower 10-year disease-specific survival than those taking no drugs. Specifically, PADT was associated with a lower 10-year prostate cancer–specific survival (80.1% vs 82.6%; hazard ratio [HR], 1.17; 95% CI, 1.03-1.33) and no increase in 10-year overall survival (30.2% vs 30.3%; HR, 1.00; 95% CI, 0.96-1.05) compared with conservative management. The only exception to these results were patients with poorly differentiated prostate cancer, in whom

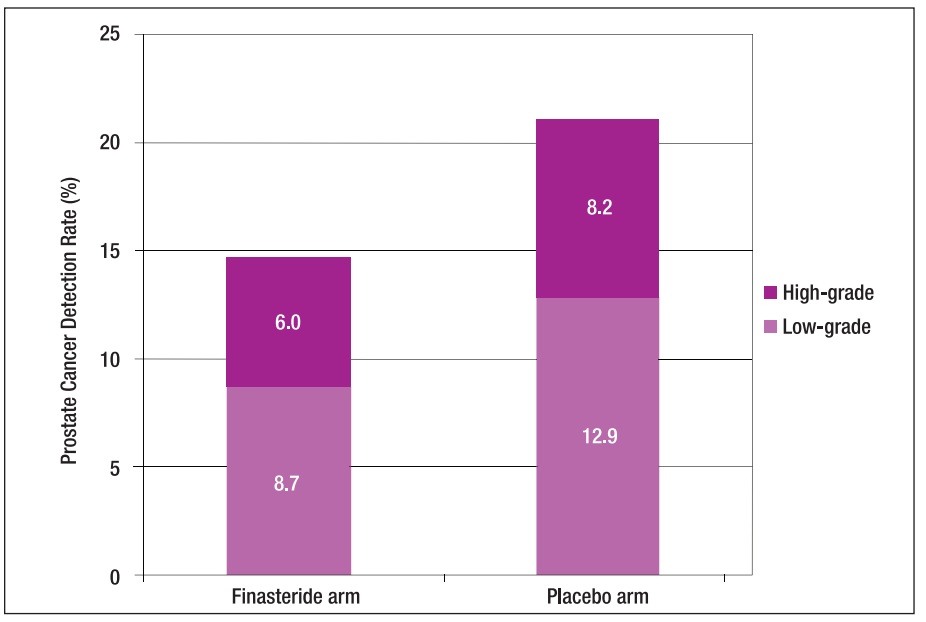

Figure 1. Prostate cancer detection rates

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Please see the following brief summary of prescribing information.

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PADT was associated with a better prostate cancer–specific survival but not better overall survival, compared with those receiving no therapy. These data, while retrospective, add to the argument that ADT has little role in improving outcomes in most men with early prostate cancer.

ADT is also utilized for patients with biochemical recurrence, as evidenced by a rising PSA after definitive local therapy. However, several studies have suggested an increased risk of fragility fractures, acute myocardial infarction, and diabetes mellitus with continuous use of ADT. Therefore, a retrospective population-based matched cohort analysis of 19,709 patients receiving ADT and 19,709 prostate cancer patients not receiving ADT, 66 years of age or older in Ontario, Canada, was conducted using propensity-based methods. The analysis revealed that continuous use of ADT for at least 6 months was associated with an increased risk of fragility fracture and diabetes, but not acute myocardial infarction or hypercholesterolemia.[9]

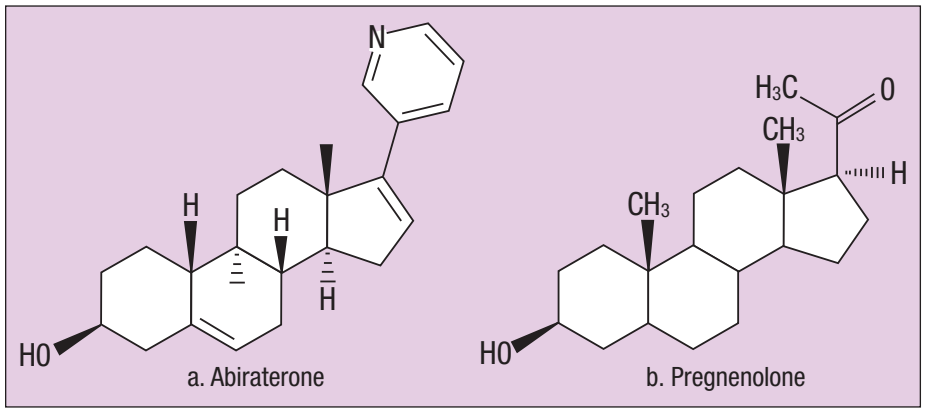

Figure 2. Chemical structures of (a) abiraterone acetate and (b) pregnenolone

Local recurrence

In patients who experience biochemical disease recurrence heralded by a rising PSA after definitive local therapy, treatment choices are varied. Salvage options include radiation therapy, hormonal therapy, combined therapy, investigational therapy, or watchful waiting. These choices could be delayed or initiated immediately. Conclusive evidence from randomized trials to determine which approach prolongs life is not available. A review of 18 randomized clinical trials and 473 observational studies revealed little high-quality prospective evidence that establishes the superiority of one therapy over another.[10] Additionally, all treatments (ADT, radical prostatectomy, and radiotherapy) were associated with urinary, bowel, or sexual dysfunction; the frequency, duration, and severity of these adverse events varied among treatments.

A recent study has proved salvage radiotherapy, administered within 2 years of biochemical recurrence of disease after prostatectomy, offers a significant increase in prostate cancer–specific survival.[11] With a median follow-up of 6 years after recurrence and 9 years after prostatectomy, investigators analyzed a cohort of 635 men who experienced biochemical and/or local recurrence and received no salvage treatment (n = 397), salvage radiotherapy alone (n = 160), or salvage radiotherapy combined with hormonal therapy (n = 78). Salvage radiotherapy initiated within 2 years of recurrence was associated with a significant threefold increase in prostate cancer–specific survival relative to those who received no salvage treatment (HR, 0.32; 95% CI, 0.19-0.54; *P* <.001), and the improvement was primarily confined to men with a PSA doubling time of less than 6 months. However, the addition of hormonal therapy to salvage radiotherapy was not associated with an additional increase in prostate cancer–specific survival.

Novel agents also have been evaluated in patients with PSA recurrent nonmetastatic prostate cancer after local definitive therapy. The results of a randomized, double-blind, placebo-controlled, crossover phase 3 study of intermittent hormonal therapy and thalidomide were presented at the 2008 American Society of Clinical Oncology

Table. Phase 1/2 Clinical Trials Involving Abiraterone Acetate

Study	Phase	Number of patients	Abiraterone dose (mg/day)	Response[a]
Attard	1	21	250–2000[b]	57%
Ryan	2	33	250–1000[b]	53% prior K 61% no prior K
Reid	2	30 chemonaïve (arm A) 31 prior docetaxel (arm B)	1000	Arm A: 60% Arm B: 52%
Danilla	2	38	1000 + 5 mg prednisone	40%

[a]Response is defined as 50% decrease in prostate-specific antigen, confirmed after 1 month that lasted for more than 3 months.
[b]Recommended phase 2 dose is 1000 mg/day.
K indicates ketoconazole.
Sources: References 13 through 16.

meeting.[12] At the time of PSA progression, patients received 6 months of a luteinizing hormone-releasing hormone (LHRH) agonist and then were randomized to thalidomide or placebo (part A) until a PSA rise to baseline or to ≥5 ng/mL, whichever occurred first. At that time, the LHRH agonist was reinitiated for 6 months followed by oral therapy with the opposite agent (part B [thalidomide patients received placebo and placebo patients received thalidomide]) until PSA progression. Of 159 enrolled patients, 147 received the study drug in part A and 103 patients proceeded to part B; of these, 51 patients received thalidomide and 38 patients received placebo. There was no difference in median time to PSA progression in part A (thalidomide 15 months, placebo 9.6 months, $P = .21$), and median progression-free survival (PFS) during part B was 17.1 months for the thalidomide arm versus 6.6 months for the placebo arm ($P = .0002$). Although the sample size of this study was small, the results revealed a possible role for thalidomide, whose effects were independent of testosterone in this clinical stage of prostate cancer. The differences in outcome in part A versus part B are unclear, but may relate to possible biological changes that occur over time in the presence of LHRH-agonist therapy. Further investigation of the role of thalidomide in the management of prostate cancer is ongoing.

Metastatic disease

In metastatic disease, much interest is focused on the 17-alpha hydroxylase C17,20-lyase cytochrome P17 (CYP17) irreversible inhibitor abiraterone acetate for the treatment of prostate cancer. CYP17 catalyzes two independently regulated corticosteroid reactions key to androgen and estrogen biosynthesis.[13] Structurally similar to pregnenolone (Figure 2), abiraterone inhibits the production of testosterone in the testis, adrenal glands, and the prostate. Ketoconazole, which also works through the inhibition of CYP17, is less potent than abiraterone and a competitive inhibitor of several cytochrome enzymes beyond CYP17. Phase 1 and 2 trials have been completed with abiraterone (Table), with responses reported in patients previously treated with multiple hormonal therapies, chemotherapy, and ketoconazole.[13-16] Importantly, no patients developed clinical adrenocortical insufficiency with toxicities caused by secondary mineralocorticoid excess, including hypertension, hypokalemia, and fluid overload. The addition of a corticosteroid, prednisone, has minimized the occurrence of toxicities associated with secondary mineralocorticoid excess and is being utilized in the ongoing phase 3 trial comparing abiraterone/prednisone to placebo/prednisone in patients with prior docetaxel and no ketoconazole.

The impact of chemotherapy and antiangiogenic therapy continues to be investigated in the metastatic setting with mixed results. Follow-up data from the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial, a multinational, randomized, double-blind, placebo-controlled trial of 950 patients comparing the oral platinum compound satraplatin plus prednisone to prednisone alone revealed no improvement in overall survival with combination therapy.[17] In patients with no prior chemotherapy for metastatic disease, the combination of docetaxel, bevacizumab, thalidomide, and prednisone was associated with an 88% response rate as measured by PSA and a 63% response rate in measurable disease.[18] The median estimated PFS was 18.2 months in this population with unfavorable prognostic factors. Although these data require validation in a randomized phase 3 setting, early results are encouraging for the management of metastatic disease.

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COMMENTARY

A NURSE'S PERSPECTIVE

Prostate Cancer 2008: Implications for Clinical Nursing Practice

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According to American Cancer Society statistics, prostate cancer is the most commonly diagnosed solid tumor in American men and the second leading cause of cancer-related death. Although these facts are without debate, prostate cancer often progresses at a slower rate than other solid tumors, and thus treatment advances have been slow as well. In 2008, however, significant strides were made in the approach to identification of high-risk patients and in prevention and treatment options not only for high-risk patients, but also for patients with locally recurring disease and those with metastatic disease.

In February 2008, data were published identifying single-nucleotide polymorphisms in three independent chromosomal regions at 8q24, 17q12, and 17q24.3. This genetic information together with family history gives us more data to better assess a man's relative risk of being diagnosed with prostate cancer.

As a result of the data and continuing reports from the Prostate Cancer Prevention Trial (PCPT), many articles have been published that support the benefit of use of finasteride at a daily dose of 5 mg for prevention of prostate cancer. Although not approved as a chemoprevention agent, the evidence supports clinical use of finasteride for high-risk men, such as African Americans or those with a family history of prostate cancer. As for use of dietary supplements for prevention, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed that neither vitamin E nor selenium taken alone or together provided clinically significant benefit.

Data derived from the Surveillance, Epidemiology, and End Results (SEER) program on the management of localized T1 and T2 disease showed no survival benefit at 10 years for androgen-deprivation therapy (ADT) as compared with conservative management. Several studies, however, have suggested an increase in the risk for myocardial infarction, diabetes mellitus, and fragility fractures with ADT. These data suggest that ADT may have little clinical benefit in terms of either improvement of patient outcomes or survival.

Patients with disease recurrence after local definitive therapy, as evidenced by rising prostate-specific antigen (PSA) levels, lack conclusive evidence for treatment choices, because little high-quality evidence supports the superiority of one treatment choice over another. One recent study showed that radiation therapy within 2 years of biochemical recurrence after radical prostatectomy offers a significant survival benefit over no salvage treatment. This benefit was achieved by men with a PSA doubling time of less than 6 months. ADT in addition to radiation was not associated with any survival benefit.

Results of a crossover phase 3 study of intermittent hormone therapy and thalidomide were very promising, with median time to survival of 17.1 months compared with 6.6 months in the placebo arm. The results were achieved by men with PSA-recurrent, nonmetastatic disease.

For patients with metastatic disease, abiraterone acetate, which inhibits the production of testosterone in the testis, adrenal glands, and the prostate, has shown a less toxic profile than ketoconazole. Additionally, prednisone is being used in phase 3 studies and has further reduced the occurrence of mineralcorticoid excess.

PSA continues to be the measure of response used for prediction of overall survival in men with prostate cancer. In 2008, there were considerable advances in the prevention and management of prostate cancer. Many findings were inconclusive, but much promising new information with positive results and survival benefits was reported. Carefully assessing risk, implementing preventive measures, educating patients on available treatment options, screening for clinical trial eligibility, and continual PSA monitoring are all within the clinical nurse arena. The ongoing quest for results, implementation in clinical practice, and acquisition of the knowledge necessary to follow recommendations for trial design and end point assessment, as outlined by the Prostate Cancer Clinical Trials Working Group, will enable us to further delay disease progression and enhance survival for men with prostate cancer.

Venous Thromboembolism in Patients with Cancer: Current Approaches to Management

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Acting Surgeon General Steven K. Galson, MD, MPH, issued a *Call to Action* in September 2008 to reduce the number of cases of deep vein thrombosis (DVT) and pulmonary embolism (PE) in the United States.[1] These conditions affect an estimated 350,000 to 600,000 Americans each year and contribute to at least 100,000 deaths. The plan as described by the Surgeon General emphasizes the need for increased awareness of DVT and PE, evidence-based practices for DVT, and more research on the causes, prevention, and treatment of the condition. In conjunction with this announcement, the Agency for Healthcare Research and Quality has released two new guides on the prevention of dangerous blood clots—one for patients and another for healthcare providers.[1] Additionally, under a subcontract with the National Quality Forum, the Joint Commission on Accreditation of Healthcare Organizations is finalizing performance measures to evaluate the quality of care for persons at risk for venous thromboembolism (VTE).[2]

VTE is a frequent complication of cancer,[3,4] occurring more often in patients with cancer than in those without cancer. Those with cancer have a four- to six-fold increased risk of developing VTE, and approximately 20% of all new VTE events in the community are cancer-related.[5,6] Recurrent VTE is also more common in cancer patients than in patients without cancer, despite treatment with anticoagulants. More important, it is associated with a poor prognosis in cancer patients. In fact, 1-year mortality rates in cancer patients diagnosed with VTE can be as high as 90%, making it one of the leading causes of death in cancer patients.[7,8]

Standard treatment of VTE has been initial therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by long-term therapy with an oral anticoagulant. Recently, increasing data have emerged regarding alternative options for therapy, particularly in the treatment of VTE in patients diagnosed with cancer. These data have led to the publication and revision of a number of practice guidelines, including the guidelines of the American College of Chest Physicians (ACCP), the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the American Society of Health-System Pharmacists (ASHP). Most notable in all of these recommendations is the expanding role of LMWH in the initial and extended treatment of VTE.

Prevalence of and risk factors for VTE in patients with cancer

The prevalence of first-time DVT or PE in the general population has been estimated at 17 per 100,000 per year.[9,10] Among patients with cancer, risk of VTE rises dramatically to approximately 1 in 200.[5,10] However, this risk differs according to type of cancer, tumor stage, and whether a patient is receiving chemotherapy.[11] It is possible that the risk of this complication is underestimated, however, as VTE is found in at least 50% of cancer patients at autopsy.[12,13] Additionally, the burden of cancer-associated VTE appears to be growing as new cancer therapies that increase the risk of VTE enter into use and combination therapy using these agents becomes more common.[14]

Metastatic disease is a strong predictor of VTE. Compared with patients with localized disease, patients with metastatic cancer have a two- to four-fold increase in the risk of VTE during the 6 months after initial diagnosis of cancer.[15,16]

Cancer treatment as a risk factor for VTE

In addition to the risk conferred by cancer itself or the presence of metastatic disease, the treatment of the disease increases the risk that a patient will experience VTE. Concomitant use of therapies such as hormonal agents, chemotherapy, invasive procedures, and catheterization add to the considerable risk these patients already have.[10] Undergoing surgery as part of the overall management of their cancer places these patients at increased risk for development of VTE for up to 1 year after the surgical procedure.[17] Agents used in the supportive care of cancer patients such as erythropoietin, granulocyte colony-stimulating factor, and high-dose corticosteroids may also increase the risk for VTE in these patients.[11,18]

Synergy between the treatment and the severity of the disease has also been noted. High rates of thrombosis have been noted in patients with advanced cancer receiving some form of antitumor therapy, including patients receiving chemotherapy for metastatic breast cancer,[19,20] advanced ovarian cancer,[21] or those receiving L-asparaginase therapy for acute lymphoblastic leukemia.[22]

Both surgery and the use of indwelling central venous catheters increase the risk of developing VTE in all patients. For cancer patients, this risk is compounded. Postoperative VTE in cancer patients occurs at least twice as often as it does in noncancer patients who receive similar surgical procedures.[23] These patients also have a three-fold higher risk of fatal PE than noncancer patients.[24] The risk for VTE associated with central venous catheters is approximately 4%, with the highest risk occurring in patients requiring multiple insertion attempts and those with prior central venous catheterizations.[25]

"In addition to the risk conferred by cancer itself or the presence of metastatic disease, the treatment of the disease increases the risk that a patient will experience VTE."

VTE as an indicator of occult cancer

While cancer is a risk factor for VTE, the occurrence of VTE in patients without other identifiable risk factors can also suggest the presence of occult cancer.[26] In large prospective studies, 4% to 5% of patients presenting with VTE have previously undiagnosed cancer. Smaller studies suggest that the risk for cancer in patients with idiopathic VTE may be as high as 7% to 12%, compared with 2% to 3% in patients with identifiable risk factors for VTE.[26] Findings such as these have led some to suggest that patients presenting with VTE, particularly those without evident risk factors, should be carefully screened for underlying cancer; however, such an approach would need to be verified and validated in the context of a clinical trial.[24]

Risk of recurrent VTE

The risk of recurrent VTE is increased in cancer patients compared with patients without cancer, even with appropriate prophylaxis.[27] In a prospective study of 355 patients with DVT who were treated with heparin followed by warfarin, 10.3% of those with cancer experienced a recurrence of VTE in the 3-month follow-up period compared with 4.7% of patients without cancer.[27] In the subgroup of patients who had achieved international normalized ratios (INRs) of 2.0 to 3.0, 8.6% of cancer patients and 1.3% of patients without cancer experienced a recurrence ($P < .01$).[28]

Risk assessment for VTE in patients undergoing cancer treatment

While it is evident that cancer patients are at an increased risk for VTE, the risk differs from one patient to the next, and can vary in an individual patient over the course of the illness. Cancer patients constitute a heterogeneous population with a wide variety of risk factors, ranging from age and disease stage to chemotherapy and surgical procedures. Thus, risk assessment requires a dynamic approach.[12] Table 1 presents selected risk factors for cancer-associated thrombosis.

Biomarkers and laboratory parameters may also help stratify patient risk for VTE. Cancer patients with elevated levels of markers for hemostatic activation are at increased risk for primary and recurrent VTE.[12] D-dimer is elevated in patients with cancer compared with normal controls, and tissue

factor expression has been associated with increased angiogenesis. VTE occurs four times more often in patients with high tissue-factor expressing carcinomas (20%) than in those with low tissue-factor expressing carcinomas (5.5%) (P = .04).[12] Additionally, elevated prechemotherapy platelet counts have been correlated with an increased risk for VTE.[12]

Although there are ample data to suggest the use of thromboprophylaxis in cancer patients requiring hospitalization, as of yet there is not enough evidence to support the systematic use of such therapy in cancer patients undergoing chemotherapy, radiotherapy, or the insertion of a central venous catheter.[29] The decision as to whether thromboprophylaxis should be administered to a particular patient or not, and the duration of such therapy, is left to the clinical judgment of the physician.[29] The patient's personal and family medical history, comorbidities, the presence of thrombophilia, and patient preferences must be carefully assessed and considered in the context of the patient's overall VTE risk factors.[29]

Prevention and treatment of VTE in patients undergoing cancer treatment

As early as 1960, trials indicated that anticoagulation reduced mortality in patients with VTE.[30,31] A seminal study by Barritt and Jordan demonstrated that untreated patients with PE had a high mortality rate, while patients treated with anticoagulation therapy experienced a reduction in mortality.[31] Anticoagulant therapy should be started as soon as a diagnosis of DVT can be objectively substantiated; it should also be initiated in cases where DVT is highly suspected but results of diagnostic tests are not yet available. Both UFH and LMWH are indicated for the initial treatment of DVT, and these agents as well as oral vitamin K antagonists such as warfarin are recommended for long-term treatment of DVT.[30]

Unfractionated heparin therapy. UFH has long been considered to be the standard of care for initial treatment of DVT. Most hospitals use standardized nomograms for the initiation and maintenance of heparin dosing. The short half-life of UFH allows rapid adjustment of doses and makes reversal of anticoagulation rather easy. There are, however, a number of factors that make the use of UFH unattractive and difficult. It has an unpredictable dose response, requiring frequent monitoring and dose adjustments. Also, it has a relatively narrow therapeutic window, and requires prolonged inpatient hospitalization for administration. Even with the advent of bridging therapy, the initiation of warfarin on the first day of UFH therapy, patients must remain in the hospital for a minimum of 5 days to receive combination therapy until a stable therapeutic INR has been attained.

Table 1. Selected Risk Factors for Cancer-associated Thrombosis

Demographics
- Older age
- Gender
- Race: higher in African-Americans, lower in Asians

Cancer-related factors
- Site of cancer: brain, pancreas, kidney, stomach, lung, bladder, gynecologic, hematologic
- Advanced stage of cancer
- Initial period after diagnosis

Treatment-related factors
- Major surgery
- Hospitalization
- Cancer therapy
- Chemotherapy
- Hormonal therapy
- Antiangiogenic agents: thalidomide, lenalidomide, bevacizumab
- Erythropoiesis-stimulating agents

Biomarkers
- Elevated prechemotherapy platelet count
- D-dimer
- Tissue factor expression by tumor cells

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In contrast, LMWHs offer a number of advantages over UFH for the initial management of patients with VTE. These agents do not require laboratory monitoring, although plasma anti-Xa level monitoring may be used in a small number of patients, such as those who are pregnant, obese, or have significant renal impairment. The LMWHs can be administered on a weight-adjusted basis and given subcutaneous (SC) once or twice daily. Evidence from studies comparing LMWH SC without monitoring to UFH with monitoring indicates that LMWH therapy may result in fewer recurrent VTE and bleeding events than UFH.[32,33]

Because of these advantages, LMWHs have replaced UFH as the first-line agents of choice in many hospitals. Randomized trials have demonstrated that outpatient LMWH therapy is as effective and safe as inpatient UFH for the management of VTE, especially when started concomitantly with an oral anticoagulant that is to be taken on a long-term basis.[34-36] Ambulatory treatment with LMWH is possible because of its convenient SC administration. This, in turn, allows early hospital discharge of patients, resulting in cost savings and improved quality of life.[30] Current ACCP guidelines actually recommend initial treatment with SC LMWH once or twice a day instead of UFH on an inpatient basis when needed (grade 1A) or otherwise on an outpatient basis (grade 1C) in patients with acute DVT.[30]

Warfarin therapy in cancer patients. As for long-term treatment of acute DVT, extended anticoagulant treatment is recommended to prevent both symptomatic progression of thrombosis and recurrence of DVT. In most patients with DVT of the legs, treatment with a vitamin K antagonist such as warfarin is recommended for long-term therapy.

The use of warfarin, especially in cancer patients, is particularly problematic. Patients receive multiple medications for the treatment of the malignancy itself and the management of treatment side effects and complications of the disease. Furthermore, cancer therapy changes depending on where the patient is in the particular cycle. Thus, at any one time, a patient may be taking an antiemetic for chemotherapy-induced nausea and vomiting, an antibiotic for neutropenic fever, growth factors, an anthracycline, a purine analog, and/or a monoclonal antibody or tyrosine kinase inhibitor for the malignancy.

Each of these interventions can have an effect on warfarin, often necessitating frequent monitoring and dose modifications to maintain a therapeutic INR. The inability to maintain a therapeutic INR can result in recurrence of VTE and potential bleeding complications from anticoagulation. In a prospective cohort study, the risk of recurrent VTE for patients with cancer who received long-term warfarin therapy was as high as 21% during the first year of anticoagulation, compared with 7% in patients who did not have cancer.[37] Major bleeding events occurred in 12% of cancer patients versus 5% of those without cancer, and the risk of this event remained higher throughout the course of warfarin therapy.[37]

Warfarin has proved to be suboptimal therapy in cancer-related VTE for other reasons as well. Cancer patients may have unpredictable anticoagulant responses caused by gastrointestinal problems, malnutrition, vomiting, and liver dysfunction associated with the cancer.[10,38-40] Interruption of anticoagulant therapy as the result of chemotherapy-related thrombocytopenia or invasive procedures is a greater problem with warfarin than heparin because of the former drug's slow onset and offset of action.[10,38,39] Thrombocytopenia also increases bleeding risk in these patients.[37] Finally, the need for frequent monitoring to maintain the INR within the therapeutic range is a quality-of-life issue that becomes greater in patients with cancer because of poor venous access.[10,38,39] As a result, patients with cancer spend less time within the therapeutic INR range than patients without cancer and are thus at greater risk for recurrent VTE.[39,41] Notably, rates of VTE recurrence are high throughout oral anticoagulation therapy, even when the INR is within therapeutic range.[37,39,41]

The Role of LMWH

As mentioned before, compared with UFH, LMWHs have a more predictable anticoagulant effect, require less monitoring, and allow for outpatient management of VTE. Because of these benefits, LMWHs have become a widely accepted option for initial therapy (first 5-7 days) in the management of VTE.

It is important to note that LMWHs must be used with caution in patients with renal insufficiency and failure and that dose adjustments may be required in patients with creatinine clearance <30 mL/min.[42]

Compared with warfarin, LMWHs also hold some significant advantages. LMWHs have far fewer drug–drug and drug–food interactions than warfarin and require much shorter interruptions in therapy for invasive procedures. Additionally, the time to elimination of drug in the event of a serious bleeding event is significantly shorter with LMWHs compared with the washout time for warfarin. A number of investigators have evaluated the potential for use of LMWHs as long-term therapy to treat VTE and prevent recurrent VTE, especially in the cancer population.

CANTHANOX. Comparison of Low-Molecular-Weight Heparin and Warfarin for the Secondary Prevention of Venous Thromboembolism in Patients with Cancer (CANTHANOX), the first published trial of an LMWH in cancer, compared 3 months of warfarin therapy with enoxaparin in 146 cancer patients with proximal DVT, PE, or both. An open-label trial, CANTHANOX evaluated whether a fixed dose (1.5 mg/kg) of enoxaparin SC given once daily was superior to standard warfarin therapy for the prevention of recurrent cancer-related VTE.[43] All patients were started on enoxaparin 1.5 mg/kg once daily, and then randomized to either enoxaparin or oral anticoagulant warfarin for the remainder of the 3-month trial. The primary outcome measure was a combined end point of major bleeding or recurrent VTE within 3 months.

The trial was stopped after 4 years due to an inability to recruit subjects. At that time, 146 patients had been randomized to the study. Of these patients, 71 in the warfarin group and 67 in the LMWH group were considered evaluable for the primary end point. During the study period, 15 patients (21.1%) receiving warfarin compared with seven (10.%) receiving enoxaparin experienced recurrent VTE or major hemorrhage (P = .09).[43] Although this was not statistically significant, enoxaparin was found to be significantly more effective in delaying time to a primary event (P = .04). The majority of combined end point events involved major bleeding: 12 (80%) of 15 in the warfarin group

and five (71%) of seven in the enoxaparin group. Over the 3-month treatment period, 17 patients (22.7%) receiving warfarin and eight (11.3%) receiving enoxaparin died (P = .07).[43] In the warfarin group, six deaths (35%) were attributable to bleeding compared with none in the enoxaparin group. No significant difference was observed between the groups for the progression of cancer or in cancer-related deaths.[43] Although these results indicate an association between warfarin and increased bleeding in patients with cancer-related VTE and provide initial safety data on extended treatment with an LMWH, no definitive conclusions could be drawn from this trial because the difficulties in patient recruitment resulted in the study being underpowered.

LITE. A second trial comparing the efficacy and safety of an LMWH to warfarin in cancer-related VTE enrolled patients with and without cancer who had a diagnosis of DVT. In this multicenter trial, 737 patients with a proximal DVT were randomized to tinzaparin, given SC for 84 days, or UFH for 5 days plus long-term warfarin for 84 days.[44] Slightly more than one quarter of the patients in each group had cancer. Follow-up took place at the completion of treatment and at 1 year following randomization. In the overall group, 18 patients (4.9%) in the tinzaparin group had recurrent VTE, compared with 21 (5.7%) in the UFH/warfarin group. At 1 year, the rate of recurrent VTE was 4.3% for both groups.[44]

In the subset of patients with cancer (n = 200), recurrent VTE within 3 months occurred in 6% of patients who received tinzaparin and 10% of those receiving UFH/warfarin.[44] At 1 year, this difference was maintained, with 7% of patients receiving tinzaparin compared with 16% receiving UFH/warfarin experiencing recurrent VTE (P = .044). While there were no significant differences in mortality or bleeding events between the two groups, these data support the finding of improved outcomes for recurrent VTE with long-term LMWH in cancer patients with thrombosis.

ONCENOX. The effectiveness of long-term enoxaparin therapy to prevent recurrent VTE in cancer patients was also evaluated in the open-label, parallel-design Initial Profiling of Cancer Patients Entering in a Secondary Prevention of Venous Thrombosis with Enoxaparin (ONCENOX) trial. As with CANTHANOX, this trial was closed due to poor recruitment.[45,46] However, results are available for the 102 patients who received 1 mg/kg of enoxaparin SC twice daily for 5 days and then were randomized to either 1.0 mg/kg enoxaparin SC twice daily for 175 days (group 1; n = 32), 1.5 mg/kg of enoxaparin SC once daily for 175 days (group 2; n = 36), or initial treatment with enoxaparin as described above, with bridging to therapeutic doses of warfarin, which was begun on day 2 and continued for a total of 180 days (group 3; n = 34).[45,46] The primary efficacy measure was the incidence of objectively documented recurrent VTE up to the end of the 180-day study period, and the main safety outcome measures were major and minor bleeding events.[45,46]

The compliance rates were high in all three groups, with mean rates of 97.6%, 94.1%, and 92.8% for groups 1, 2, and 3, respectively. Recurrent VTE was experienced by 7.1% of the lower-dose enoxaparin group, 3.2% of the higher-dose enoxaparin group, and 10.3% of the warfarin group. No significant differences in major or minor bleeding rates were noted between the three groups, and there were no fatal or intracranial bleeding events.[45,46]

Table 2. LMWH vs Warfarin for Treatment and Secondary Prevention of VTE

Trial Name	Study design	Number of patients	Treatment	Recurrent VTE rate, %	*P* value	Mortality rate, %
ONCENOX	Open-label, parallel design, randomized	102	Enoxaparin: Low-dose High-dose	 7.1 10.3	 NS	—
CANTHANOX	Open-label, multicenter, randomized	138	Enoxaparin Warfarin	10.5 21.1	NS	11.3 22.7 at 3 mo
LITE	Open-label, multicenter, randomized	200[a]	Enoxaparin Warfarin	6 at 3 mo 7 at 1 yr 10 at 3 mo 16 at 1 yr	NS at 3 mo .044 at 1 yr	20 19 at 12 wk 47 for both groups at 1 yr
CLOT	Open-label, multicenter, randomized	676	Dalteparin Coumarin derivative	8 15.7	.002	39 41 at 6 mo

[a]200 patients represent those with cancer only; total patient population included patients with and without cancer (n = 737).
LMWH indicates low-molecular-weight heparin; NS, not significant; VTE, venous thromboembolism.
Adapted with permission from Newcomb T, Sheth S. Therapeutic approaches to coagulopathy in cancer patients. *US Pharmacist*. 2007;32:5-10.

"Overall, more bleeding events occurred in the oral anticoagulant group (19%) than in the dalteparin group (14%) (P = .09)."

As with the earlier CANTHANOX trial, the results of ONCENOX support the safety and efficacy of enoxaparin as long-term therapy, but again, the failure to enroll a large patient population hinders the ability to draw conclusions from these data.

CLOT. The Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) study is the definitive trial to date involving extended LMWH treatment in patients with cancer-associated thrombosis.[38,47] This 6-month, international, multicenter, open-label trial randomized 676 cancer patients with proximal DVT, PE, or both to either dalteparin 200 IU/kg (maximum: 18,000 IU) SC given once daily for 5 to 7 days, followed by long-term warfarin therapy (or acenocoumarol in a few countries) titrated to achieve a target INR of 2.0 to 3.0, or to initial therapy with dalteparin 200 IU/kg SC (maximum: 18,000 IU) once daily, continued for the first month, then followed by long-term dalteparin therapy given in prefilled syringes at 75% to 80% of the full dose (approximately 150 IU/kg) for the remaining 5 months.[38] The primary efficacy end point was objectively documented, symptomatic, recurrent DVT, PE, or both during the 6-month study period. Secondary outcome events were major bleeding, any bleeding, and mortality at 6 and 12 months.[38]

Unlike previous trials, adequate recruitment to this trial was successful. Baseline characteristics of both groups were well matched, 90% of patients had solid tumors, and 67% had metastatic disease at trial entry.[38] Eighty patients experienced a recurrent VTE during the 6-month treatment period: 27 in the dalteparin group and 53 in the oral anticoagulant group. The relative risk reduction was 52%, favoring dalteparin (P = .002).[38] In the oral anticoagulant group, only 38% of thrombotic events occurred when the INR was below 2.0, so a subtherapeutic INR did not account for these events in the majority of patients in that group. The hazard ratio for recurrent VTE in the dalteparin group versus the oral anticoagulant group was 0.48 (95% confidence interval, 0.30-0.77). Kaplan-Meier estimates of the probability of recurrent VTE at 6 months were 9% for patients treated with dalteparin and 17% for those with anticoagulant.[38]

Over the course of the study, 6% of patients in the dalteparin group and 4% in the oral anticoagulant group had a major bleeding event (P = .27).[38] Overall, more bleeding events occurred in the oral anticoagulant group (19%) than in the dalteparin group (14%) (P = .09). There was no correlation between major bleeding events and a supratherapeutic INR in the anticoagulant group.[38] Major bleeds occurred at critical sites (intracranial, retroperitoneal, or pericardial) in seven patients: three in the dalteparin group and four in the oral anticoagulant group.[38] Most other bleeds occurred in the gastrointestinal or genitourinary tracts.

As for mortality, 39% of patients in the dalteparin group and 41% in the oral anticoagulant group had died at the 6-month follow-up (P = .53).[38] Progressive cancer was the cause of death in 90% of cases in each group; however, there were five fatal PEs in the dalteparin arm and seven in the oral anticoagulant arm. Although no significant difference in mortality was found between the two groups at 6 or 12 months, a post hoc analysis of the 12-month mortality data showed a survival benefit for dalteparin in patients without metastatic cancer.[48] Table 2 summarizes the four LMWH trials discussed here.

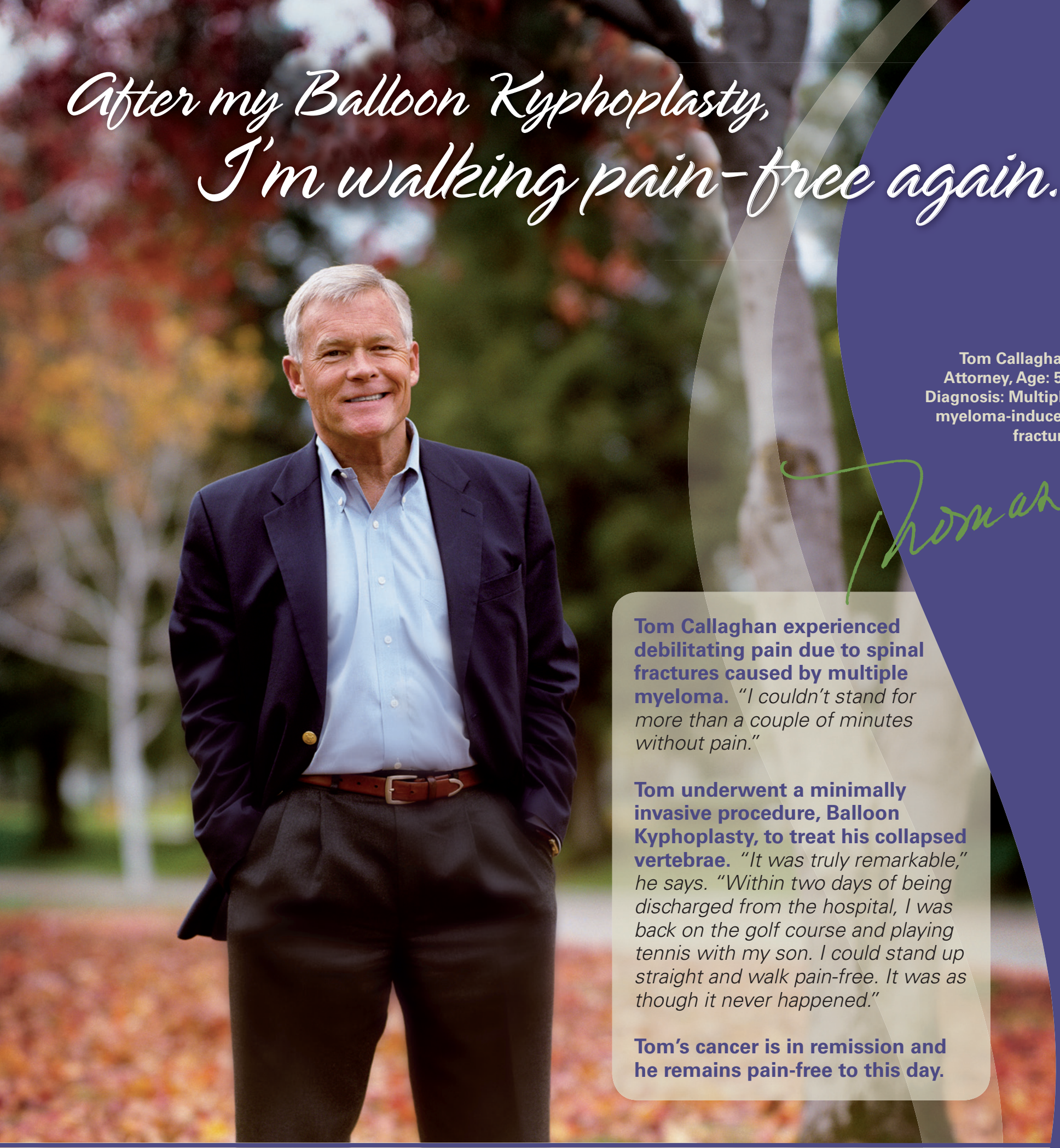
As a result of the trials described above, guidelines from several groups, including ACCP and NCCN, include recommendations for long-term treatment of cancer-associated VTE with an LMWH.

Guidelines on the management of VTE

Guidelines on the treatment of acute VTE and prophylaxis of VTE in patients with cancer have been issued by a number of organizations, including

Continued on page 27

After my Balloon Kyphoplasty, I'm walking pain-free again.



Tom Callaghan
Attorney, Age: 58
Diagnosis: Multiple myeloma-induced fracture

Tom

Tom Callaghan experienced debilitating pain due to spinal fractures caused by multiple myeloma. *"I couldn't stand for more than a couple of minutes without pain."*

Tom underwent a minimally invasive procedure, Balloon Kyphoplasty, to treat his collapsed vertebrae. *"It was truly remarkable," he says. "Within two days of being discharged from the hospital, I was back on the golf course and playing tennis with my son. I could stand up straight and walk pain-free. It was as though it never happened."*

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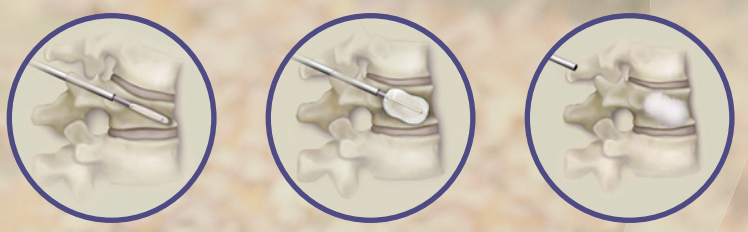

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Chemotherapy-induced Nausea and Vomiting

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Although great strides have been made in the management of chemotherapy-induced nausea and vomiting (CINV), it remains a feared side effect of cancer treatment. CINV is classified into three primary categories: acute, delayed, and anticipatory. Acute CINV is thought to be mostly serotonin related and occurs within 24 hours of administration of chemotherapy. Delayed CINV is, in part, substance P related and occurs 24 hours to several days after initial treatment. Anticipatory CINV is a learned or conditioned response that can be triggered by taste, odors, sight, thoughts, or anxiety related to therapy. It is usually secondary to a history of poor response to antiemetic agents or inadequate antiemetic prophylaxis in previous cycles of chemotherapy.

Overview

Cancer chemotherapy is thought to elicit nausea and vomiting through activation of the chemoreceptor trigger zone, the gastrointestinal (GI) tract, the cerebral cortex, and other areas in the emetic center in the central nervous system (CNS).[1] The emetic center sends out signals to the esophagus, stomach, and abdominal muscles to cause emesis.[1] Multiple neurotransmitters are involved in the emetic pathway; however, serotonin, substance P, and dopamine are believed to be the most important. These neurotransmitters are found in the vagal nerve complex, the chemoreceptor trigger zone, and the GI tract. Other receptors involved include corticosteroid,[2] histamine, cannabinoid, acetylcholine, gabaminergic, and opiate receptors. Combinations of antiemetics are necessary to target multiple neurotransmitters for adequate relief of CINV.[1]

Although the neurochemical systems and pathways mediating chemotherapy-induced emesis are reasonably well understood, the neurochemical processes for nausea are less well defined. The 5-hydroxytryptamine (HT_3)-receptor antagonists are believed to play a pivotal role in the mechanism of acute emesis but have lesser impact on delayed emesis. The mechanism of delayed emesis is thought to result from several nonserotonergic mechanisms. Delayed emesis is also believed to be the result of visceral inflammation involving mediators that activate the emetic reflex, such as prostaglandins, histamine, and substance P.[2]

The symptoms of nausea and vomiting are usually considered under the umbrella term, CINV, but actually two separate phenomena are occurring, which many believe are caused by separate processes and respond differently to pharmacologic intervention. Some researchers contend that whereas the serotonin antagonists have been very successful at controlling chemotherapy-induced vomiting, the incidence of posttreatment nausea may have actually increased.[3] The lack of adequate control of CINV may be partly due to the fact that antiemetic treatments are based on risk factors such as level of emetogenicity of chemotherapy agents. In a recent study by Cohen and associates, as many as 13% of patients receiving chemotherapy experienced acute vomiting and 33% experienced delayed vomiting during cycles 1 to 3.[4] Acute and delayed nausea were more significant problems, with up to 35% of patients experiencing acute nausea and 62% experiencing delayed nausea during cycles 1 to 3. Patients who developed CINV during cycle 1 were more likely to develop CINV at cycle 2.[4] The neuropharmacologic mechanism of delayed CINV is not well understood. Despite improvements in emesis control, nausea, which is less well understood at the neurochemical level, continues to be a problem for patients receiving chemotherapy.

CINV affects patients' quality of life (QOL); in fact, nausea has a stronger negative impact on QOL than vomiting.[4,5] In addition, delayed nausea has a greater impact on QOL than acute nausea.[6] Even infrequent episodes of emesis are associated with significant decline in QOL and in physical and cognitive functioning, and can eventually cause patients to delay or refuse potentially curative therapy.[7] Uncontrolled CINV can lead to decreased morale and decreased ability to participate in activities of daily life, such as work, personal care, or recreational activities. In addition, uncontrolled symptoms are more likely to lead to depression and fatigue.[1]

Chemotherapeutic agents are classified into four emetic risk groups based on the percentage of patients having emetic episodes when no prophylactic antiemetic protection is provided. The risk groups are: high (90%), moderate (30%-90%), low (10%-30%), and minimal (<10%).[8] The risk of CINV is influenced by dosage of the chemotherapeutic drug, duration of its infusion, and patient characteristics. Patient-related risk factors include female sex, younger age, a history of motion sickness, consumption of minimal amounts of alcohol (<1.5 ounces of alcohol per day), emesis during pregnancy, impaired QOL, and previous experience with chemotherapy.[8]

"Even infrequent episodes of emesis are associated with significant decline in QOL and in physical and cognitive functioning, and can eventually cause patients to delay or refuse potentially curative therapy."

Pharmacologic management of CINV

Pharmacologic interventions to prevent and manage CINV are the only modalities supported by enough evidence to be recommended for practice[9] (Table 1). With the correct use of antiemetics, CINV can be prevented in at least 70% to 80% of patients. Nonpharmacologic interventions lack sufficient evidence to be recommended for practice.[9] Pharmacologic interventions are recommended based on the type of nausea and vomiting and the level of emetogenicity of the chemotherapy. Oral and intravenous (IV) antiemetics are equally effective. The specific antiemetic used should be based on the level of emetogenicity anticipated by the chemotherapy regimen the patient is to receive. The period when nausea and vomiting are anticipated, based on the chemotherapy regimen received, should be covered by the antiemetics provided. However, the lowest effective dose should be used. Contributing factors that may enhance nausea and vomiting include reflux, the patient's underlying disease, comorbid conditions, and other medications.[9]

Serotonin antagonists. The 5-HT_3-receptor antagonists are the most effective antiemetics for prophylaxis of acute CINV (Table 2). Ondansetron, granisetron, dolasetron, and palonosetron are serotonin antagonists that are useful in the prevention of acute nausea and vomiting. Although granisetron and dolasetron have different pharmacologic profiles, including differences in binding affinity for the 5-

Table 1. Interventions for Nausea and Vomiting Supported by Empirical Studies

Recommended for practice
- Pharmacologic interventions, including benzodiazepines, 5-HT_3-receptor antagonists, corticosteroids, and NK-1 receptor antagonists

Likely to be effective
- Acupuncture
- Acupressure
- Guided imagery
- Hypnosis
- Music therapy
- Progressive muscle relaxation
- Psychoeducational support and information

Benefits balanced with harm
- Virtual reality

Effectiveness not yet established
- Exercise
- Massage
- Aromatherapy
- Acustimulation with wristband device
- Ginger

Sources: References 9 and 13.

HT_3-receptor, serum half-life, and metabolism, they do not offer improved control of acute or delayed emesis or vomiting over ondansetron.[2] Because palonosetron is effective in prevention of delayed CINV, the theory that serotonin receptors have little impact in this area has been questioned. Palonsetron has distinct structural features that may give it a different mode of binding to 5-HT_3-receptors. In addition, it exhibits a substantially higher binding affinity and longer half-life compared with other serotonin receptor antagonists.[7]

The major routes of administration of serotonin antagonists are oral or IV. Oral forms have been shown to be as effective as IV forms.[1] In October 2008, a granisetron transdermal patch was approved for the management of CINV and can offer 5 days of protection.[10] In a noninferiority randomized study, the patch provided equivalent control of nausea and vomiting; 60.2% of patients receiving the patch and 64.8% of patients receiving oral granisetron achieved complete control of CINV. Tropisetron is an additional 5-HT_3-receptor antagonist but is not available in the United States. As single agents, the serotonin antagonists have a response rate of 60% to 80%; when combined with corticosteroids, however, the response rates are higher. The primary side effect of 5-HT_3-receptor antagonists is headache. Change in bowel habits with either constipation or diarrhea also has been reported.[7,11]

Neurokinin-1-receptor antagonists. Substance P induces vomiting and binds to neurokinin (NK)-1 receptors. Agents that block NK-1 receptors lessen emesis. Aprepitant, an NK-1-receptor antagonist, is the first antiemetic in this class to be approved. Its delayed antiemetic activity is thought to be due to inhibition of the action of substance P in the emetic pathways in both the central and peripheral nervous systems. Aprepitant is approved for prevention of both acute and delayed emesis in combination with 5-HT_3-receptor antagonists. It may also exert some effect at the level of the gut. Current National Comprehensive Cancer Network (NCCN) guidelines include the use of aprepitant along with a serotonin antagonist and dexamethasone for the prevention of CINV associated with highly emetogenic chemotherapy.[12] Aprepitant is a moderate inhibitor of cytochrome P450 (CYP) 3A4, and therefore, the dexamethasone dose administered along with aprepitant is lowered because aprepitant may reduce the elimination of dexamethasone and other corticosteroids.[8]

Dexamethasone. Dexamethasone plays a major role in the prevention of acute and delayed CINV and is included in almost all antiemetic regimens. Corticosteroids are potent antiemetics and are often combined with other antiemetics for enhanced benefit. When dexamethasone is added to serotonin antagonists, the complete response rates are about 15% to 20% higher. Dexamethasone is important in the prevention and management of CINV secondary to both moderate and highly emetic chemotherapy agents. While dexamethasone is effective in managing acute CINV, it is particularly active in the management of delayed CINV. The most common side effects of corticosteroids are insomnia, jitteriness, increased appetite, hyperglycemia, and heartburn or other GI distress.[1]

Table 2. Doses of Antiemetics for Prevention or Breakthrough Nausea and Vomiting

Antiemetic	Prevention	Breakthrough
Aprepitant	125 mg PO day 1, then 80 mg PO days 2-3	
Dexamethasone	12 mg PO or IV day 1, then 8 mg PO or IV days 2-4	12 mg PO or IV daily
Dolasetron	100 mg PO or 1.8 mg/kg IV or 100 mg IV day 1	100 mg PO daily or 1.8 mg/kg IV or 100 mg IV
Dronabinol		5 mg-10 mg PO every 3-6 hr
Granisetron	1 mg-2 mg PO or 1 mg PO bid or 0.01 mg/kg (max: 1 mg) IV day 1 or transdermal patch containing 34.3 mg applied 24-48 hr prior to first dose of chemotherapy	1 mg-2 mg PO daily or 1 mg PO bid or 0.01 mg/kg IV (max: 1 mg) or transdermal patch containing 34.3 mg granisetron
Haloperidol		1 mg-2 mg PO every 4-6 hr
Lorazepam	0.5 mg-2 mg PO or IV or sublingual either every 4 or every 6 hr	0.5 mg-2 mg PO every 4-6 hr
Metoclopramide	10 mg-40 mg PO or IV every 4-6 hr	10 mg-40 mg PO or IV every 4-6 hr
Nabilone		1 mg-2 mg PO bid
Olanzapine		2.5 mg-5 mg bid
Ondansetron	8 mg-24 mg PO or 8 mg-12 mg IV	16 mg PO or 8 mg IV daily
Palonosetron	0.5 mg PO or 0.25 mg IV day 1	
Prochlorperazine	10 mg PO or IV every 4-6 hr	25-mg suppository every 12 hr or 10 mg PO or IV every 4-6 hr
Promethazine		12.5 mg-25 mg PO or IV every 4 hr

IV indicates intravenous; PO, by mouth.
Source: Reference 12.

Cannabinoids. Cannabinoid-receptor agonists are known to exert antiemetic effects. Although two cannabinoid receptors have been identified (CB 1 and CB 2), CB 1 is believed to play the important role in CINV. The mechanism of action of the CB 1 agonists (dronabinol and nabilone) is not clearly defined, but it is thought to act through the CB 1 receptors in the brain stem. The efficacy of cannabinoids in CINV, along with potentially beneficial side effects such as sedation and euphoria, may make cannabinoids a useful adjunct to other antiemetics. Their usefulness may be limited, however, by the relatively high incidence of bothersome side effects such as dizziness, dysphoria, and hallucinations.[8]

Dopamine-receptor antagonists. These agents represent an older class of antiemetics. Examples of agents that impact dopamine receptors include phenothiazines (eg, prochlorperazine and promethazine), butyrophenones (eg, haloperidol and droperidol), and a benzamide (eg, metoclopramide). These agents are used for breakthrough CINV and for refractory nausea and vomiting. Metoclopramide may be effective in moderate doses in the delayed period but can cause sedation and extrapyramidal side effects.[7] Although listed in previous guidelines, it is not currently recommended and should be reserved for special circumstances, such as intolerance to 5-HT_3-receptor antagonists or corticosteroids. All these medications cause more sedation, extrapyramidal symptoms, and adverse effects than other antiemetics. Their usefulness is due in part to their oral and parenteral availability.

"The efficacy of cannabinoids in CINV, along with potentially beneficial side effects such as sedation and euphoria, may make cannabinoids a useful adjunct to other antiemetics."

Benzodiazepines. Lorazepam is available in both oral and parenteral forms. It is approved as an antianxiety agent but is widely used as an antiemetic, especially in patients with breakthrough nausea and vomiting. Its action on nausea and vomiting may be through inhibition of impulses from the cerebral cortex to the emetic center in the CNS. Lorazepam reduces symptoms of anticipatory nausea and vomiting but causes CNS depression.[1]

Gabapentin. Gamma-aminobutyric acid (GABA) is the major inhibitory transmitter in the brain, and GABA-receptor agonists are used clinically for seizure disorders and as sedatives. Their mechanism of action involves calcium channels that control neurotransmitter release.[1] Gabapentin, a cyclic analog of GABA, has been shown to improve CINV in an open-label study of patients with breast cancer. Gabapentin has also been studied in patients receiving highly emetogenic and moderately emetogenic chemotherapy regimens. In this group of patients who had significant previous CINV, gabapentin used in addition to a 5-HT_3-antagonist and dexamethasone enhanced control of nausea and vomiting. Further research is necessary to determine the usefulness of gabapentin in CINV.

Olanzapine. Olanzapine is an atypical antipsychotic used to treat mania and schizophrenia. It also antagonizes several neurotransmitters involved in CINV, such as serotonin, dopamine catecholamines, acetylcholine at muscarinic receptors, and histamine.[11] Olanzapine appears to be an effective alternative for treating refractory CINV. It is well tolerated, and few side effects have been reported. The major side effects include fatigue, drowsiness, and dry mouth.[1]

Casopitant. Casopitant is a new potent and selective oral NK-1-receptor antagonist that has shown efficacy in managing CINV in patients receiving highly emetogenic chemotherapy regimens. Overall, it has been well tolerated.[1]

Midazolam. Midazolam is a short-acting benzodiazepine with a rapid onset of action. It decreases dopamine input at the chemoreceptor trigger zone and serotonin release by binding to the GABA-benzodiazepine complex. Midazolam is generally well tolerated, sedation being the most common side effect.

Nonpharmacologic interventions

In a review of the evidence for interventions to manage CINV, Tipton and colleagues concluded that there was insufficient empirical evidence to recommend nonpharmacologic interventions for CINV for use in clinical practice.[9] Based on the data, however, acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation, and psychoeducational support were judged likely to be effective. The data also suggested that exercise, massage, aromatherapy, acustimulation with a wrist device, and consumption of ginger did not yet have established effectiveness, and that hypnosis was not sufficiently efficacious to support its use.[9]

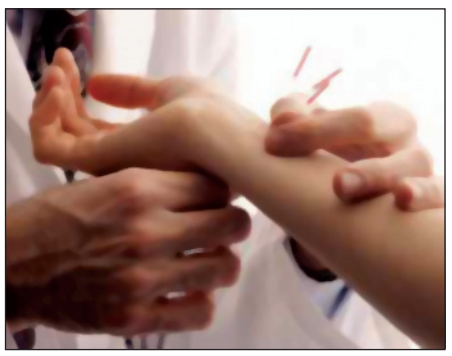

Figure. Acupuncture at the P6 point
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Hypnosis. Richardson and colleagues conducted a meta-analysis of six randomized controlled trials, five of which focused on CINV in children.[13] Although these studies tended to have small samples, they revealed a large effect size of hypnotic treatment compared with treatment as usual. These findings suggest that hypnosis is likely to be beneficial, especially in children, but additional trials are needed to clarify its benefit.

Acupuncture/acupressure. Acupuncture at P6 (Figure) is frequently used to treat nausea and vomiting. The P6 acupoint is located on the anterior surface of the forearm approximately three finger-widths from the wrist crease. P6 acupuncture plus antiemetics has been shown to be more effective than antiemetics alone or antiemetics with placebo acupuncture. Electroacupuncture with antiemetics has also proved more effective in controlling emesis than placebo acupuncture with antiemetics or antiemetics alone.[14] In a meta-analysis, Ezzo and associates found that acupuncture was effective in reducing the incidence of acute vomiting but not the severity of acute nausea.[15] In a randomized trial, Dibble and associates showed that acupressure (ie, the application of pressure to acupoints digitally or with acustimulation bands) at P6 is useful for managing delayed nausea and vomiting.[16]

Other interventions. In a meta-analysis of 15 studies of guided imagery, a clinically significant reduction of nau-

COMMENTARY

A PHARMACIST'S PERSPECTIVE

Chemotherapy-induced Nausea and Vomiting

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As outlined in the accompanying article by Rogers, there have been significant developments in controlling chemotherapy-induced nausea and vomiting (CINV) but less progress has been made in the control of nausea. The availability of neurokinin-1 antagonists has impacted the rate of delayed emesis with cisplatin and both acute and delayed emesis for regimens, such as doxorubicin plus cyclophosphamide for breast cancer.[1,2] With these and other advances in recent years come a new set of questions. Three important questions for patient care are:

- How should clinicians apply current CINV guidelines?
- What is the place of serotonin and dopamine antagonists in current antiemetic therapy?
- How should antiemetics be dosed for multiday chemotherapy regimens?

Guidelines for the prevention of CINV have become commonplace from both a general patient care and an institutional or health-system perspective. Some aspects of the different guidelines are outlined in the Table.[3-6] Generally speaking, the American Society of Health-System Pharmacists guidelines, although old and missing information on newer medications, offer the most thorough review of medication dosing. The American Society of Clinical Oncology guidelines offer the best evidence basis for antiemetic use and comprehensive clinical guidance. The National Comprehensive Cancer Network guidelines, while the most up-to-date, are most likely to be influenced by common practice without clinical evidence. The Multinational Association of Supportive Care in Cancer guidelines offer a more international perspective on the control of CINV. Depending on the clinician's needs, each has useful information to offer but must always be interpreted in the above-mentioned contexts when designing institutional guidelines.

Serotonin antagonists are clearly the mainstay of acute CINV prophylaxis, with multiple studies showing clinical evidence for separation of the acute, serotonin-driven and delayed, substance P–driven phases of CINV.[7,8] Despite continued use by community oncologists, the use of these agents in the delayed setting continues to be controversial because of inadequately controlled trials.[9,10] In contrast, dopamine antagonists, which were once favored for control of acute emesis, have been relegated to use in the delayed or salvage settings because of their lower efficacy and higher adverse event rates compared with serotonin antagonists. In this setting, they continue to show patient benefit.

Additional study of CINV prophylaxis for patients receiving multiday chemotherapy is needed. Current guidelines provide minimal guidance regarding multiday therapies, although recent trials support the need for daily administration of serotonin antagonists, dexamethasone, and potentially aprepitant or dopamine antagonists. Dose and duration of dose generally are individualized based on limited study data or local treatment norms.[11-13]

There has been slow, continuous improvement in our clinical and scientific understanding of the prevention of CINV, but many questions remain unresolved and there is much room for improvement in our understanding of how to best utilize new therapies.

Table. Antiemetic Guidelines

Guideline	Last updated	Comments
American Society of Health-System Pharmacists	1999	Need substantial updating
American Society of Clinical Oncology	2008	
National Comprehensive Cancer Network	2009	Updated multiple times per year. Criteria for update unclear
Multinational Association of Supportive Care in Cancer	2004	Due for review and update in June 2009

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- Summarize new data from clinical trials in relapsed/refractory MM as reported at the 2008 American Society of Hematology annual meeting
- Review the side effect profiles of novel agents for MM
- Identify effective strategies for the management of common toxicities associated with MM therapies

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sea was found[17]; the effect on vomiting could not be analyzed, however, because of its low incidence. Virtual reality has been shown to be a possible intervention for nausea and vomiting, but it may have adverse effects. This computer-simulated technique allows individuals to hear and feel stimuli that correspond with a visual image. It is interactive and engages multiple senses simultaneously. Although virtual reality can decrease emesis following chemotherapy, it also can cause motion sickness, which can increase nausea and vomiting. In addition, its prohibitive cost can limit its usefulness.[17] Progressive muscle relaxation can decrease the duration of nausea and vomiting considerably. Meta-analyses have shown a consistent positive effect on reduction of nausea and vomiting as well as other symptoms, but limited data are available.[17]

Psychosocial support and information. Psychosocial support and information can be effective in managing CINV. Williams and Schreier assessed the level of CINV in 70 women with breast cancer and found that informational audiotapes on self-care behaviors and the occurrence and intensity of side effects of treatment were helpful in managing the side effects that women often have with breast cancer treatment.[18] A meta-analysis of 116 intervention studies showed that psychoeducational and psychosocial care have beneficial effects in managing nausea and vomiting in patients with cancer.[19]

Clinician interventions

A significant component of prevention and management of CINV relates to patient education regarding which antiemetics to use and when to take oral medications at home. Antiemetics should be taken early enough before meals to ensure that the effect is present during and after meals. Although not supported by sufficient data, dietary interventions may also be beneficial. Exposure to aromas of food and other substances, such as perfumes, should be minimized. Patients should be instructed to eat small, more frequent meals and to avoid foods that are spicy, fatty, or highly salty, because these foods may enhance nausea and vomiting.[9]

Conclusion

During the past two decades, many advances have been made in the understanding and control of CINV. Although acute emesis is well controlled with the use of 5-HT_3-antagonists, delayed nausea is less well understood and not optimally controlled with modern antiemetic therapy. Continued research is necessary to better understand this symptom. Currently, only pharmacologic interventions have sufficient data to support their use. Although data exist on the use of some nonpharmacologic interventions (such as acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation, and psychoeducational support), additional evidence is necessary before they can be recommended as a component of CINV therapy. Anecdotal evidence supports the efficacy of lemon, peppermint, ginger, and chamomile, but there is no research that examines the use of these herbal products in the management of CINV.[9]

Clinicians must have an attitude of zero tolerance for nausea and vomiting in patients receiving cancer therapy. With an emphasis on open communication about CINV and ongoing modifications in interventions, optimal control of CINV can be achieved for the majority of patients receiving chemotherapy.

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COMMENTARY

A NURSE'S PERSPECTIVE

Chemotherapy-induced Nausea and Vomiting

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Many significant advances have been made in the past 20 years that have improved the care of patients with chemotherapy-induced nausea and vomiting (CINV). Delayed nausea is still an issue, however. Rogers explains the physiologic reasons for this symptom in the accompanying article, but there are psychosocial and financial issues to consider as well. For example, does the patient take the antiemetics as prescribed? Does the patient have prescription insurance issues, such as a high copayment for the medication? Does the patient actually purchase the drug if there are monetary concerns? Taking a proactive approach and assigning a nurse to call all patients on day 3 of the treatment cycle can improve management of delayed nausea.

Palonosetron, the only intravenous (IV) 5-HT_3-receptor antagonist approved for delayed CINV, works on both acute and delayed CINV.[1] Both palonosetron and aprepitant are now available in IV and oral formulations.[2,3] Oral antiemetics are effective only if the patient has adequate absorption or a functioning gut. The 5-HT_3 granisetron transdermal patch presents an exciting new route of antiemetic delivery. The patch may be a good option for those with oral intake issues or those who forget to take medications. Other routes being researched are novel formulations of ondansetron in a lingual spray and a quick-dissolving film.[4]

Many patients are taking some type of oral therapy for their cancer. Patients may believe that side effects may not be "as strong" with these agents. It is important to explain that the emetic risk applies to all agents—regardless of route of administration. Scripps Cancer Center has added the relative emetogenicity of chemotherapeutic agents along with those associated with delayed emesis on the back of the chemotherapy order sheet to serve as a second check for the oncology nurse to ensure that appropriate antiemetics are ordered according to medication administered. Education must be provided to both clinician and patient proactively to reduce the risk of CINV.

Enrollment of patients in supportive care trials is critical to our knowledge of CINV. Research helps to improve patient care. For example, Grunberg and colleagues reviewed the use of palonosetron (25 mg), dexamethasone (20 mg), and aprepitant (285 mg) in a single dose on day 1, avoiding the multiday regimen. One hundred percent (n = 41) were emesis free in the acute phase, and 97% in the delayed phase.[5] As Rogers pointed out, it is particularly critical for nonpharmacologic interventions to be studied because of the lack of research. Nurses must have an open relationship with patients to ensure that they disclose use of herbal, over-the-counter, and complementary therapies.

As Rogers explained, there must be zero tolerance for CINV. Oncology nurses are at the forefront of managing CINV and educating patients about zero tolerance. Nurses must be proactive instead of reactive in terms of choosing the best medications from the current armamentarium in this battle. We must ask ourselves what antiemetic regimen would I want if that were me?

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Beyond Chemotherapy:
Non-Hodgkin's Lymphoma Update

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Despite the fact that non-Hodgkin's lymphomas (NHLs) represent only 4% of all newly diagnosed cancers, they remain the most common hematologic malignancy in adults, with an estimated 66,000 new cases diagnosed in the United States in 2008.[1,2] The current front-line standard of care for NHL utilizing the combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has resulted in initial response rates of 60% to 80%, yet most patients will ultimately relapse and die of their disease.[3,4] For this reason, research has focused on the development of new therapies, including the monoclonal antibodies (Table 1).[5] This review focuses on some of the newer nonchemotherapy treatments for NHL.

Rituximab

Rituximab is a murine chimeric monoclonal antibody directed against the CD20 cell-surface antigen found primarily on pre-B and mature B lymphocytes.[6] Physiologically, it is believed that CD20 plays a role in B-cell activation, proliferation, and differentiation, which may be essential to the expansion of lymphoma cells. Because as many as 85% of all adult cases of NHL are of B-cell origin, CD20 has become an important target for improving the efficacy of NHL treatment regimens.[7] Multiple studies have demonstrated that the addition of rituximab to CHOP chemotherapy improves overall survival and event-free survival in patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL).[8] Infusion-related toxicities are relatively common with rituximab and include fever, chills, orthostatic hypotension, bronchospasm, and rigors. Although these toxicities affect as many as 80% of patients, they are typically limited to the infusion period.[5]

Ofatumumab

Ofatumumab is a fully human CD20 monoclonal antibody developed as an alternative for patients who do not respond or become resistant to rituximab. It differs from rituximab by targeting a novel epitope of CD20 and having a very slow release from the target that appears to be related to an increase in complement-dependent cytotoxicity.[5,9] As a result, ofatumumab may have efficacy in patients with relapsed or refractory NHL who have previously been treated with rituximab.[10] Additionally, preclinical data have shown that patients who express high levels of CD59, a complement-regulatory protein, in addition to CD20, derive the greatest benefit from ofatumumab.[11] Phase 2/3 studies demonstrated efficacy in patients with follicular lymphoma and relapsed or refractory B-cell chronic lymphocytic leukemia (CLL), with an overall response rate of 63%, including a 57% response rate in patients previously treated with rituximab.[9,10,12] Furthermore, the adverse event profile of ofatumumab is very similar to that of rituximab, and toxicities (or hypersensitivity) appear primarily during the infusion period.[9,10]

"Because as many as 85% of all adult cases of NHL are of B-cell origin, CD20 has become an important target for improving the efficacy of NHL treatment regimens."

Galiximab

CD80 is a mediator of B-cell and T-cell activation and frequently is constitutively activated in a variety of NHLs, including follicular lymphoma.[13] Galiximab is a primate–human chimeric antibody, which upon binding CD80 results in an upregulation of apoptosis, antiproliferation, and induction of antibody-dependent cellular cytotoxicty.[14] Additionally, preclinical models have demonstrated the potential for galiximab to sensitize resistant B-cell malignancies, resulting in the synergistically enhanced cytotoxicity of traditional chemotherapeutic drugs.[15] Galiximab has been evaluated alone and in combination with rituximab in patients who had relapsed or failed primary therapy for follicular NHL. Phase 2/3 studies reported superior results with the combination therapy than with single agents, including a 66% overall response rate for patients receiving galiximab (500 mg/m^2) and rituximab (375 mg/m^2).[16] Structurally, galiximab is indistinguishable from human antibodies because of its human constant regions and primate variable regions, rendering the antibody unlikely to induce immunogenicity in humans. This results in minimal adverse events, which include primarily nausea, fatigue, and headache.[17]

Table 1. Monoclonal Antibodies for B-cell Non-Hodgkin's Lymphoma

Antibody	Target	Phase of development
Rituximab	CD20	Commercially available
Ofatumumab	CD20	Phase 1/3
Galiximab	CD80	Phase 2/3
Epratuzumab	CD22	Phase 2
Lumiliximab	CD23	Phase 3
Radioimmunotherapy		
^{90}Y-ibritumomab tiuxetan	CD20	Commercially available
^{131}I-tositumomab	CD20	Commercially available

Source: Reference 5.

Epratuzumab

Epratuzumab is a humanized antibody targeting the CD22 surface antigen. CD22 appears to be preferentially expressed on the surface of mature B cells and has been identified in 60% to 80% of B-cell malignancies.[18] Although the function of CD22 is not fully understood, it is believed to function in cell adhesion and B-cell activation, making it a novel target for antibody therapy.[19,20] In contrast to its murine antibody predecessor, LL2, epratuzumab was developed with the goal of reducing immunogenicity, prolonging half-life, and increasing effector function.[21] Efficacy has been demonstrated with epratuzumab as both a single agent and in combination with rituximab for patients with relapsed or refractory B-cell NHL.[4] In a recent international, multicenter study of epratuzumab plus rituximab in patients with recurrent indolent NHL, 24% of patients exhibited a complete response (CR) that was maintained at a median follow-up of 44.3 months. These results confirm that this combination shows promising efficacy for patients with indolent NHL, the adverse event profile for the combination being no more severe than for rituximab alone.[22] Ongoing studies are currently evaluating the combination regimen as initial therapy for indolent NHL (CALGB 50701) and for DLBCL in combination with CHOP plus rituximab (NCCTG N0489).

Lumiliximab

Follicular lymphoma and CLL B cells overexpress CD23. When CD23 is targeted by lumiliximab, a primatized antibody, immunoglobulin E production is inhibited and cellular apoptosis is stimulated.[23] In single-agent trials, lumiliximab was observed to have limited effectiveness in patients with CLL.[24] However, a phase 1/2 study evaluating the combination of lumiliximab with fludarabine, cyclophosphamide, and rituximab (FCR) for patients with relapsed CLL resulted in a 71% overall response rate with 48% CR. These results suggest a higher response rate for FCR plus lumiliximab than for FCR alone. Common toxicities included nausea, pyrexia, chills, neutropenia, and fatigue.[25]

Radioimmunotherapy

With the long-term success of monoclonal antibodies such as rituximab in the treatment of patients with NHL, anti-CD20 antibodies have been combined with radioisotopes in an attempt to "home" radiation therapy to CD20-positive B cells to improve efficacy. Studies have demonstrated radiation sensitivity of lymphoma cell lines, making radioimmunotherapy an attractive option for patients with NHL.[26] In addition to the direct effect of killing cells by targeted radiation, these drugs have the potential to kill surrounding cells that may not adequately express surface antigen or may be poorly vascularized.[27] Two radioimmunotherapy drugs are currently commercially available.

^{90}Y-labeled ibritumomab tiuxetan. Ibritumomab tiuxetan is a murine, anti-CD20 antibody that is the parent compound of rituximab and acts by targeting the same CD20 epitope as rituximab. It has been combined with yttrium-90 (^{90}Y), a beta emitter, resulting in an 80% overall response rate in patients with follicular or low-grade NHL, without the toxicity of total body irradiation.[28] Furthermore, ibritumomab therapy has been demonstrated to be efficacious in patients with rituximab-refractory follicular lymphoma, with response rates of 74% and a CR rate of 15%.[29] Recent studies evaluating the use of ibritumomab as consolidation therapy in patients with advanced stage follicular lymphoma in first remission resulted in an 87% unconfirmed CR rate and a prolongation of progression-free survival (PFS) of 2 years.[30] Adverse reactions with ibritumomab include severe cutaneous and mucocutaneous skin reactions.

^{131}I-labeled tositumomab. Similar to ibritumomab, tositumomab is a murine anti-CD20 antibody conjugated to a radioactive isotope, iodine-131 (^{131}I). Dosing of tositumomab occurs over the course of a week and must be accompanied by drugs to protect the thyroid, given the avidity of the thyroid gland for iodine. The pivotal phase 3 trial evaluating the efficacy of tositumomab in patients with chemotherapy-refractory NHL reported a 65% response rate, with 20% CR.[31] Additionally, treatment with tositumomab has shown to result in a 20% complete remission rate in patients with rituximab-refractory lymphoma.[32] A recent phase 3 study evaluating the effect of tositumomab versus R-CHOP on PFS rates in newly diagnosed patients with follicular NHL has completed enrollment and may create a paradigm shift in front-line therapy for this patient population. Hypersensitivity reactions and severe or life-threatening cytopenias have been reported in patients treated with tositumomab. For this reason, exclusion criteria include patients with greater than 25% bone marrow involvement, less than 15% bone marrow cellularity, platelet counts of less than 100,000 cells/mm^3 or neutrophil counts of less than 1500 cells/mm^3, extensive previous radiation therapy, pregnancy (due to potential fetal risk), lactation, or previous stem-cell transplantation (due to unknown safety).[5]

Bortezomib and other proteasome inhibitors

The body of literature for the use of bortezomib in NHL continues to grow and may have the most compelling data as compared with other nonchemotherapy, nonmonoclonal agents. The bulk of study results are on the use of bortezomib for mantle-cell lymphoma (MCL). This is in part due to the December 2006 US Food and Drug Administration (FDA) approval of bortezomib for the treatment of patients with MCL who have received at least one prior therapy. This approval has heightened the interest in using bortezomib in combination with other agents. Table 2 summarizes some of the newer data on use of bortezomib for MCL.[33-37]

Bortezomib is also being studied in other forms of NHL. As a single agent, it has shown a response rate of 50% in patients with relapsed or refractory gastric marginal zone B-cell lymphoma.[38] An interesting phase 1 trial ongoing in Korea has "replaced" rituximab with bortezomib when given with dose-dense CHOP as first-line therapy in DLBCL.[39] In this study, doses of bortezomib used were 1 mg/m^2, 1.3 mg/m^2, or 1.6 mg/m^2 on days 1 and 4, with a 1-week recovery period. Eight of nine evaluable patients had CR. The authors concluded that first-line bortezomib plus dose-dense CHOP every 2 weeks was safe and had promising antitumor activity. Further testing in phase 2 trials is under way. Study results are now emerging for new proteasome inhibitors, such as carfilzomib, in lymphomas and other hematologic malignancies. These newer agents may offer minimal cross-reactivity with other catalytic sites within the proteosome as compared with bortezomib.

Acetylase inhibitors

In October 2006, vorinostat, the first of a new class of agents, was approved by the FDA for cutaneous T-cell lymphoma (CTCL). Vorinostat is a histone deacetylase (DAC) inhibitor. Histone is the major protein component, or framework, that DNA wraps around. Histone acetylase is an enzyme that acts to create a less compact and more transcriptionally active DNA/protein structure, thus allowing easier replication. Conversely, histone DAC works to create a condensed and transcriptionally silenced chromatin. By altering the structure of a chromosome, gene transcription can also be altered. A histone DAC inhibitor would allow genes that have been previously silenced, for example a gene that helps to suppress

Table 2. Recent Trials of Bortezomib in Mantle-cell Lymphoma

Reference	Phase	N	Bortezomib dose	Plus chemotherapy	Response	Toxicities
Goy A et al	2	155	1.3 mg/m^2, days 1, 4, 8, 11	None	1-y OS = 69% 1-y survival in responders = 91% Refractory patients, median survival = 17.3 mo ORR = 31% CR + Cru = 8%	Neuropathy, fatigue, thrombocytopenia
Drach J et al	2	16	1.3 mg/m^2, days 1, 4, 8, 11	Rituximab 375 mg/m^2, day 1; dexamethasone 40 mg orally days 1–4; repeat every 21 days for 6 cycles; rituximab maintenance; BORID	ORR = 69% (11/16) CR = 38% (6/16)	Zoster, bacterial pneumonia, mucosal candidiasis, peripheral neuropathy, vasculitic skin infiltrates
Guariglia R et al	2	6 > 75 years	1.3 mg/m^2, days 1, 4, 8, 11	Rituximab 375 mg/m^2, day 1, hyperfractionated cyclophosphamide 600 mg/m^2/d as double infusion, days 1–3; repeat every 21 days; RBC	ORR = 66.6% PR = 1/6 (17%) CR = 3/6 (50%)	Thrombocytopenia, neutropenia
Gerecitano JF et al	1	Total = 27 MCL = 9	1.3–1.8 mg/m^2, days 2 and 8 or 1.1–1.5 mg/m^2, days 2, 5, 9, 12	Rituximab 375 mg/m^2, day 1, cyclophosphamide 750 mg/m^2 or 1000 mg/m^2, day 1; oral prednisone 100 mg, days 2–6; up to 8 cycles R-CB or P	Combined: CR = 5/27 (19%) PR = 13/27 (48%) SD = 8/27 (30%) ORR = 96%	Neutropenic fever, diarrhea, dehydration, neuropathy
Agathocleous A et al	1/2	Total = 45 MCL = 18	1.3 mg/m^2, days 1, 4, 8, 11 of 21-day cycle (arm A) or 1.6 mg/m^2, days 1, 8, 15, 22 of 35-day cycle	Rituximab 375 mg/m^2, day 1 for 8 cycles (arm A) or rituximab 375 mg/m^2, days 1, 8, 15, 22, cycles 1 and 4 for 6 cycles (arm B)	ORR = 56% ORR in MCL = 46%	Neutropenia, thrombocytopenia, fatigue, nausea, diarrhea, lethargy, neurotoxicity

BORID indicates bortezomib, rituximab, and dexamethasone; CR, complete response; Cru = complete response unconfirmed; MCL, mantle-cell lymphoma; OS, overall survival; ORR, overall rate of response; PR, partial response; RBC, rituximab, bortezomib, and hyperfractionated cyclophosphamide; R-CB or P, bortezomib with rituximab, cyclophosphamide, prednisolone; SD, stable disease.

Sources: References 33 through 37.

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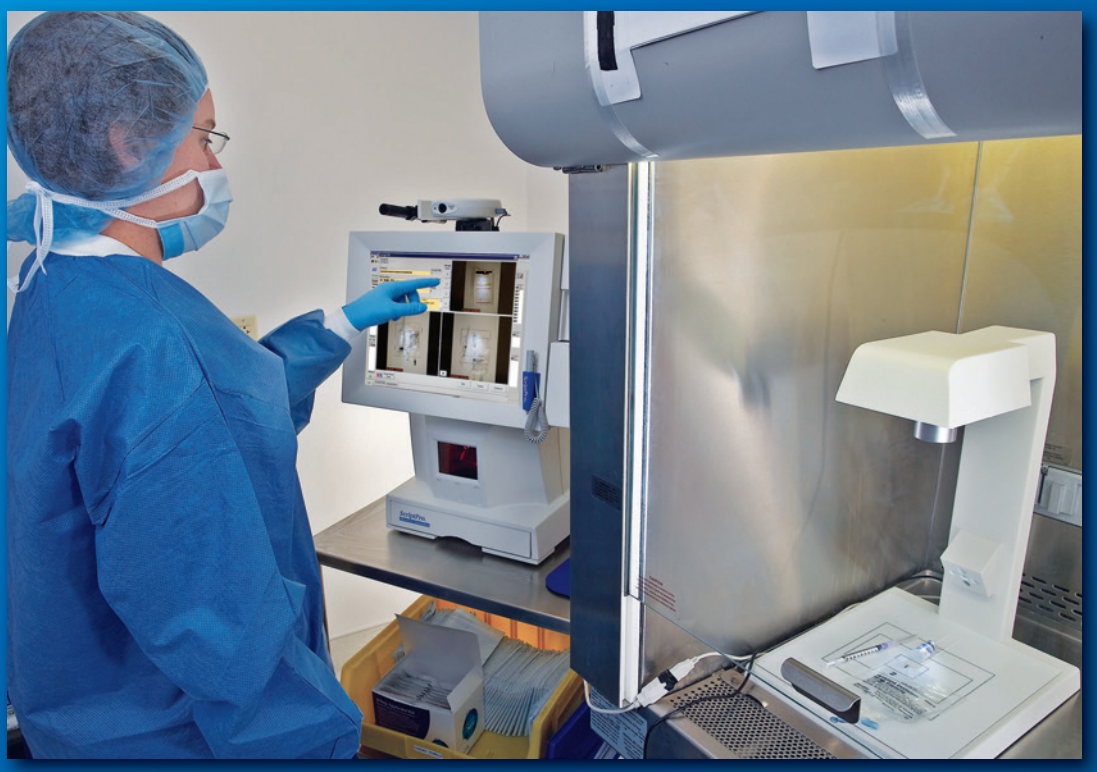

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In a recently published phase 2 trial, 33 patients with CTCL were randomized into three arms of various dosing schemas of vorinostat.[40] Most patients (69%) had either stage III or IV disease, and had received a median of five previous systemic therapies for CTCL. The overall intent-to-treat response rate was 24.2% (eight of 33 patients); all were partial responses (PRs). The median treatment duration for all patients was 8 weeks, with a range of 1 to 67 weeks. Nineteen percent of patients discontinued vorinostat because of an adverse event, and 68% discontinued because of progressive disease. Time-to-treatment response (in patients who responded) ranged from 3.6 to 21.9 weeks. Fourteen of 31 patients (45%) had symptomatic relief of their baseline pruritus: 73% in group 1, 18% in group 2, and 44% in group 3. Common toxicities of this therapy included fatigue (78%), diarrhea (60%), nausea (60%), thrombocytopenia (54%), dysgeusia (51%), and dry mouth (38%). Toxicity-related reasons for discontinuation of therapy included anemia, drug eruption, fatigue, tingling, pulmonary embolism, thrombocytopenia, pyrexia, and subdural hematoma. The authors concluded that there was a clinical benefit to 19 of the 33 patients, 58% had either symptom relief or disease response. A dose of 400 mg per day was recommended, which is now the FDA-approved dosing for adults.

Now, data are emerging using vorinostat in combination with other agents for CTCL. At the 2008 American Society of Clinical Oncology Annual Meeting, Hymes and colleagues reported on a phase 1 dose-finding study of the combination of bexarotene and vorinostat in advanced CTCL.[41] Nineteen patients have been enrolled to receive vorinostat in doses from 200 mg to 400 mg daily with bexarotene doses from 150 mg per day to 300 mg/m^2/day. Preliminary data indicate encouraging results, with 18 evaluable patients and 16 patients having at least stabilization of disease (one CR, three PR, 12 stable disease). The maximum tolerated doses had not been reached. Hypertriglyceridemia (50%), hypercholesterolemia (28%), hypothyroidism (28%), and lethargy/fatigue (28%) were the most common toxicities. Additionally, a few case studies have emerged indicating responses of advanced CTCL with the combination of vorinostat to other therapies, including interferon and ultraviolet-light-B therapy.[42]

Other DAC inhibitors are being studied in lymphoma. In T-cell lymphoma, belinostat and panobinostat are in phase 2 trials. Both of these agents are pan-DAC inhibitors. In a trial of intravenous (IV) belinostat that enrolled patients with refractory peripheral T-cell lymphoma (PTCL) or CTC, seven of 11 PTCL patients had at least stable disease (two with CRs), and four of 16 responders were CTCL patients for a median duration of 10 weeks.[43] Belinostat was well tolerated with most of the toxicities reported as grade 1 and 2. Grade 3 toxicities included peripheral edema, apraxia, ileus, pruritus, rash, and infection. One grade 4 thrombocytopenia was reported. Oral panobinostat, 20 mg on days 1, 3, and 5 weekly, was given to patients with CTCL.[44] In the 25 patients who were previously treated with bexarotene (group 1), three patients have had a PR and four had stabilization of disease. The median number of prior therapies for CTCL in group 1 was 5. Based on current data, response rates to the DAC inhibitors in previously treated CTCL are between 20% and 30%; however, an additional number of patients showed symptomatic improvement with minimal toxicities from this class of drug.

"A histone DAC inhibitor would allow genes that have been previously silenced, for example a gene that helps to suppress malignant growth, to be available for transcription."

The DAC inhibitors are also being studied in DLBCL, follicular lymphoma, and Hodgkin's lymphoma. In heavily pretreated DLBCL, a 23.5% response rate (PR + CR) has been reported to an oral histone DAC with a PFS in the responders ranging from 112 to 336 days or better.[45] With at least six agents in this intriguing new drug class, much more data will be emerging in the near future.

Temsirolimus

Initially marketed for renal cell carcinoma, temsirolimus is being studied for treatment of NHL. The bulk of information to date is in MCL. Temsirolimus is the first mammalian target of rapamycin inhibitor (mTOR) marketed in the United States. These agents are critical in the initiation of mRNA translation and thus cell replication. Twenty-nine patients were enrolled in a phase 2 trial using temsirolimus 25 mg weekly in relapsed MCL.[46] Eighty-six percent of patients had stage IV disease and had received a median of four previous therapies (range 1-9). Half of the patients were deemed refractory to previous treatment. The overall response rate of this therapy was 41% (11 of 27 patients) with one CR and 10 PRs. In those who responded, the tumor response was rapid, with a median time to response of 1 month; however, responses were also observed at 6 months or more of therapy. Both the median duration of response and median time to progression was 6 months in this poor-prognosis group. Dose reductions or treatment delays were warranted in 19 patients due to thrombocytopenia (five patients), neutropenia (two patients), both thrombocytopenia and neutropenia (two patients), and surgery (one patient). The primary toxicity in this trial was reversible myelosuppression. The most common toxicities included thrombocytopenia (82%), fatigue (75%), hyperglycemia (71%), hypertriglyceridemia (71%), anemia and neutropenia (57%), nausea (39%), and stomatitis (39%). In a recent report of a phase 3 trial, comparing two dosing schemas of temsirolimus with "investigator's choice" of therapy for MCL, increased PFS and objective response rate was shown in the increased-dose temsirolimus arm.[47] One hundred seventy-seven patients were randomized 1:1:1 to receive: temsirolimus 175 mg weekly × 3 followed by 75 mg (arm 1), 25 mg (arm 2) weekly, or investigator's choice (arm 3). Investigator's choice included single-agent gemcitabine 42%, single-agent fludarabine 26%, other chemotherapies, such as thalidomide, alemtuzumab, and lenalidomide, made up the remainder of the choices. Half of the patients had received more than three previous therapies for MCL, which had to include rituximab, an alkylating agent, and an anthracycline. Based on the results of 162 patients, the median PFS in arms 1, 2, and 3 were 4.8 (P = .0009), 3.4, and 1.9 months, respectively. Overall survival in the three groups was not significant at 10.9, 8.5, and 5.8 months, respectively. The objective response rates were 22% in arm 1, 6% in arm 2, and 2% in arm 3, indicating that in this study the higher dose of temsirolimus is more effective in treating refractory MCL.

In a study by Smith and associates, 82 patients with non-MCL were given temsirolimus 25 mg IV weekly for 8 weeks.[48] Early results including patients with DLBCL, follicular lymphoma, and small lymphocytic lymphoma/CLL show an overall response rate of 46% (26 of 56 evaluable patients) in patients completing two or more cycles of temsirolimus. Another 25 of the 82 patients had stable disease. More mature results from this phase 2 trial are anticipated. There is also a growing body of literature on the use of everolimus (RAD001), another mTOR inhibitor that is administered orally, for treatment of lymphomas.

Lenalidomide

Lenalidomide is being studied in a variety of lymphoma subtypes, including aggressive and indolent NHL. The option of an active oral medication is attractive to many patients and providers. Based on safety data from two phase 2 trials of lenalidomide in relapsed or refractory aggressive NHL, Habermann and associates concluded that 25 mg per day for days 1 through 21 of a 28-day cycle is a tolerable regimen in the majority of these patients.[49] Of 131 patients evaluable for safety of this drug, adverse effects that occurred in > 10% included fatigue, neutropenia, rash, thrombocytopenia, constipation, anemia, diarrhea, pyrexia, nausea, peripheral edema, decrease white blood cell count, anorexia, and cough. Serious adverse effects included febrile neutropenia, pyrexia, pneumonia, back pain, deep-vein thrombosis, dehydration, and diarrhea. This toxicity profile is not dissimilar to previous findings in patients with myelodysplastic syndromes. Lenalidomide's activity in one of the above-mentioned studies was reported by Czuczman and colleagues.[50] These authors reported an objective response rate of 28% (13 of 46 evaluable patients), with stable disease in another 10 patients. Lenalidomide response was associated with a low tumor burden and shorter duration from the last rituximab dose to lenalidomide treatment.

In the more indolent small lymphocytic NHL, 25 mg per day for days 1 to 21 of a 28-day cycle has similarly demonstrated a 22% objective response rate in 18 patients, and stable disease was seen in an additional seven of these 18 patients.[51] In this study, the PFS is 6.5 months or more and ongoing. Of note, three (14%) of the 18 patients experienced grade 1 or 2 tumor flare. All the above trials conclude that lenalidomide oral monotherapy has activity in NHL with manageable toxicities.

Conclusion

Many available nonchemotherapy agents are emerging that have activity in NHL and frequently a more favorable toxicity profile than chemotherapy. Whether used as monotherapy or combination therapy, these classes of drugs will continue to change the standard of care in NHL treatment. These agents help us move away from a "shot-gun" approach to cancer therapy to a more targeted, rational therapy. Although the phase 1 and 2 data currently available are intriguing, confirmation of activity versus accepted standard therapies in phase 3 trials is warranted.

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Venous Thromboembolism

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ACCP, NCCN, and ASCO. The ACCP Guidelines on Antithrombotic and Thrombolytic Therapy recommend the use of an LMWH for the management of VTE events in cancer for the first 3 to 6 months (grade 1A), followed by treatment with LMWH or a vitamin K antagonist as long as the cancer is active (grade 1C).[30] Cancer patients undergoing surgical procedures should receive prophylaxis that is appropriate to their current risk state, as should hospitalized cancer patients who are bedridden (both grade 1A).[23] Routine prophylaxis is not recommended, however, for prevention of thrombosis related to long-term indwelling central venous catheters in cancer patients (grade 2B). Specifically, clinicians should not use LMWH (grade 1B) or minidose warfarin (grade 1B) for this indication.[23]

The most recent version of the NCCN guidelines regarding VTE in patients with cancer recommends that LMWH be used as monotherapy for long-term treatment of proximal DVT (3-6 months) or PE (6-12 months), and prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation (grade 2A).[49] The guidelines stop short, however, of solely recommending LMWHs for long-term management; they do state that warfarin may be given in place of LMWH, with a target INR of 2.0 to 3.0. Continuation of anticoagulation for an indefinite period should be considered if the patient has active cancer or persistent risk factors. For catheter-associated thrombosis, anticoagulation therapy should be continued as long as the catheter is in place and for 1 to 3 months after it is removed.

Initial prophylaxis is recommended for the high-risk hospitalized cancer population, using either anticoagulation therapy or mechanical prophylaxis (ie, pneumatic venous compression device). In patients who have undergone surgery, the NCCN guidelines recommend that primary VTE prophylaxis be continued for up to 4 weeks postoperatively. In medical oncology patients, VTE prophylaxis should be considered in high-risk settings. Recommended anticoagulant options for both inpatient and outpatient settings include LMWH (dalteparin, enoxaparin, or tinzaparin), factor Xa antagonist (fondaparinux), or UFH.[49]

ASCO guidelines recommend that all hospitalized cancer patients be considered for VTE prophylaxis with anticoagulants in the absence of bleeding or other contraindications.[50] They do not, however, recommend the routine prophylaxis of ambulatory cancer patients with anticoagulation therapy, with the exception of patients receiving thalidomide or lenalidomide plus chemotherapy and/or dexamethasone. Patients who are undergoing major surgery for malignant disease should be considered for pharmacologic thromboprophylaxis. Prophylaxis should be initiated preoperatively or as early as possible in the postoperative period and continued for at least 7 to 10 days postoperatively. Prolonged prophylaxis for up to 4 weeks may be considered in patients undergoing major abdominal or pelvic surgery for cancer who have high-risk features such as residual malignant disease after the operation, obesity, or a history of VTE. LWMHs are the preferred agent for both the initial and continuing treatment of cancer patients with established VTE. Vitamin K antagonists with a targeted INR of 2.0 to 3.0 are acceptable for long-term therapy if LMWH is not available. After 6 months, indefinite anticoagulant therapy should be considered for selected patients with active cancer, such as those with metastatic disease and those receiving chemotherapy.

Antitumor effects of LMWHs

Although current guidelines do not recommend the use of LMWHs or anticoagulation therapy to improve survival in cancer patients without VTE,[48,50] there are some intriguing data suggesting that anticoagulation with LMWH may have antitumor effects.[42] Although the mechanisms involved in these possible antitumor effects have yet to be elucidated, inhibition of angiogenesis, inhibition of release of coagulation proteases, immunomodula-

tory effects, and apoptosis are all proposed theories.[42] Higher survival rates have been reported in patients receiving prophylactic doses of LMWH compared with no treatment or placebo.[51-53] A meta-analysis of randomized trials in cancer patients found that the addition of prophylactic LMWH to conventional cancer treatment resulted in an increased overall survival time as compared with placebo or no anticoagulation (relative risk, 0.87; 95% CI, 0.77-0.99; P = .04).[54] Despite the promise offered by these studies, further investigation is required before any conclusions regarding the antineoplastic effects of LMWHs can be made.[42]

Practical considerations

LMWHs provide patients with a medication that unlike warfarin requires no monitoring and no special diet. Notably with this class of agent, the prospect of patients self-administering injections on a daily basis does not appear to present a problem. In the ONCENOX trial, the compliance rate for daily administration of enoxaparin was 94% to 97%.[45] In the CLOT trial, patients found long-term self-injection of dalteparin to be acceptable. Furthermore, only 21 patients (6%) receiving dalteparin stopped taking the study medication before the end of the trial compared with 14 patients (4%) in the oral anticoagulant group.[55]

Despite the advantages in terms of patient convenience and clinical efficacy as demonstrated in the CLOT trial, cost of therapy with LMWHs has long been a concern for practitioners, pharmacists, and patients. When evaluating the cost-effectiveness of LMWH versus UFH in the initial management of patients with DVT or PE, investigators in one study found that use of dalteparin resulted in less anticoagulant monitoring and shorter hospital stays than UFH, making dalteparin a less expensive regimen for initial treatment of DVT.[56]

The concern over cost has not been as well studied in the prolonged-use setting. None of the four trials described previously included economic implications of long-term LMWH therapy. In one study, investigators designed a decision-analytic model to compare a 6-month regimen with dalteparin to a similar regimen with warfarin.[57] Pharmacy costs constituted 46% of total costs associated with LMWH. While LMWH therapy achieved higher incremental quality-adjusted life expectancy than warfarin, this clinical benefit was offset by a substantial cost increase of $7609.[57]

Conclusion

Cancer carries a considerable risk for VTE. The disease itself contributes to this risk, as do the treatment regimens and invasive procedures that many cancer patients endure. More important, the presence of VTE in a cancer patient implies a poor prognosis, including increased rates of VTE recurrence, worsened quality of life, and a greater risk of death. Available treatment options, while effective, are limited by a number of important issues, including toxicities, complications, and intensity of monitoring.

The emergence of LMWHs as a treatment option for DVT and PE has dramatically changed the landscape of VTE treatment. In the acute setting, LMWHs are more cost-effective than UFH, despite higher initial acquisition costs, due to the shortened hospital stays associated with LMWH therapy. LMWHs have demonstrated greater efficacy than and comparable safety to warfarin, and are now widely considered to be the treatment of choice in extended settings to prevent recurrent, cancer-associated thrombosis. The cost of extended therapy with LMWH must be balanced against its increased efficacy in preventing VTEs and the better quality of life associated with this medication class as compared with warfarin.

The possibility that LMWHs may have substantial antineoplastic effects remains a theory that has yet to be thoroughly explored. More clinical trials are necessary to determine whether the survival benefit seen in earlier studies is robust enough to warrant a broadening of indications for these agents.

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Evaluating and Treating Patients with Multiple Myeloma

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The 49th annual meeting of the American Society of Hematology (ASH) in December 2007 marked a decisive turning point in the way clinicians care for patients with multiple myeloma (MM). The stage was set to embark on patient-centered care with the presentation of numerous abstracts showing promising outcomes for the treatment of patients in both the newly diagnosed and relapsed-disease setting. Scientific presentations focused on both genomics and prognostics in an effort to customize care and improve knowledge about the anticipated course of the disease. The 45th annual meeting of the American Society of Clinical Oncology (ASCO) was a follow-up to ASH, with presentations that focused on updated response data and subgroup analysis of previously reported studies. This article provides an overview of our progress in the treatment of MM and highlights our course for the future.

Multiple myeloma: an overview

MM is characterized by an abnormal proliferation of clonal B cells within the bone marrow.[1] The average age at diagnosis is 70 years, and symptomatic disease can manifest with any or all of the following: osteolytic lesions, anemia, hypercalcemia, renal insufficiency, and infection[1] (Table 1). During the past two decades, the incidence of myeloma has increased, but the mortality rate remains relatively stable.[2] It accounts for 1% of all malignancies, and it was estimated that 19,920 new patients would be diagnosed with MM in 2008, with more than 10,000 deaths attributed to the disease annually.[3]

Although MM is an incurable disease, according to a recent study published by a group from the Mayo Clinic, patients diagnosed in the past decade had a median overall survival (OS) of 44.8 months versus those diagnosed before the past decade (29.9 months).[4] The introduction of novel therapies into the treatment paradigm and an evolving understanding of the disease have played key roles in OS and quality of life improvements. The use of novel therapeutics in combination with standard and investigational agents will continue to be explored in the setting of clinical trials.

Therapy options in the setting of newly diagnosed disease

The focus of myeloma therapy is not only on the development of new therapeutic agents, but also on the combination of standard chemotherapy agents and novel agents that have proven success rates. Research presented at the ASH 2007 and ASCO 2008 meetings revealed many combination regimens that were efficacious and tolerable, with 1-year survival rates of at least 80%. Response criteria used in those studies are shown in Table 2.

"The introduction of novel therapies into the treatment paradigm and an evolving understanding of the disease have played key roles in OS and quality of life improvements."

Harousseau and colleagues presented updated data from the Intergroupe Francophone du Myélome (IFM) 2005-01 trial.[5] In this study, patients were randomized to induction therapy with either vincristine-doxorubicin-dexamethasone (VAD) or bortezomib-dexamethasone (VD), followed by a second randomization to either receive or not receive dexamethasone-cyclophosphamide-etoposide-cisplatin (DCEP) prior to stem-cell mobilization followed by either single or tandem autologous stem-cell transplantation (ASCT) as determined by response. The overall response rate (ORR) was significantly higher following induction with VD (80%) versus VAD (62.8%), with a greater than or equal to very good partial response (VGPR) of 46.7% and 18.6%, respectively. This improvement was maintained in the posttransplant evaluation with ORR of 89.4% and 72.8%, and a greater than or equal to VGPR of 61.7% versus 41.7%, respectively. The occurrence of grade 3/4 adverse events was comparable in both arms, although the increase in the number of neurological events was higher in the VD induction arm.

The Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) group, led by Cavo also presented data regarding pretransplant induction therapy.[6] Patients were randomized to receive bortezomib-thalidomide-dexamethasone (VTD) or VD prior to tandem ASCT. The ORR favored induction with VTD (93%) over VD (80%), with a notable improvement in VGPR pretransplant/posttransplant (60%/77%) versus (27%/54%) maintained. The adverse event profile was similar in both arms, except for an increased frequency of rash and peripheral neuropathy noted in the bortezomib arm.

An analysis revealed that the improvement of response depth occurred independent of prognostic factors such as beta-2 microglobulin level and cytogenetic risk in both studies. Of note, these are also the first studies that demonstrate a correlation between depth-of-response postinduction and improved depth-of-response posttransplant. Although more follow-up time is required to evaluate time-to-progression (TTP) and OS, we can use these data to help answer the question, "Does the depth of response matter?"

Both the Eastern Cooperative Oncology Group (ECOG) and the Southwest Oncology Group (SWOG) evaluated the use of lenalidomide-dexamethasone in the front-line setting. The treatment schema differed, but similar results were seen, supporting it use.

Rajkumar presented the ECOG 4A03 data, including pertinent subgroup analysis.[7] The trial was designed to compare differences in outcomes related to dexamethasone dose. Patients were randomized to received lenalidomide (L) plus high-dose (D) or low-dose (d) dexamethasone. The trial

Table 1. Diagnostic Work-up for Multiple Myeloma with Expected Findings

Test	Finding(s) with multiple myeloma
CBC with differential counts	↓ HB, ↓ WBC, ↓ platelets
Chemistries	↑ Creat, ↑ Ca+, ↑ Uric acid, ↑ Alb
Serum electrophoresis with quantitative immunoglobulins	↑ M-protein in serum, may have ↓ levels of normal antibodies
Immunofixation	Identifies light-/heavy-chain types M-protein
Beta-2 microglobulin	↑ Levels (measure of tumor burden)
C-reactive protein	↑ Levels (marker for myeloma growth factor)
24-hour urine protein electrophoresis	↑ Monoclonal protein (Bence Jones)
Serum free light chain	↑ Free light chains
Bone marrow biopsy and cytogenetics	≥ 10% plasma cells
Skeletal survey	Osteolytic lesions, osteoporosis
MRI	Evaluation of involvement of disease

Alb indicates albumin; CBC, complete blood cell count; Creat, creatinine; Hgb, hemoglobin; MRI, magnetic resonance imaging; WBC, white blood cell.

Sources: Abella. *Oncology News International*. 2007;16:27; Barlogie B, Shaughnessy J, Munshi N, Epstein J. Plasma cell myeloma. In: *Williams Hematology*. 7th ed. New York, NY: McGraw Hill; 2006:1501; Durie BG, Kyle RA, Belch A, et al. Myeloma management guidelines: a consensus report from the Scientific Advisors of the International Myeloma Foundation. *Hematol J*. 2003;4:379-398; MM Research Foundation. MM: *Disease Overview*. 2006. www.multiplemyeloma.org; Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005;106:812-817.

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Table 2. International Myeloma Working Group Uniform Response Citeria: CR and Other Response Categories

Response subcategory	Response criteria[a]
sCR	CR as defined below plus: Normal FLC ratio and absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine Disappearance of any soft-tissue plasmacytomas ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hr
PR	≥ 50% reduction of serum M-protein and reduction in 24-hr urinary M-protein by ≥ 90% or to < 200 mg per 24 hr If the serum and urine M-protein are unmeasurable, ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above listed criteria, if present at baseline, ≥ 50% reduction in the size of soft-tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates)	Not meeting criteria for CR, VGPR, PR, or progressive disease

CR indicates complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a]All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b]Confirmation with repeat bone marrow biopsy not needed.

[c]Presence/absence of clonal cells is based upon the κ:λ ratio. An abnormal κ:λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ:λ of > 4:1 or < 1:2.

Reprinted with permission from Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for MM. *Leukemia.* 2006;20:1467-1473.

ended early because of a significant difference in 1-year OS seen in the Ld arm, despite an improvement in response rate with LD (71% vs 83%) (Table 3). The toxicity profile showed a significant difference in grade 3 or greater deep-vein thrombosis (DVT)/pulmonary embolism, infection, and nonhematologic adverse events. [1]

The SWOG data were presented by Zonder comparing lenalolidomide plus D with D alone for three 35-day induction cycles, followed by a 28-day maintenance schedule.[8] Although no significant 1-year OS difference was seen between arms (93% vs 91%), the dexamethasone dosing was decreased following the release of the ECOG 4A03 survival data. The ORR was 85.3% versus 51.3% favoring the combination arm. The most common grade 3/4 toxicities reported were neutropenia and infection, and, based on a high incidence of thrombosis in the combination arm seen early, daily oral aspirin, 325 mg, was mandated.

Three studies presented were undertaken in an effort to improve upon the OS and response rates in nontransplant-eligible patients. Hulin and associates reported data from the IFM 01/01 study of melphalan-prednisone with or without thalidomide in patients aged 75 years or older.[9] A twofold increase in ORR was noted, 62% versus 31%, in the thalidomide-containing arm with an increase in a VGPR or better from 8% to 29%. The median OS was increased by more than 1.5 years, from 27.7 months to 45.3 months. This is consistent with the data published by Facon and colleagues in patients 65 to 75 years of age.[10] Although there was no significant difference in rate of thrombosis or somnolence, both of which would be worrisome in the elderly population, there were significant increases in rates of peripheral neuropathy, neutropenia, and depression in the thalidomide-containing arm.

San Miguel, on behalf of the VELCADE as Initial Standard Therapy in multiple myeloma: Assessment with melphalan and prednisone (VISTA) trial investigators, presented data on melphalan-prednisone with or without bortezomib.[11] The researchers reported an ORR of 71% with the bortezomib-containing regimen versus 35% with the other. The improvement in TTP favored the bortezomib arm, 24 months versus 16.6 months. The benefit was seen in this group independent of age, renal function, and high-risk cytogenetics. The toxicity profiles were consistent with the reported profiles for melphalan-prednisone and bortezomib, with a higher incidence of grade 3 events seen in the bortezomib arm.

"The median OS was increased by more than 1.5 years, from 27.7 months to 45.3 months."

The third study by the National Cancer Institute of Canada Clinical Trials Group represented by White, evaluated the potential feasibility of combining two myelosuppresive agents, melphalan plus lenalidomide, in a dexamethasone-sparing regimen.[12] Although no response results have been reported, hematologic dose-limiting toxicities (DLT) with various dosage combinations have led to a single-arm study design. The plan is to study safety and efficacy with oral melphalan 5 mg/m^2 on days 1 to 4, plus daily oral lenalidomide, 10 mg on days 1 to 21 in a 28-day cycle.

The oral combination regimen of cyclophosphamide-lenalidomide-dexamethasone was studied by Kumar and associates, and early data were presented on the first 19 evaluable patients.[13] The ORR was 79% with a VGPR or better of 10%. One fifth of the patients experienced a grade 4 hematologic toxicity and that, along with early withdrawal of five of 19 patients, led to the exploration of use of lower cyclophosphamide doses. The nonhematologic toxicities of grade 3 or more reported were fatigue, thrombosis, and renal failure.

Another regimen containing cyclophosphamide together with novel agents was reported by Jagannath and colleagues.[14] The combination of bortezomib-cyclophosphamide-thalidomide-dexamethasone achieved a 100% ORR in the first 13 patients enrolled. The toxicity profile included neutropenia, hyperglycemia, pneumonia, perforated viscus, and neuropathy with a severity of grade 2 or more. Patients received thrombosis prophylaxis with 325 mg aspirin, and no DVT has been reported to date.

The last front-line trial, presented by Richardson and colleagues, combined two novel therapeutics, lenalidomide and bortezomib with dexamethasone.[15] The phase 1 portion was a dose-finding study that showed that dexamethasone was the source of DLT (grade 3 hyperglycemia) at a dose of 40 mg on days 1,

Table 3. Survival Data from ECOG 4A03 Based on Age

	N	1-year survival probability	2-year survival probability
Age < 65 years			
LD	104	92%	85%
Ld	108	97% *P* = .13	91% *P* = .16
Age ≥ 65 years			
LD	119	84%	67%
Ld	114	95% *P* = .01	82% *P* = .009

LD indicates lenalidomide plus high-dose dexamethasone (40 mg PO days 1-4, 9-12, 17-20); Ld, lenalidomide plus low-dose dexamethasone (40 mg PO days 1, 8, 15, and 22).

2, 4, 5, 8, 9, 11, and 12. The DLT cohort was safely treated with the following schema: oral lenalidomide, 25 mg on days 1 to 14, bortezomib, 1.3 mg/m^2 intravenous (IV) push on days 1, 4, 8, and 11 with oral dexamethasone 20 mg or IV on days 1, 2, 4, 5, 8, 9, 11, and 12. The response data were reported for phase 1; with phase 2 enrollment ongoing. The ORR was 89%, with 35% achieving a VGPR or better. The toxicity profile was manageable, with reports of one grade 4 thrombocytopenia, one grade 3 DVT treated with low-molecular-weight heparin, and no grade 3 or more peripheral neuropathy reported.

"The efficacy and safety data thus far in trials with PR-171 demonstrate the potential for a promising new proteosome inhibitor that does not appear to cause peripheral neuropathy."

Although many ASCO presenters updated the front-line studies already mentioned, Reeder and associates presented new data on the combination of cyclophosphamide (oral), bortezomib, and dexamethasone (CyBorD) prior to ASCT.[16] The ORR seen following four cycles of induction therapy was 100%, with 71% achieving VGPR or better and 46% achieving near complete response (nCR)/complete response (CR). The reported adverse events with a severity of grade 3/4 included anemia, neutropenia, thrombocytopenia, hyperglycemia, diarrhea, hypokalemia, peripheral neuropathy, and thrombosis. In view of the considerable response data, including excellent depth of response, but less than ideal toxicity profile, the study was reopened with a change in bortezomib frequency to once weekly and a reduction of the dexamethasone dose following the completion of two cycles. The plan is to proceed with a three-arm study to compare three novel combinations in a randomized fashion, cyclophosphamide/lenalidomide/bortezomib/dexamethasone versus lenalidomide/bortezomib/dexamethasone versus CyBorD, to evaluate whether one is superior to the others in safety.

Therapy options in the setting of relapsed and/or refractory disease

Although the focus this year was on the newly diagnosed MM therapy, several studies in the relapsed and/or refractory setting were also presented. Data were presented on a wide array of investigational agents, either alone or in combination, that are targeting novel pathways in an effort to identify unique areas of cell proliferation, survival, and migration that can be targets for therapy.

Carfilzomib (PR-171), a novel proteosome inhibitor that is both structurally and functionally different from bortezomib, was studied in hematologic malignancies, including MM, on different dosing schedules. Orlowski and colleagues presented safety and efficacy data from a phase 1 study of 29 patients receiving PR-171 at variable doses IV push daily for 5 days every 14 days.[17] Preclinical studies showed that consecutive-day dosing with continuous proteosome inhibition was superior to split dosing, as used with bortezomib. This was the rationale for the dosing schedule used in this study. Of six MM patients treated, one achieved a partial response (PR), and two achieved minor responses (MRs) when treated at a dose greater than or equal to the established minimal effective dose (MED) of 11 mg/m^2. The DLTs that established the maximum tolerated dose (MTD) were febrile neutropenia and grade 4 thrombocytopenia. The majority of the reported grade 3/4 adverse events were hematologic. Of note, the withdrawals were mainly attributed to either progressive disease or inconvenience of treatment schedule.

The second dosing schedule for PR-171 studied twice-weekly, consecutive-day dosing at variable doses as an IV push on days 1, 2, 8, 9, 15, and 16 on a 28-day cycle.[18] Alsina and colleagues reported three PR, one MR, and two stable disease (SD) in the 13 MM patients treated at the MED dose of 15 mg/m^2 or greater. The DLTs reported at 27 mg/m^2 were one hypoxic event and reversible grade 4 thrombocytopenia. A potentially significant finding was the observance of a reversible grade 2 creatinine (≥ 2 mg/dL) following day-2 dosing with a rapid reduction in serum M-protein without associated tumor lysis syndrome in three of five MM patients treated at a dose of 27 mg/m^2. The efficacy and safety data thus far in trials with PR-171 demonstrate the potential for a promising new proteosome inhibitor that does not appear to cause peripheral neuropathy.

Weber and colleagues presented an update on the long-term follow-up data available from the MM-009/010 studies, which showed a significant improvement in TTP, ORR, CR, and median OS in patients with relapsed or refractory MM when given lenalidomide plus dexamethasone versus dexamethasone alone.[19] The median OS as of January 2007 was 35 months in the combination arm and 31 months in the control arm; the median OS of those who had only one prior line of therapy had not been reached in the combination arm. The TTP was 11.2 versus 4.7 months; ORR, 60.6% versus 21.9%; and CR, 15% versus 2%, all favoring the combination arm.

Orlowski and associates previously reported an improved TTP in a phase 3 study comparing pegylated liposomal doxorubicin plus bortezomib versus bortezomib alone, one of the first corticosteroid-sparing regimens in the relapsed/ refractory setting to do this.[20] Blade and coworkers analyzed the data to determine whether prior anthracycline exposure (naïve vs median dose of 144 mg/m^2) or the number of prior therapies (1 vs ≥ 2) had an effect on the results.[21] It was determined that the improvement in TTP was maintained across all four subgroups with no significant difference in observed toxicities.

ASCO 2008 updates

Rajkumar presented information on behalf of the ECOG 4A03 trial investigators, who sought to determine whether the high OS seen was due to the primary induction therapy, or the result of ASCT.[22] Although only a small cohort of patients continued on therapy after 4 months without transplant, there is a suggestion that novel therapies, in the setting of an ORR of 89% (CR 22% and ≥VGPR 56%) and an OS of 93% at 2 years, may provide a rationale not to incorporate ASCT as part of front-line management. This will require further investigation with a direct comparison of novel agent therapy versus ASCT in the form of a randomized trial in newly diagnosed MM patients.

Zonder and associates assessed data from SWOG S0232 to determine whether cytogenetic abnormalities had an impact on LD efficacy.[23] The analysis showed that abnormal karyotypes that included a deletion of chromosome 13 and/or 17 by fluorescence in situ hybridization did affect outcomes, with inferior progression-free survival (PFS) and OS at 1 year, regardless of which therapy the patient was randomized to receive. It is important to note, however, that those with abnormal karyotypes receiving LD did better than those receiving D alone.

"68% of patients had at least a one-level improvement in their renal function, with 47% of patients who had any degree of renal impairment achieving a level of no renal impairment."

Richardson and colleagues presented updated response data on both the phase 1 and phase 2 portions of the lenalidomide-bortezomib-dexamethasone front-line setting study.[24] Thirty-five patients were evaluable for response in the MTD (4M) cohort (phase 2). The reported ORR was 100%, with 72% achieving VGPR or better, similar to the results seen in phase 1.

The final analysis of MM-014, single-agent lenalidomide in the relapsed and refractory setting, was presented by Hussein and colleagues.[25] Based on the intention-to-treat population, the ORR was 44%, with a duration of response of 13 months and a median TTP of 5.2 months. The PFS was 4.9 months and the median OS was 23.2 months. The most common grade 3/4 toxicities were myelosuppression, all of which were easily managed by dose delay, reduction, or growth factor support.

Two studies presented evaluated differences in efficacy and safety of novel therapies in the relapsed–refractory setting in patients with varying degrees of renal insufficiency. . Weber presented a subset analysis of patients in the MM-009/010 studies receiving lenalidomide.[26] The degree of renal impairment was defined by creatinine clearance (CrCl) levels. The analysis revealed that with increasing renal insufficiency, dose reductions occurred more frequently, as did an increased incidence of thrombocytopenia. Within 4 months of therapy, 68% of patients had at least a one-level improvement in their renal function, with 47% of patients who had any degree of renal impairment achieving a level of no renal impairment. Lenalidomide improved TTP, PFS, and OS in all patients, regardless of renal impairment, although those with severe renal impairment tended to gain a lesser degree of benefit.

Blade presented data on behalf of the DOXIL-MMY-3001 study investigators from a subgroup analysis of patients with renal insufficiency (defined as a CrCl ≤ 60 mL/min).[27] The analysis showed a significant increase in TTP for patients with inadequate renal function treated with pegylated liposomal doxorubicin plus bortezomib versus bortezomib alone, 331 days versus 190 days. An improvement in mean CrCl for those with renal insufficiency was seen in both arms. The only toxicities noted to be higher in the arm with renal insufficiency were grade 3/4 anemia and diarrhea.

Badros and collegues presented data from a phase 1 trial of vorinostat plus bortezomib in relapsed/refractory MM.[28] The MTD was 400 mg of oral daily vorinostat on days 4 to 11 plus bortezomib 1.3 mg/m^2 IV push on days 1, 4, 8, and 11. The DLTs of vorinostat at 500 mg were prolonged QTc and fatigue. There were 21 patients evaluable for

response following two cycles of therapy, with ORR 42%, including seven PR and two VGPR, with SD seen in 10 patients. The common grade 3/4 toxicities included myelosuppression and fatigue, with diarrhea, shingles, and pneumonia occurring to a lesser extent. This agent shows promising activity with a manageable toxicity profile and is currently being investigated in numerous combinations with other agents known to be effective in MM.

New prognostic considerations

As our knowledge of MM and technology improves, we need to identify prognostic values that can help in understanding the disease process and the development of successful therapies.

The Mayo Clinic group, based on current knowledge of the prognostic value of the serum free light chain (sFLC) ratio in determining the risk of conversion from monoclonal gammopathy of undetermined significance,[29] studied the peripheral blood of 790 patients; diagnosed with MM.[30] Serum-free kappa (κ)- and lambda (λ)-concentrations were quantified in these patients; the κ:λ ratio was then calculated. The normal reference range for the ratio was 0.26-1.65. Of the patients tested, 95.1% had FLC ratios outside the reference range. Patients were then divided into two groups—those with a sFLC ratio between 0.03 and 32 and those falling below 0.03 or above 32. The patients outside the new reference range had a significant decrease in median OS of 30 months versus 39 months for those within range. The sFLC ratio made the most significant contribution to predicting prognosis in patients with International Staging System (ISS) stage II disease; 5-year OS was 20.5% in those outside the reference range compared with 35.2% in those within the range. When the ratio was incorporated into the ISS, and patients were evaluated based on the number of risk factors 0, 1, 2, and 3 (low albumin: < 3.5 g/dL, high beta-2 microglobulin: ≥ 3.5 g/dL, and sFLC ratio: < 0.03 or > 32), the median OS rates in months were 51, 39, 30, and 22, respectively. Although this factor has not yet been incorporated into the ISS, it will continue to be evaluated and may lead to a change in the future.

In addition, the Mayo Clinic researchers explored whether restaging at the time of relapse would be predictive of median OS from that timepoint in the course of the disease.[31] They evaluated a uniform group of 131 patients who relapsed (according to European Blood and Marrow Transplant Registry criteria) following ASCT and obtained serum albumin and beta-2 microglobulin levels within 30 days of relapse. Of the patients evaluated at the time of relapse, 49% were stage I, 38% were stage II, and 13% were stage III, with predicted OS from that timepoint of 27.3, 17.8, and 12.3 months, respectively. Based on this evaluation, levels of beta-2 microglobulin and albumin at the time of relapse appear to have prognostic value, and it may be useful to incorpoate these values into clinical trials in the relapsed setting.

The study of genomics is constantly under investigation in an effort to help determine the right course of treatment for the right type of disease, based on knowledge of how it works. Every patient's disease is different, and an understanding of that will help to personalize treatment in the future in the effort to improve outcomes.

Hyperdiploid (H)-MM is characterized by an increased number of chromosomes seen in cytogenetic testing.[32] Nonhyperdiploid (NH)-MM is characterized not by the number of chromosomes seen on genetic testing, but by the number of structural changes that occur within the normal chromosome complement. Chng and associates performed cytogenetic testing on 194 patients with MM and looked at not only the ploidy, but also the number of genomic aberrations. They found that both H-MM and NH-MM had a high number of genomic aberrations, with a mean of 15.8 ± 7.5 versus 20.6 ± 17.0, respectively. The patients were then segregated into two distinctively different groups with respect to OS based on number of aberrations per tumor (NAPT). Those with fewer than 20 NAPT had a median OS of 88 months, and those with more had a significantly shorter median OS of 20 months. This information enables us to identify a small subset of patients who would be considered high-risk/low-risk based on their ploidy, but who may actually fall into the opposite risk category based on the NAPT in their disease.

Clinical implications

As we continue to identify new targets for therapy that affect different pathways and act by different mechanisms, we have the potential to subject patients to new side effects that they have not encountered in the past. The current tendency when treating MM is combination therapy with novel agents, standard chemotherapies, and investigational drugs. Being able to predict the potential toxicities and understanding the treatment interventions will enable us to optimize response and quality of life by minimizing toxicity. Educating patients about potential toxicities associated with their treatment and the need for prompt reporting is our best tool for improving patient outcomes.

Each individual with MM has a unique profile of supportive-care needs related to his or her diagnosis, comorbidities, and therapeutic choice. A needs assessment must be performed on each and must take into account psychosocial fitness, including but not limited to support network, psychological wellness, and access to care (transportation/financial). We also need to evaluate the patient's overall health to determine what existing or potential comorbid conditions must be managed or screened for to facilitate the best quality care a patient can receive.

COMMENTARY

A PHARMACIST'S PERSPECTIVE

Evaluating and Treating Patients with Multiple Myeloma

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As pharmacists, we have a very important role to play as a reference not only for patients and caregivers but for practitioners as well. With increasing numbers of new therapies and combination therapies available, overall survival for patients with cancer has increased. At the same time, however, the management of bothersome and sometimes severe side effects is becoming a more prevalent concern in clinical practice. Peripheral neuropathies (with the immunomodulators [IMiDs] and bortezomib), severe constipation (specifically with thalidomide), rashes (primarily with liposomal doxorubicin or IMiDs, deep-vein thromboses (DVTs)/pulmonary embolisms (PEs) (with IMiDs and steroids), anemia, diarrhea, herpes zoster virus (HSV) (with bortezomib), pneumonia, and thrombocytopenia are just a few of the major adverse events requiring possible prevention and management. Pharmacists must advise whether agent A or B would be more suitable for each patient based on current or anticipated side effects, such as peripheral neuropathies or hyperglycemia.

With some medications, proper timing of doses can help. We need to be very specific in telling patients with multiple myeloma (MM) when to take their medications such as thalidomide or dexamethasone; for example, both should be taken in the evening.

We also must counsel patients about the possibility of liposomal doxorubicin–induced palmar-plantar erythrodysesthesias, which are charactherized by abnormal sensation in the hands and feet, edema, and fissuring and ulceration of fingers, toes, palms, and plantar aspects of the feet that can progress, causing severe pain. Dose reduction and delayed administration of liposomal doxorubicin is sometimes needed, but in our institute, we find that treatment with topical Biafin, vitamin B_6 (50 mg-200 mg daily), and application of ice packs at the first signs of redness or tingling is effective.

Because drug–drug interactions are so important and there is sometimes minimal information about potential interactions with the newer therapies, pharmacists must consider theoretical interactions and discuss them with the healthcare team.

With agents such as liposomal doxorubicin, is also important to monitor liver function tests and hematologic parameters. Adjustments of some drug regimens are clearly indicated when certain combinations of drugs are used. For example, published guidelines recommend reducing the dose of bortezomib when it is used with liposomal doxorubicin or avoiding it altogether, depending primarily on the absolute neutrofil count, fever, and other nonhematologic toxicities.

As pharmacists, we can predict what side effects are most likely to occur and help our patients avoid them. For example, we can help prevent peripheral neuropathies and HSV with bortezomib and possible DVTs/PEs and constipation with thalidomide, dexamethasone, and other IMiDs. For example, we can ensure that patients who are taking bortezomib also take acyclovir at the appropriate dose for HSV prevention. Patients with MM are usually taking many medications, most of them following complicated regimens. In our clinic, each patient with MM has a consult with a clinical pharmacist. We have found that meeting with patients and their families and giving them written information about their drug combinations has greatly improved compliance.

With the increased number of oral and intravenous medications now available to treat MM (in both transplant- and nontransplant-eligible patients), more onus is placed on patients to take their medications correctly. Pharmacists in the clinic can play a huge role in preventing and managing drug toxicity as well as increasing patient compliance.

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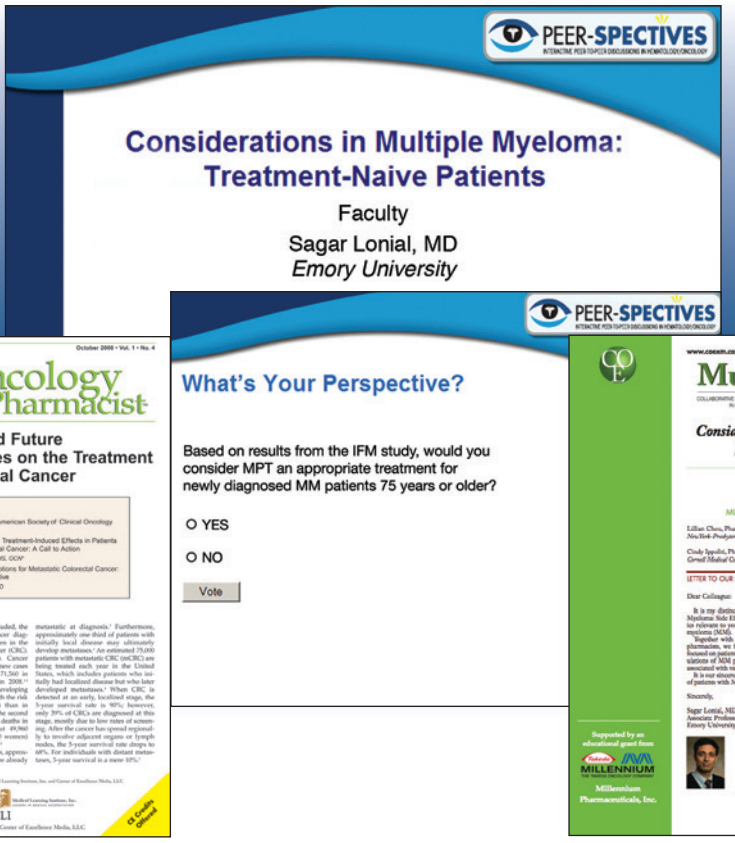

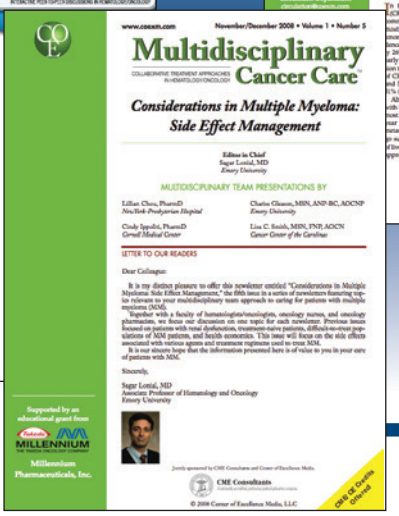

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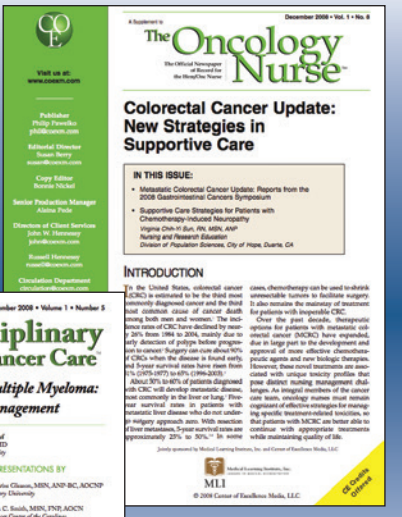

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Prostate Cancer 2008

Continued from page 13

Predictors of outcomes

Prognostic markers in early-stage disease, beyond Gleason grade, primary tumor, regional node, metastasis stage, and serum PSA predictive of outcome in men with prostate cancer, have been the focus of a number of studies in recent years. Diabetes, a leading cause of death in the United States, is associated with decreased prostate cancer incidence.[19] However, obesity, a risk factor for diabetes, is associated with greater prostate cancer mortality. Therefore, to clarify the relationship between diabetes and prostate cancer outcomes, Smith and colleagues assessed this relationship using data from the Radiation Therapy Oncology Group protocol 92-02.[20] This protocol was a randomized trial of 1554 men treated with radiation therapy and either short-term (4 months) or long-term (28 months) adjuvant goserelin for locally advanced prostate cancer. The authors utilized proportional hazard models to evaluate the relationship between prevalent diabetes and all-cause mortality, prostate cancer mortality, and nonprostate cancer mortality with standard covariates. Diabetes was associated with greater all-cause mortality and nonprostate cancer mortality but not prostate cancer mortality in both a univariate analysis and when controlling for covariates. Conversely, weight was associated with greater prostate cancer mortality but not all-cause or nonprostate cancer mortality.

In patients with metastatic prostate cancer, PSA has been used as a marker of response in clinical trials. A recent analysis of data from S9346 and S9916, which involved treatment of metastatic prostate cancer, revealed that PSA progression is a predictor of overall survival.[21] The 1015 patients enrolled in S9346 received continuous androgen deprivation, while the 573 patients from S9916 were treated with docetaxel and prednisone or mitoxantrone and prednisone. The investigators reported that a PSA progression defined as an increase of ≥25% over baseline or nadir with an absolute increase of at least 2 ng/mL to 5 ng/mL is a strong predictor of overall survival in metastatic hormone-sensitive and-resistant prostate cancer.

Conclusions

In 2008, there were significant advances in the understanding of the molecular biology of prostate cancer as well as the management of disease. A challenge to interpreting earlier data has been the lack of standard criteria for the end points of many trials. The publication of the recommendations of the Prostate Cancer Clinical Trials Working Group provides standards of evaluation in prostate cancer trials.[22] Utilizing these recommendations for trial design and end point assessment, future trials based on recent data should continue to result in significant advances in the prevention and management of prostate cancer.

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Scientific Developments in the Management of Myelodysplastic Syndromes

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Several key scientific events within the past decade have shaped the current strategy for management of myelodysplastic syndromes (MDS). The majority of these have occurred in the past 5 years. An improved understanding of this heterogeneous group of myeloid stem-cell malignancies, including insights into key elements of the malignant clone, the bone marrow microenvironment, and the variability in disease trajectory, have been key to clinical advances.

A revised World Health Organization (WHO) classification system has been recently published incorporating this new information.[1] Hematopathologists and clinicians must develop the ability to translate data obtained using older definitions into current clinical trials that will be based on the revised nomenclature. The rate of scientific discovery creates a number of challenges to clinical application of the findings, including transition of practice patterns, education of the clinician and the patient, safety, and financial or reimbursement obstacles.

Table 1. Novel Agents and Targeted Therapies for the Treatment of MDS

Mechanism of action	Therapeutic compound	Application
Immunosuppression	ATG, cyclosporine	Low-risk hypocellular disease
Immune modulation	Thalidomide, lenalidomide	Low to intermediate-1 risk, in particular del(5q) In combination with demethylating agents
Inhibitors of angiogenesis	Bevacizumab, lenalidomide, thalidomide, arsenic trioxide	Variable applications
DNA hypomethylation	Azacitidine, decitabine	All risk categories
Inhibition of histone deactylation	Valproic acid, depsipeptide, MS275	In combination with demethylating agents or purine analogs
Oncogene deactivation	Farnesyl transferase inhibitors: tipifarnib, lonafarnib	In combination with demethylating agents or purine analogs
Enzyme and kinase inhibition	TLK199, Src family kinase inhibitors, p38 MAPK inhibitor	In clinical trials for variable populations
Purine analogs	Clofarabine, cytarabine	Combinations for high-risk MDS in the elderly
Monoclonal antibodies	Gemtuzumab ozogamicin	High-risk disease in the elderly
Thrombopoiesis-stimulating hormone	Romiplostim	Treatment-associated thrombocytopenia in all risk categories

Core therapies

The establishment of an epidemiological data reporting system specific to MDS in the United States has validated similar trends in incidence and age to those in the more established data from European sites.[2,3] These data provide a critical resource for analysis of therapies for MDS and confirm that the highest incidence is in individuals more than 70 years of age. There is an expected increase in incidence as the population ages.

To date, allogeneic stem-cell transplants are the only potentially curative therapy for MDS. This is not an option for the majority of MDS patients, however, based on age, comorbid conditions, and donor availability. Therefore, treatment strategies that are feasible in the older population will be the core of MDS therapy. Improved quality of life, limited toxicity, reduced need for hospitalization, and affordability will be critical to successful therapies. Oncology clinicians will need a basic understanding of treating the older adult with cancer.

"Treatment strategies that are feasible in the older population will be the core of MDS therapy."

The term myelodysplastic syndromes was first used in 1982 by John Bennett, MD, and colleagues, who differentiated MDS from acute myeloid leukemia.[4] The clinical application of scientific advances in the diagnosis, risk stratification, and treatment of MDS since the disease was recognized as a unique entity have been concentrated in the past 5 years. Three active agents—azacitidine, decitabine, and lenalidomide—are currently approved by the US Food and Drug Administration (FDA) in the United States as well as many other countries for the treatment of MDS. Direct clinical comparison of these agents is limited as each of these drugs has only recently been approved for use in the setting of monotherapy and broad inclusion criteria (all risk groups).

Based on key clinical trials and ongoing investigation, the first treatment guidelines for MDS were developed by the National Comprehensive Cancer Network in 2004. They have been revised a number of times each year since then, consistent with the relatively new understanding of key aspects of this disease and strategies for treatment. In addition, definitions of response, desired primary end points (survival vs response), and evolving recommendations for risk-adapted treatment selection based on prognostics and individual patient profiles continue to evolve. A comparative trial using azacitidine and decitabine, which are both demethylating agents, is planned for 2009. Development of novel agents with unique therapeutic targets is ongoing (Table 1). Key clinical trials for FDA-approved therapies for MDS will be highlighted in this review with discussion of the implications for clinical practice and patient care.

Risk-adapted therapy for MDS

Harris and colleagues[1] in the revised WHO classification for MDS state that "classification is the language of medicine: disease must be described, defined, and named before it can be diagnosed, treated, and studied." Understanding the pathobiology of MDS has allowed identification of therapeutic targets and refinement of treatment strategies, including the concept of risk-adapted therapy. The heterogeneous nature of the disease entities described within the MDS nomenclature presents a challenge for hematopathologists and clinicians.

The integration of the International Prognostic Scoring System (IPSS) and, more recently, the World Health Prognostic Scoring System (WPSS) have guided the selection of therapy based on projected disease trajectory and the risk of leukemic transformation. The accepted classification for clinical management uses two primary categories: low to intermediate-1 risk or intermediate-2 to high-risk disease based on blasts percentage, cytogenetic profile, and number of cytopenias. Several studies have proposed additional adverse risk factors, including thrombocytopenia, transfusion burden, lactic dehydrogenase, and performance sta-

tus.[5-9] Continued review is certain as an improved understanding of the pathobiology of this disease and resulting clinical implications are realized.

Lower risk MDS is accepted as a chronic myeloid malignancy with an emphasis on improved hematopoiesis, including transfusion independence, improved quality of life, and extended overall survival (OS). Treatment until disease progression or unacceptable toxicity is now an accepted paradigm, emphasizing the need to refine supportive care strategies.[10,11]

In addition, trials using the immunomodulatory agent lenalidomide for low-intermediate risk MDS have elucidated a difference in mechanism of action for selected patient subsets. Analysis of the data from the three lenalidomide trials in MDS suggests that lenalidomide has a different mechanism of action in patients with or without chromosome 5q deletion, a possible direct cytotoxic effect on the malignant clone with del(5q) and effect on the microenvironment in patients without the deletion of chromosome 5q.[12-14] Cytogenetic responses have been shown to correlate with improved survival in patients with chromosome 5q deletion. A follow-up evaluation of six patients participating in the MDS-001 trial indicated the response to lenalidomide to be durable with sustained transfusion independence up to 6.5 years and provided evidence of sustained cytogenetic remissions in some patients.[14]

Higher risk disease presents a particular challenge in the older population, in whom the focus of treatment is on survival, suppression of the leukemic clone, and management of disease and treatment toxicities. A fundamental principle of active therapy for any stage of MDS is that sustained treatment for a minimum of 3 to 4 months is necessary to effectively evaluate efficacy, and the depth of response may continue to improve up to 6 to 9 months after initiating therapy.[15] The challenge is in aggressively managing potential toxicities during the initial therapy to minimize gaps in treatment or unnecessary discontinuation of therapy.[16] Data supporting the potential to improve OS in this disease, even in patients with high-risk features, reinforce the need to refine clinical strategies for supportive care.

Chromosome 7 abnormalities are an unfavorable risk factor in MDS. An important study by Mufti and colleagues[17] indicated a survival benefit with standard-dose azacitidine in high-risk MDS, including chromosome 7 abnormalities (-7/del[7q]). For the 57 patients with -7/del(7q) alone or as part of a complex karyotype, the hazard ratio (HR) for risk of death was 0.33 (95% confidence interval, 0.16-0.68), indicating that azacitidine reduced the risk of death by 67% in these patients. OS was significantly longer in the azacitidine group than in the conventional care response group (13.1 months vs 4.6 months).

Fenaux and colleagues studied 358 patients with intermediate-2 or high-risk MDS.[18] The primary end point was OS in patients treated with azacitidine 75 mg/m^2 per day on days 1 through 7 for 28 days compared with conventional chemotherapy (cytarabine [ARA-C]/daunorubicin 7 + 3, or low-dose ARA-C). The patients treated with azacitidine had a significant improvement in OS compared with conventional care (P = .0001, HR = 0.58). Median survival was improved, from approximately 15 months on conventional care to 24.4 months with azacitidine treatment. Approximately 52% of patients treated with azacitidine were alive at 2 years compared with 26% of patients who received conventional care. Considering the original survival data from the IPSS and WPSS with median survival of 1.2 years for intermediate-2 and 4 months for high-risk disease, this provides hope to patients with MDS. This is the first trial in MDS to document a survival advantage for active therapies.

"The goals of therapy have shifted from supportive care alone to aggressive management of cytopenias."

Wijermans and colleagues reported results from a phase 3 trial using low-dose decitabine versus best supportive care for 223 patients with high-risk MDS.[19] Decitabine was administered at a dose of 15 mg/m^2 intravenously over 4 hours every 8 hours for 3 consecutive days (n = 119) versus base supportive care (n = 114). In a population of patients with intermediate-2 or high-risk MDS (93%), many of whom had poor cytogenetic risk profiles (46%), the median OS was not significantly longer with the decitabine group (10.1 months vs 8.5 months). It is important to note that patients who did achieve a complete response received a maximum of eight cycles, and the median number of cycles in this high-risk group was three. Given the recent shift toward treatment until progression and the expectation of a minimum of 4 to 6 months of therapy before achieving a response, these disappointing data may be a reflection of clinical trial design. It underscores the challenge of integrating rapidly changing primary end points into a meaningful clinical trial and the importance of continued enrollment of patients in clinical trials.

Supportive care

Supportive care strategies have also been refined and are recognized as essential components of the overall treatment strategy, including quality of life. The goals of therapy have shifted from supportive care alone to aggressive management of cytopenias, including achievement of transfusion independence, iron chelation therapy, and development of new cytokines for the treatment of thrombocytopenia. Myelosuppression is the most common dose-limiting toxicity associated with active therapies, and thus strategies to minimize cytopenias may allow patients to maintain active therapy.

Iron overload is associated with increased morbidity and mortality in patients with MDS, and iron chelation therapy has been shown to improve OS.[5,8] Sanz and colleagues studied 2994 patients with primary MDS. The majority of these patients (78) had low-intermediate-1 risk disease.[5] The study end points were OS and leukemia-free survival (LFS). Results of the study showed that red blood cell (RBC) transfusion-dependency (OS–HR = 7.20, P <.001; LFS–HR = 2.9, P <.001) and iron overload (OS–HR = 2.11, P <.001; LFS–HR = 1.57, P <.001) have prognostic value independent of the IPSS score. This study is thought to confirm the validity of adding RBC transfusion dependency to the revised WHO prognostic scoring system. It also supports transfusion dependence as a valid indicator for initiation of active therapies. Patients with MDS should be screened using a serum ferritin at the time of diagnosis with continued monitoring of these values. Ferritin levels >1000 have been shown to be associated with adverse outcomes.

Myelosuppression is the most common treatment-related toxicity in therapeutic regimens for MDS. Thrombocytopenia is a particular challenge because of the increased risk of bleeding in a primarily elderly population.

Romiplostim, a thrombomimetic agent, was used in combination with azacitidine and compared with azacitidine and placebo. In patients receiving romiplostim, the platelet count before each course of therapy and the platelet nadir were higher than the counts for patients in the placebo group. In addition, the group receiving the romiplostim required fewer platelet transfusions, and the incidence of grade 3 bleeding events was lower.[20] The addition of this type of agent to active therapies for MDS, which require several months for maximum response while inducing significant myelosuppression, can provide the supportive care necessary to maintain therapy long enough to achieve response.

Summary

The robust pace of scientific discoveries relative to understanding the pathobiology of MDS and the development and clinical application of therapies based on this understanding provides great hope for patients and clinicians. Several key concepts for effective treatment of MDS have been identified (Table 2). There are still many questions unanswered and a need to continue refinement of the diagnostic and risk stratification for this disease. New agents will be necessary to provide continued treatment options. This underscores the benefit of clinical trial participation in diseases with limited available treatment options and evolving scientific discoveries. MDS is one of many diagnoses with a rapidly changing treatment paradigm based on scientific advances and clinical management strategies. The goals of therapy in patients with MDS are to improve quality of life, minimize toxicity, improve hematopoiesis, reduce cytopenias, achieve transfusion independence, and prolong survival. These outcomes have now been realized in several of the studies discussed. Consideration of the unique needs of the elderly patient are critical to achieve optimal clinical man-

Table 2. Key Concepts in the Treatment of MDS

- Myelodysplatic syndromes represent a myeloid stem-cell malignancy
- Clinical trial end points have shifted from efficacy and safety alone to include improved overall survival
- Complete eradication of the malignant clone is not necessary to prolong survival, but suppression is associated with transfusion independence, cytogenetic response, improved survival, and a reduced risk of leukemic transformation
- Clinical responses often require a minimum of 4 to 6 months of therapy, and prolonged therapy (treating until disease progression or unacceptable toxicity) is likely to become the standard approach
- Concurrent supportive care is essential to optimal therapeutic outcomes including iron chelation, transfusion management, cytokine support, and aggressive management of comorbidities; however, supportive care does not affect the underlying disease
- Treatment-related MDS is associated with a poor prognosis and will require specific approaches to treatment that are similar to those used for acute myeloid leukemia
- MDS is most common in individuals over the age of 70; therefore, treatment strategies that are feasible for the older adult will be the core of MDS therapy

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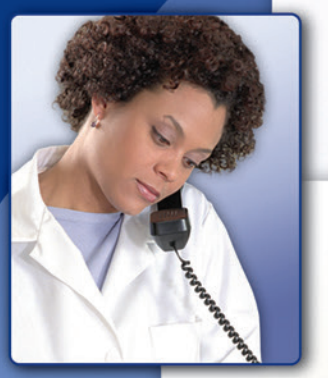

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agement and quality of life; however, advanced age alone should not exclude older patients from active therapies.

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NEXAVAR (sorafenib) tablets, oral
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BRIEF SUMMARY
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1 INDICATIONS AND USAGE

1.1 Hepatocellular Carcinoma NEXAVAR is indicated for the treatment of patients with unresectable hepatocellular carcinoma (HCC).

1.2 Renal Cell Carcinoma NEXAVAR is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

4 CONTRAINDICATIONS

NEXAVAR is contraindicated in patients with known severe hypersensitivity to sorafenib or any other component of NEXAVAR.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Cardiac Ischemia and/or Infarction In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in NEXAVAR patients compared with 1.3% in the placebo group and in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the NEXAVAR group (2.9%) compared with the placebo group (0.4%). Patients with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of NEXAVAR should be considered in patients who develop cardiac ischemia and/or infarction.

5.2 Risk of Hemorrhage An increased risk of bleeding may occur following NEXAVAR administration. In the HCC study, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in NEXAVAR patients and 4% in placebo patients. Bleeding with a fatal outcome from any site was reported in 2.4% of NEXAVAR patients and 4% in placebo patients. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of patients in the NEXAVAR group and 8.2% of patients in the placebo group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in NEXAVAR patients, and 1.3% and 0.2%, respectively, in placebo patients. There was one fatal hemorrhage in each treatment group in RCC Study 1. If any bleeding necessitates medical intervention, permanent discontinuation of NEXAVAR should be considered.

5.3 Risk of Hypertension Blood pressure should be monitored weekly during the first 6 weeks of NEXAVAR therapy and thereafter monitored and treated, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of NEXAVAR-treated patients and 4.3% of patients in the placebo group. In RCC Study 1, hypertension was reported in approximately 16.9% of NEXAVAR-treated patients and 1.8% of patients in the placebo group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension, despite institution of antihypertensive therapy, temporary or permanent discontinuation of NEXAVAR should be considered. Permanent discontinuation due to hypertension occurred in 1 of 297 NEXAVAR patients in the HCC study and 1 of 451 NEXAVAR patients in RCC Study 1.

5.4 Risk of Dermatologic Toxicities Hand-foot skin reaction and rash represent the most common adverse reactions attributed to NEXAVAR. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with NEXAVAR. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification of NEXAVAR, or in severe or persistent cases, permanent discontinuation of NEXAVAR. Permanent discontinuation of therapy due to hand-foot skin reaction occurred in 4 of 297 NEXAVAR HCC patients and 3 of 451 NEXAVAR RCC patients.

5.5 Risk of Gastrointestinal Perforation Gastrointestinal perforation is an uncommon adverse reaction and has been reported in less than 1% of patients taking NEXAVAR. In some cases this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, NEXAVAR therapy should be discontinued.

5.6 Warfarin Co-Administration Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on NEXAVAR therapy. Patients taking concomitant warfarin should be monitored regularly for changes in prothrombin time, INR or clinical bleeding episodes.

5.7 Wound Healing Complications No formal studies of the effect of NEXAVAR on wound healing have been conducted. Temporary interruption of NEXAVAR therapy is recommended in patients undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of NEXAVAR therapy following major surgical intervention. Therefore, the decision to resume NEXAVAR therapy following a major surgical intervention should be based on clinical judgment of adequate wound healing.

5.8 Interactions with UGT1A1 Substrates Sorafenib can cause increases in plasma concentrations of drugs that are substrates of UGT1A1. Caution is recommended when administering NEXAVAR with compounds that are metabolized/eliminated predominantly by the UGT1A1 pathway (e.g. irinotecan) *[see Drug Interactions (7.1)**]*.

5.9 Interaction with Docetaxel Sorafenib can cause increases in plasma concentrations of docetaxel. Caution is recommended when NEXAVAR is co-administered with docetaxel *[see Drug Interactions (7.2)**]*.

5.10 Interaction with Doxorubicin Sorafenib can cause increases in plasma concentrations of doxorubicin. Caution is recommended when NEXAVAR is co-administered with doxorubicin *[see Drug Interactions (7.3)**]*.

5.11 Pregnancy: Pregnancy Category D

Sorafenib may cause fetal harm when administered to a pregnant woman. In rats and rabbits, sorafenib has been shown to be teratogenic and to induce embryo-fetal toxicity (including increased post-implantation loss, resorptions, skeletal retardations, and retarded fetal weight). The effects occurred at doses considerably below the recommended human dose of 400 mg twice daily (approximately 500 mg/m^2/day on a body surface area basis). Adverse intrauterine development effects were seen at doses ≥1.2 mg/m^2/day in rats and 3.6 mg/m^2/day in rabbits (approximately 0.008 times the AUC seen in cancer patients at the recommended human dose). A NOAEL (no observed adverse effect level) was not defined for either species, since lower doses were not tested.

There are no adequate and well-controlled studies in pregnant women using NEXAVAR. Women of childbearing potential should be advised to avoid becoming pregnant while on NEXAVAR. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5.12 Hepatic Impairment Hepatic impairment may reduce plasma concentrations of sorafenib. Comparison of data across studies suggests that sorafenib levels are lower in HCC patients than in non-HCC patients (without hepatic impairment). The AUC of sorafenib is similar between HCC patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. The optimal dose in non-HCC patients with hepatic impairment is not established *[see Use in Specific Populations (8.6**) and Clinical Pharmacology (12.3)**]*.

6 ADVERSE REACTIONS The following risks are discussed in greater detail in the WARNINGS AND PRECAUTIONS section (5):

- Cardiac ischemia, infarction *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Hand-foot skin reaction and rash *[see Warnings and Precautions (5.4)]*
- Gastrointestinal perforation *[see Warnings and Precautions (5.5)]*
- Wound healing complications *[see Warnings and Precautions (5.7)]*
- Teratogenicity and embryofetal toxicity *[see Warnings and Precautions (5.11)]*

The data described in sections 6.1 and 6.2 reflect exposure to NEXAVAR in 748 patients who participated in placebo controlled studies in hepatocellular carcinoma (N=297) or advanced renal cell carcinoma (N=451).

The most common adverse reactions (≥20%), which were considered to be related to NEXAVAR, in patients with HCC or RCC are fatigue, weight loss, rash/desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea and abdominal pain.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Adverse Reactions in HCC Study Table 2 shows the percentage of HCC patients experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 39% of patients receiving NEXAVAR compared to 24% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 6% of patients receiving NEXAVAR compared to 8% of patients receiving placebo.

Table 2 Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – HCC Study

	NEXAVAR N=297			Placebo N=302		
Adverse Reaction NCI- CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reaction	98	39	6	96	24	8
Constitutional symptoms						
Fatigue	46	9	1	45	12	2
Weight loss	30	2	0	10	1	0

Renal Cell Carcinoma *Continued from page 9*

metastatic RCC. Agents that have been FDA approved as well as others that have been investigated in clinical trials have shown improved survival and are more tolerable than the traditional immunologic agents used to treat this disease. Although more tolerable, the side effects of these newer agents are unique and still require monitoring. As more experience is gained with these therapies, clinicians may be better able to select therapies based on unique characteristics of the patient.

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Table 2 continued:

	NEXAVAR N=297			Placebo N=302		
Adverse Reaction NCI- CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Dermatology/skin						
Rash/desquamation	19	1	0	14	0	0
Pruritus	14	<1	0	11	<1	0
Hand-foot skin reaction	21	8	0	3	<1	0
Dry skin	10	0	0	6	0	0
Alopecia	14	0	0	2	0	0
Gastrointestinal						
Diarrhea	55	10	<1	25	2	0
Anorexia	29	3	0	18	3	<1
Nausea	24	1	0	20	3	0
Vomiting	15	2	0	11	2	0
Constipation	14	0	0	10	0	0
Hepatobiliary/ pancreas						
Liver dysfunction	11	2	1	8	2	1
Pain						
Pain, abdomen	31	9	0	26	5	1

Hypertension was reported in 9% of patients treated with NEXAVAR and 4% of those treated with placebo. CTCAE Grade 3 hypertension was reported in 4% of NEXAVAR treated patients and 1% of placebo treated patients. No patients were reported with CTCAE Grade 4 reactions in either treatment group.

Hemorrhage/bleeding was reported in 18% of those receiving NEXAVAR and 20% of placebo patients. The rates of CTCAE Grade 3 and 4 bleeding were also higher in the placebo group (CTCAE Grade 3 - 3% NEXAVAR and 5% placebo and CTCAE Grade 4 - 2% NEXAVAR and 4% placebo). Bleeding from esophageal varices was reported in 2.4% in NEXAVAR treated patients and 4% of placebo treated patients.

Renal failure was reported in <1% of patients treated with NEXAVAR and 3% of placebo treated patients.

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (32% of NEXAVAR patients and 35% of placebo patients).

Laboratory Abnormalities The following laboratory abnormalities were observed in HCC patients:

Hypophosphatemia was a common laboratory finding, observed in 35% of NEXAVAR-treated patients compared to 11% of placebo patients; CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 11% of NEXAVAR-treated patients and 2% of patients in the placebo group; there was 1 case of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in the placebo group. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 40% of patients treated with NEXAVAR compared to 37% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 9% of patients in each group. Elevated amylase was observed in 34% of patients treated with NEXAVAR compared to 29% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 2% of patients in each group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 1 of 297 NEXAVAR-treated patients (CTCAE Grade 2).

Elevations in liver function tests were comparable between the 2 arms of the study. Hypoalbuminemia was observed in 59% of NEXAVAR-treated patients and 47% of placebo patients; no CTCAE Grade 3 or 4 hypoalbuminemia was observed in either group.

INR elevations were observed in 42% of NEXAVAR-treated patients and 34% of placebo patients; CTCAE Grade 3 INR elevations were reported in 4% of NEXAVAR-treated patients and 2% of placebo patients; there was no CTCAE Grade 4 INR elevation in either group.

Lymphopenia was observed in 47% of NEXAVAR-treated patients and 42% of placebo patients.

Thrombocytopenia was observed in 46% of NEXAVAR-treated patients and 41% of placebo patients; CTCAE Grade 3 or 4 thrombocytopenia was reported in 4% of NEXAVAR-treated patients and less than 1% of placebo patients.

6.2 Adverse Reactions in RCC Study 1 Table 3 shows the percentage of RCC patients experiencing adverse reactions that were reported in at least 10% of patients and at a higher rate in the NEXAVAR arm than the placebo arm. CTCAE Grade 3 adverse reactions were reported in 31% of patients receiving NEXAVAR compared to 22% of patients receiving placebo. CTCAE Grade 4 adverse reactions were reported in 7% of patients receiving NEXAVAR compared to 6% of patients receiving placebo.

Table 3: Adverse Reactions Reported in at Least 10% of Patients and at a Higher Rate in NEXAVAR Arm than the Placebo Arm – RCC Study 1

	NEXAVAR N=451			Placebo N=451		
Adverse Reactions NCI- CTCAE v3 Category/Term	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Any Adverse Reactions	95	31	7	86	22	6
Cardiovascular, General						
Hypertension	17	3	<1	2	<1	0
Constitutional symptoms						
Fatigue	37	5	<1	28	3	<1
Weight loss	10	<1	0	6	0	0
Dermatology/skin						
Rash/desquamation	40	<1	0	16	<1	0
Hand-foot skin reaction	30	6	0	7	0	0
Alopecia	27	<1	0	3	0	0
Pruritus	19	<1	0	6	0	0
Dry skin	11	0	0	4	0	0
Gastrointestinal symptoms						
Diarrhea	43	2	0	13	<1	0
Nausea	23	<1	0	19	<1	0
Anorexia	16	<1	0	13	1	0
Vomiting	16	<1	0	12	1	0
Constipation	15	<1	0	11	<1	0
Hemorrhage/bleeding						
Hemorrhage – all sites	15	2	0	8	1	<1
Neurology						
Neuropathy-sensory	13	<1	0	6	<1	0
Pain						
Pain, abdomen	11	2	0	9	2	0
Pain, joint	10	2	0	6	<1	0
Pain, headache	10	<1	0	6	<1	0
Pulmonary						
Dyspnea	14	3	<1	12	2	<1

The rate of adverse reactions (including those associated with progressive disease) resulting in permanent discontinuation was similar in both the NEXAVAR and placebo groups (10% of NEXAVAR patients and 8% of placebo patients).

Laboratory Abnormalities The following laboratory abnormalities were observed in RCC patients in Study 1:

Hypophosphatemia was a common laboratory finding, observed in 45% of NEXAVAR-treated patients compared to 11% of placebo patients. CTCAE Grade 3 hypophosphatemia (1–2 mg/dL) occurred in 13% of NEXAVAR-treated patients and 3% of patients in the placebo group. There were no cases of CTCAE Grade 4 hypophosphatemia (<1 mg/dL) reported in either NEXAVAR or placebo patients. The etiology of hypophosphatemia associated with NEXAVAR is not known.

Elevated lipase was observed in 41% of patients treated with NEXAVAR compared to 30% of patients in the placebo group. CTCAE Grade 3 or 4 lipase elevations occurred in 12% of patients in the NEXAVAR group compared to 7% of patients in the placebo group. Elevated amylase was observed in 30% of patients treated with NEXAVAR compared to 23% of patients in the placebo group. CTCAE Grade 3 or 4 amylase elevations were reported in 1% of patients in the NEXAVAR group compared to 3% of patients in the placebo group. Many of the lipase and amylase elevations were transient, and in the majority of cases NEXAVAR treatment was not interrupted. Clinical pancreatitis was reported in 3 of 451 NEXAVAR-treated patients (one CTCAE Grade 2 and two Grade 4) and 1 of 451 patients (CTCAE Grade 2) in the placebo group.

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18. Clement P, Wolter P, Stefan C, et al. Thyroid dysfunction in patients (pts) with metastatic renal cell carcinoma (RCC) treated with sorafenib. *J Clin Oncol.* 2008;26(suppl 20): Abstract 16145.
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Lymphopenia was observed in 23% of NEXAVAR-treated patients and 13% of placebo patients. CTCAE Grade 3 or 4 lymphopenia was reported in 13% of NEXAVAR-treated patients and 7% of placebo patients. Neutropenia was observed in 18% of NEXAVAR-treated patients and 10% of placebo patients. CTCAE Grade 3 or 4 neutropenia was reported in 5% of NEXAVAR-treated patients and 2% of placebo patients.

Anemia was observed in 44% of NEXAVAR-treated patients and 49% of placebo patients. CTCAE Grade 3 or 4 anemia was reported in 2% of NEXAVAR-treated patients and 4% of placebo patients.

Thrombocytopenia was observed in 12% of NEXAVAR-treated patients and 5% of placebo patients. CTCAE Grade 3 or 4 thrombocytopenia was reported in 1% of NEXAVAR-treated patients and 0% of placebo patients.

6.3 Additional Data from Multiple Clinical Trials The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of NEXAVAR as monotherapy (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Uncommon:* hypertensive crisis*, myocardial ischemia and/or infarction*, congestive heart failure*

Dermatologic: *Very common:* erythema *Common:* exfoliative dermatitis, acne, flushing *Uncommon:* folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin

Digestive: *Very common:* increased lipase, increased amylase *Common:* mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon:* pancreatitis, gastrointestinal reflux, gastritis, gastrointestinal perforations*

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common:* hemorrhage (including gastrointestinal* & respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain) *Common:* decreased appetite, influenza-like illness, pyrexia *Uncommon:* infection

Hematologic: *Very common:* leukopenia, lymphopenia *Common:* anemia, neutropenia, thrombocytopenia *Uncommon:* INR abnormal

Hypersensitivity: *Uncommon:* hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common:* hypophosphatemia *Common:* transient increases in transaminases *Uncommon:* dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, cholecystitis, cholangitis

Musculoskeletal: *Common:* arthralgia, myalgia

Nervous System and Psychiatric: *Common:* depression *Uncommon:* tinnitus, reversible posterior leukoencephalopathy*

Renal and Genitourinary: *Common:* renal failure

Reproductive: *Common:* erectile dysfunction *Uncommon:* gynecomastia

Respiratory: *Common:* hoarseness *Uncommon:* rhinorrhea

*adverse reactions may have a life-threatening or fatal outcome.

In addition, the following medically significant adverse reactions were uncommon during clinical trials of NEXAVAR: transient ischemic attack, arrhythmia, thromboembolism, acute renal failure. For these adverse reactions, the causal relationship to NEXAVAR has not been established.

** See specific section in full prescribing information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category D *[see Warnings and Precautions (5.11)].*

8.3 Nursing Mothers It is not known whether sorafenib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from NEXAVAR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Following administration of radiolabeled sorafenib to lactating Wistar rats, approximately 27% of the radioactivity was secreted into the milk. The milk to plasma AUC ratio was approximately 5:1.

8.4 Pediatric Use The safety and effectiveness of NEXAVAR in pediatric patients have not been studied.

Repeat dosing of sorafenib to young and growing dogs resulted in irregular thickening of the femoral growth plate at daily sorafenib doses ≥ 600 mg/m^2 (approximately 0.3 times the AUC at the recommended human dose), hypocellularity of the bone marrow adjoining the growth plate at 200 mg/m^2/day (approximately 0.1 times the AUC at the recommended human dose), and alterations of the dentin composition at 600 mg/m^2/day. Similar effects were not observed in adult dogs when dosed for 4 weeks or less.

8.5 Geriatric Use In total, 59% of HCC patients treated with NEXAVAR were age 65 years or older, and 19% were 75 and older. In total, 32% of RCC patients treated with NEXAVAR were age 65 years or older, and 4% were 75 and older. No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment *In vitro* and *in vivo* data indicate that sorafenib is primarily metabolized by the liver. Comparison of data across studies suggests that patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment have sorafenib AUCs that may be 23- 65% lower than subjects with normal hepatic function. Systemic exposure and safety data were comparable in HCC patients with Child-Pugh A and B hepatic impairment. NEXAVAR has not been studied in patients with Child-Pugh C hepatic impairment *[see Warnings and Precautions (5.12) and Clinical Pharmacology (12.3)].*

8.7 Patients with Renal Impairment NEXAVAR has not been studied in patients undergoing dialysis. No dosage adjustment is necessary when administering NEXAVAR to patients with mild, moderate or severe renal impairment not undergoing dialysis *[see Clinical Pharmacology (12.3)].*

Monitoring of fluid balance and electrolytes in patients at risk of renal dysfunction is advised.

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COMMENTARY

A NURSE'S PERSPECTIVE

Changes, Choices, and Challenges

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A relatively rare cancer, renal cell carcinoma (RCC) is often diagnosed at late stages or progresses after primary therapy. The majority of RCC patients seen in a busy medical oncology office are of these categories. The therapeutic options for the stage IV population have changed and are expanding as a result of several clinical trials.

These changes are welcome for both seasoned and newer nurses, providing choices that are improving outcomes and allow for greater optimism when speaking with patients about treatment options. Nurses at an advanced level will take an active role in discussing treatment options with patients. All nurses, however, can benefit from knowing and anticipating the adverse events expected or likely to occur with these therapies. Many events may have been underreported in clinical trials, as they seem to occur more often in clinical practice.

There is growing evidence that sunitinib, sorafenib, and temsirolimus can have an effect on thyroid function. Thus, baseline laboratory evaluation should include thyroid evaluation with follow-up monitoring of thyroid-stimulating hormone during therapy. As with other treatment considerations, the use of targeted therapies should include the investigations of body system functions and comorbid conditions. Age alone, should not negate their use.

Whatever their level in practice or experience, nurses "own" the management of side effects. It is our responsibility to address and incorporate into a plan of care strategies that allow for quality of life for patients while they go through their various treatment modalities. There should be few surprises.

Understanding the possible side effects provides a framework for discussion. This understanding can also facilitate the development of assessment tools and management guidelines. It is the responsibility of nurses to accept the challenges of managing side effects: know what they are, know when they will occur, know what evidence there is on treatment strategies.

Research is being conducted on prophylactic and ongoing treatment of anticipated toxicities with targeted therapies. For example, Lacouture and colleagues at Northwestern University, Chicago, have published recommendations on skin care issues.[1] This information will allow a more thorough treatment plan, when implementing new therapies for advanced renal cancer. Other research is ongoing. Nurses will take an active part in bringing the evidence to the bedside.

Reference

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Oral Mucositis: The Challenging Issues Facing Oncology Clinicians

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The terms stomatitis and oral mucositis (OM) are used interchangeably in the literature. Although the clinical appearance may be the same for both, the actual processes are different. OM is the inflammation of the oral mucosa, ranging from erythema to ulcerations caused either by radiation and/or chemotherapy (CT).[1] Broader in scope, stomatitis refers to any inflammatory condition of oral tissues (mucosa, dentition, and periodontium) and infections of oral tissues (gingivitis, glossitis). Hence, the defining features of stomatitis encompass OM.[2,3]

OM is one of the challenging symptoms facing oncology clinicians in practice today, but there is no rapid turnover of information. During the National Comprehensive Cancer Network (NCCN) 2008 Annual Conference on Clinical Practice Guidelines and Quality Cancer Care, OM emerged as a topic of interest. Affecting at least 400,000 cancer patients annually, OM is a debilitating side effect, complicated by its dependence on type and dosing of CT regimen and irradiation of the head and neck.[4] Comments by Mark Schattner, MD, a member of the NCCN Task Force on Prevention and Management of Mucositis in Cancer Care, highlighted the major implications of OM. He cited six potential issues: nutritional problems, systemic infections, increased morbidity, increased emergency department visits with longer hospitalization stays, increased medical costs, and possible dose reductions with its corollary diminished response.[5]

"Affecting at least 400,000 cancer patients annually, OM is a debilitating side effect."

Discussions continue to surround prevention, anticipation, management, and patient education. This article reviews the current research regarding these areas, along with documentation strategies. Selected current clinical trials are reviewed, and the barriers that oncology clinicians face in delivering care are discussed.

Prevention strategies

Dental evaluation. The first step in prevention of OM includes a complete oral health examination by a dentist familiar with the oral side effects of anticancer treatments. The dentist can identify and treat teeth at risk for infection or decay to avoid problems during and after radiation and CT. In an attempt to prevent OM, fluoride treatments also should be initiated by the dental provider. Concurrently with the dental examination, patients should be instructed to use a soft-bristled toothbrush and dental floss to remove plaque and debris. Additional preventive techniques cited in the literature include smoking cessation, avoiding alcohol, and good nutrition.[6-9] The best place to begin patient education would be in the dental office, closely followed by a visit to the oncology interdisciplinary team.

Fluoride products. Although not evaluated in clinical trials side by side, topical fluorides frequently are used to induce fluoride incorporation into tooth enamel and dentin. Topical fluorides can be in the form of gels, rinses, vacuum-formed vinyl splints filled with fluoride gels, and varnishes. Any of these treatments will reduce oral bacteria.[10]

Calcium and phosphate rinses. Calcium and phosphate ions are crucial in maintaining the oral health of patients who are receiving oncology treatments.[11] At the 2008 Oncology Nursing Society Advance Practice Conference, Haas and Mercedes presented data from a large multisite, open-label, observational registry on use of a supersaturated calcium and phosphate oral rinse (Caphasol) in radiation and chemotherapy settings.[12] The registry investigated the dosing of and compliance with the rinse, the satisfaction levels of physicians and patients, and monitoring treatment delays. Secondary objectives assessed were OM frequency, duration, and severity according to the National Cancer Institute (NCI) common toxicity scales. The rinse was begun at the initiation of treatment with high-dose radiation and CT agents having high risk of causing OM. The trial of 218 patients from 26 sites consisted of 140 patients who received CT alone and 78 patients who received chemotherapy in combination with radiation (CT/RT).

Overall, patients rinsed with the solution at least once a day (96% patients), an average of four times a day among CT patients, and an average of at least five times a day among CT/RT patients. Twelve patients stopped using the oral rinse, nine for reasons unrelated to the rinse, two for their experience with bad taste, and one for nausea induced by swishing with the rinse.

Global physician and patient satisfaction rates were high within the CT group (75% excellent ratings by physicians and 80% very satisfied ratings by the patients) and the CT/RT group (81%, 82%, respectively). Of the CT patients, 93% experienced clinical NCI grade 0-1 OM, as compared with 54% of the CT/RT patients. The majority of CT patients experienced none-to-mild functional OM (97%), as compared with 48% by CT/RT patients. CT/RT patients experienced more grade 3 dysphagia and pain (23%, 14%, respectively), as compared with CT patients (1%, 1%, respectively). No groups reached grade 4 in regard to dysphagia and pain. The researchers concluded that the use of this electrolyte solution was beneficial to patients.

"The best place to begin patient education would be in the dental office, closely followed by a visit to the oncology interdisciplinary team."

Palifermin. Studies of palifermin in hematologic cancers have shown this agent beneficial in treating OM,[13,14] and its use in solid tumors is now being discussed.[17] At the American Society for Therapeutic Radiology and Oncology (ASTRO) 2008 conference, Le and colleagues presented their findings using palifermin in patients with locally advanced head and neck cancer treated with chemoradiotherapy.[15] This phase 3, multinational, randomized, double-blind, placebo-controlled study enrolled 188 patients to either intravenous (IV) palifermin or placebo 3 days before the initiation of concurrent cisplatin and radiation and once a week thereafter for 7 weeks.

The incidence of World Health Organization (WHO) grade 3/4 recombinant human keratinocyte growth factor was significantly lower in the group given IV palifermin (54% vs 69%, $P = .041$). Median time to onset of severe OM was 47 days; duration of severe OM was 5 days; and development of grade 2 or higher xerostomia was 67% among patients given palifermin (placebo onset time 35 days, duration 26 days, and 80% of patients developed xerostomia). The researchers concluded that palifermin was effective in reducing severe OM.

Another clinical trial presented at the ASTRO conference in 2008 was conducted by Lee and colleagues, who investigated palifermin in head and neck cancer patients receiving radiotherapy with or without CT.[16] In this phase 2 study, 113 patients from six institutions were divided into three groups, each of which was receiving radiation therapy with conventional fractionation. The researchers found that palifermin, administered as a spray twice a day, showed significant reduction in the incidence of severe OM using the Radiation Therapy Oncology Group (RTOG) scale (63% palifermin vs 34% control, $P = .0227$).

Glutamine. Glutamine is a nonprescription supplement.[17] In early studies, oral glutamine was found to protect animals from the toxic effects of abdominal radiation and methotrexate-induced CT. Although not regulated by the US Food and Drug Administration (FDA), many medical and radiation oncologists, oncology nurses, and dieticians continue to prescribe the supplement to prevent OM.

An investigational oral glutamine suspension shows promising results. In a randomized, placebo-controlled clinical trial, Peterson and associates evaluated 326 breast cancer patients receiving anthracycline-based CT.[18] Compared with placebo, the suspension significantly reduced the incidence of grade 3 OM using the WHO grading scale (1.2% suspension vs 6.7% placebo; $P = .005$). This trial also revealed a lower-than-expected OM rate when crossing over from cycle 1 during which patients received the suspension to cycle 2 when patients received placebo. The carryover effect was significant ($P = .027$).

Benzydamine HCl. Despite several clinical trials, benzydamine HCl is approved only for use in Europe. Benzydamine is a nonsteroidal drug, with analgesic, anesthetic, antiinflammatory, and antimicrobial properties.[19]

Studies have shown benefit in preventing OM when patients used benzydamine while receiving moderate doses of radiation (50 Gy).[3,20]

Previous studies provide evidence demonstrating the effectiveness of benzydamine, but a recent study by Putwatana and colleagues from Mahidol University, Bangkok, Thailand, reported less efficacy when compared with glycerin payayor (a Thai-prepared herbal product).[21] Sixty patients were randomized to two treatment arms and given either glycerin payayor dripped into the mouth or benzydamine used as a mouth rinse. Comparisons were performed in relationship to onset of OM, pain, severity, xerostomia, treatment delays, patient satisfaction, and body weight. Significantly higher patient satisfaction and body weight were seen in the payayor group. The researchers concluded that payayor prevented or relieved radiation-induced OM better than benzydamine based on satisfaction and body weight.

Table 1. Nonprescription Products for Oral Care

Side effects	Available products
Dry mouth	Oasis rinse, spray
	Orajel gel, spray, toothpaste
	OraMoist time-released dry mouth discs
	Biotène rinse, spray, toothpaste, gum, liquid moisturizer
	Thayers Natural Remedies spray, lozenges
	Salivart spray
	BetaCell rinse
	MedOral spray
	Moi-Stir moisturizer
	GC Dry Mouth Gel
	Rain dry mouth spray
	Glycerin (mix ¼ tsp in 8 oz of water, swish)
Taste changes	Zinc (18 mg-45 mg)
Dental caries (prevention)	Mouthwashes: Perox-A-Mint (contains no alcohol), Biotène antibacterial
	Fluoride toothpastes: Biotène, Gel-Kam, PreviDent

Anticipated side effects

Erythematous OM generally begins to appear 7 to 10 days after initiation of high-dose cancer therapy.[22] Oncology clinicians, whether in CT or radiation settings, should be alert to potential CT agents or radiotherapy with a high risk of causing OM in patients. Increased toxicity can be expected in patients when receiving combined chemoradiation. Knowledge of when to expect the physical signs of OM will be important in assessments, patient education, and intervention strategies.

Chemotherapy. Depending on the therapeutic agent, CT-induced OM is dose dependent; the severity of which depends on treatment schedule. Possible offending agents would include antimetabolites, anthracyclines, and taxanes.[23] Generally, patients can expect CT-induced OM to begin 4 to 5 days after treatment and for it to last at least 1 week but no longer than 3 weeks.[24]

Radiation therapy. With standard daily radiation treatment of 2.0 Gy, mucosal changes occur within the first week.[25] Factors that influence the degree and severity of OM are radiation source, cumulative dose, dose intensity, and volume of irradiated mucosa. OM becomes visible within 2 to 3 weeks after starting radiation in head and neck cancer patients. OM can intensify with induction or concurrent CT, as well as ongoing use of tobacco, ingestion of alcohol, and poor nutritional status. All of these factors can slow mucosal recovery.

Management

At the 2008 ASTRO annual meeting, Xu and colleagues quantified healthcare personnel time spent in managing OM.[26] Experienced physicians and registered nurses (n = 101), working in radiation oncology with head and neck cancer patients, responded to a Web-based survey. Physicians reported spending 7.2 hours per patient during radiation therapy, while nurses spent considerably more time, 12.1 hours total during the course of radiation treatments. The researchers concluded that estimates of time spent caring for patients who developed OM was substantial and more emphasis on prevention strategies should be a priority for healthcare professionals.

Practices for managing OM have not changed in recent years. Normal saline (1 teaspoon of table salt added to 32 ounces of water) remains one of the mainstays of therapy. Experts agree that normal saline (either refrigerated or room temperature) provides oral comfort.[22,27,28] If patients begin to develop thick, ropey secretions, sodium bicarbonate (1-2 teaspoons per quart of normal saline) can be added to help remove secretions, sooth the mucosa, and normalize pH of the oral cavity.[25] Today, the use of hydrogen peroxide rinses are discouraged in the presence of OM because of the damage to fibroblasts and keratinocytes that can cause delay in wound healing.[29,30]

Topical anesthetics also relieve OM pain; however, they neither protect the integrity nor hasten the recovery of the oral mucosa. Unfortunately, there is no standardization between prepared mixtures. Coating agents (antacids) are frequently added to 2% viscous lidocaine, diphenhydramine solution, or dyclonine rinses. The proportions and ingredients can differ between providers and institutions. When topical anesthetics become ineffective, systemic analgesics should be prescribed. Short-acting narcotics are the initial choice, followed by extended-release, long-acting narcotics. The implementation of the WHO step approach to pain management is preferred; however, most OM patients will require starting with narcotics rather than nonsteroidal agents.

Once healed from acute OM, patients may experience other long-lasting problems: dry mouth, taste changes, and dental caries. The healthcare team can assist patients in maintaining oral health after treatment. Products that can alleviate dry mouth, help with taste changes, and prevent future dental caries can be purchased over-the-counter (Table 1). In general, clinicians should follow and monitor patients closely after completing therapy to ensure pain is controlled, healing continues, and education about the long-term effects of cancer therapies has begun.

Patient education

The close working relationships that oncology healthcare professionals form with their patients enable them to fulfill important roles as educators. These professionals should inform patients about expected side effects and their timing and also offer supportive care measures. After review of the patient's history and initial patient assessment, the educational plan should be inclusive of relief measures for oral discomfort, dental hygiene needs, and any nutritional issues (loss of weight, hypogeusia, dysphagia). After each treatment visit, a clinician should examine for presence of OM and other oral problems to further educate about prevention or management of complications (oral candidiasis, bleeding, acute xerostomia).

Documentation

In their third revision, the NCI has developed an assessment documentation tool for OM. Their scale, Common Terminology Criteria for Adverse Events, separates OM into clinical and functional ratings.[31] This update distinguishes between the functional abilities and the clinical assessment of OM. Clinical grades 1 and 2 are less severe (erythema to noncontiguous patches of pseudomembranous reactions) than higher grades 3 and 4, which represent confluent pseudomembranous reactions to deep ulcerations or possibly necrosis. Functional grades rate the patients' ability to eat a normal diet and swallow and hydrate and whether the disease has become life-threatening (grades 0-5).

Other available assessment instruments are the WHO Oral Toxicity Scale, the Oral Assessment Guide, the RTOG and European Organization for Research and Treatment of Cancer Scale, the McDibbs Mouth Assessment, and the Oral Mucositis Assessment Scale. These tools differ from each other in content and ratings of OM. For continuity between assessments, clinicians should select one tool to achieve consistency at their institution.

Clinical trials

Clinical trials provide an excellent opportunity for patients who face OM as a result of their therapy to enroll in a study that could prevent or manage their side effects. Whether at clinical rounds, interdisciplinary tumor boards, or one-on-one interactions with patients, oncology team members can encourage patients to participate in clinical studies.

Today, more patients are searching online for supportive care studies and are becoming more knowledgeable about potential beneficial research. MedLine Plus, a service of the US National Library of Medicine and the National Institutes of Health, has an excellent patient tutorial about enrolling in clinical trials (www.nlm.nih.gov/medlineplus/tutorials/cancerclinicaltrials/htm/index.htm). A site produced by the National Library of Medicine (www.clinicaltrials.gov) provides a database of current clinical research studies for patients, family members, and the public. The NCI Clinical Trials Resources and Physician Data Query (PDQ) (www.cancer.gov/clinicaltrials) also offers searches, results of clinical trials, and educational materials for patients.

Cochrane Reviews are intended to assist oncology providers in clinical decision making and developing an evidence-based approach to managing OM. Worthington and colleagues discussed their findings on the effectiveness of prophylactic agents for OM in cancer patients.[32] Of 565 reviewed studies, 288 were excluded because of lack of information on OM. Of the remaining studies, only 89 had pertinent prevention information on a total of 7523 randomized patients. The researchers evaluated 33 interventions (Table 2).[32] Although the strength of the evidence was variable, several of the interventions were found to have benefit in preventing or reducing OM. Furthermore, the re-

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Table 2. Interventions for Preventing Oral Mucositis in Patients Receiving Cancer Treatment

Possible interventions reviewed	Interventions with > 1 meta-analysis showing benefit	Intervention with 1 study showing benefit
Acyclovir, allopurinol mouth rinse, aloe vera, antibiotic pastille or paste, benzydamine, beta carotene, calcium phosphate, chamomile, Chinese medicine, chlorhexidine, etoposide, folinic acid, glutamine, granulocyte-macrophage colony-stimulating factor, histamine gel, honey, hydrolytic enzymes, ice chips, iseganan, keratinocyte growth factors, misonidazole, piolcarpine, pentoxifylline, povidone, prednisone, propantheline bromide anticholinergics, prostaglandin, sucralfate, systemic antibiotic clarithromycin, traumeel, zinc sulphate	Amifostine (RR = 0.95), Chinese medicine (RR = 0.44), hydrolytic enzymes (RR = 0.52), ice chips (RR = 0.64)	Benzydamine, calcium phosphate, etoposide bolus, honey, iseganan, oral care, zinc sulphate

RR indicates risk ratio (calculated using random-effects models).
Source: Reference 32.

searchers identified the need for better well-designed studies that would enroll sufficient numbers to analyze by subgroups (type of disease and/or CT agents).

Another Cochrane Review focused on treatment of OM in the setting of CT and radiation therapy.[33] Clarkson and colleagues found four agents that improve symptoms of OM, one agent that eradicates OM, and several agents that are not effective (Table 3).[33] Additionally, patient-controlled analgesia pumps were compared with continuous infusion pumps, and no statistical difference was found in controlling patients' OM pain.

Barriers to care

The lack of standardized protocols from institution to institution complicates the management of OM. While guidelines generally should include atraumatically cleansing the oral mucosa (soft-bristled toothbrush, fluoride toothpaste, and nonastringent mouthwash), lubricating lips and oral tissues, and relieving pain and inflammation, healthcare providers and patients still follow different protocols. Implementing a stepped approach would be preferred. Begin with both bland rinsing for cleansing and a supersaturated electrolyte oral rinse. Go on to topical anesthetics and mucosal coating agents when OM begins to become painful. Proceed to pain-relieving narcotics when appropriate. Oncology clinicians can develop evidence-based protocols for patients and the interdisciplinary team by utilizing resources from the Oncology Nursing Society Putting Evidence into Practice card, Managing Oral Mucositis.[34]

Aside from the lack of treatment standardization, patient compliance/adherence with dental care can be an issue at the beginning of, during, or after therapy. Adherence to a regular oral regimen has shown to impact duration and severity of OM.[3,35] Historically, patients with head and neck cancer typically consume alcohol and use tobacco products. Head and neck cancer patients are frequently men, have lower socioeconomic status, and are less health conscious.[36] When patients are not compliant with performing oral care three to four times a day every 1 to 4 hours and at bedtime, it can complicate therapy and impede healing. After therapy is complete and OM begins to heal, dental aftercare recommendations may not be followed consistently. Oncology nurses should take responsibility for ensuring that follow-up appointments with dentists are arranged, fluoride trays are utilized daily, and high intake of sugars are avoided.

Documenting various stages of OM can be complicated. Numerous tools are available, which makes it difficult to compare institutional outcomes to those in the literature or at other institutions. Each member of the oncology healthcare team may want to use a familiar instrument, but providers must reach an agreement and be consistent in documentation.

Conclusions

OM is a direct effect of cytotoxic agents and/or ionizing radiation and represents a challenge for oncology care providers. The treatment side effects (pain, odynodysphagia, dysgeusia, dehydration, and possibly malnutrition) interfere with the patient's quality of life, can have significant morbidity, may demand treatment delays, can increase therapeutic expenses, and add additional time to patient care. Several steps can be taken prophylactically to reduce OM severity, manage the symptoms using nonpharmaceutical and pharmaceutical approaches, and offer patient teaching and support.

Table 3. Interventions for Treating Oral Mucositis for Patients Receiving Cancer Care

Interventions showing improvement benefit	Intervention showing eradicating benefit	Interventions showing no benefit
Allopurinol (RR = 3.33), granulocyte-macrophage colony-stimulating factor (RR = 4.23), immunoglobulin (RR = 1.81), human placental extract (RR = 4.50)	Allopurinol (RR = 19.0)	Benzydamine HCl, sucralfate, tetrachloro decaoxide, chlorhexidine and "magic" (lidocaine solution, diphenhydramine hydrochloride, and aluminum hydroxide suspension)

RR indicates risk ratio (calculated using random-effects models).
Source: Reference 33.

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[1] Mouridsen HT et al. Treatment of anthracycline extravasation with savene (dexrazoxane). Results from two prospective clinical multicentre studies. Ann Oncol 2007; 18:546-550.

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No differences in safety or efficacy were observed between older and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older patients has been observed. This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. **Adverse reactions:** Adverse reactions of nausea/vomiting, diarrhea, stomatitis, bone marrow suppression (neutropenia, thrombocytopenia), altered liver function (increased AST/ALT), and infusion site burning have been observed. These adverse reactions have been reversible.

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Extravasation: Assessment and Treatment

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Can you come? I think I have an extravasation." I have had these calls throughout my career and seen the concerned look on the faces of the nurse, patient, and family. The Oncology Nursing Society (ONS) and the Infusion Nurses Society have both created guidelines for the prevention, assessment, and treatment of infiltration and extravasation. Nurses involved in infusion therapy in the oncology setting are generally familiar with these guidelines. No matter how careful the nurse and the preventive measures undertaken, however, the potential for infiltration and extravasation exists. Dexrazoxane for injection is a relatively new treatment for anthracycline extravasations, packaged in an emergency toolkit,[1] which has been added to the new 2009 ONS guidelines.

What is extravasation?

Extravasation refers to the escape of a chemotherapy drug into the extravascular space, either by leakage from a vessel or by direct infiltration. The overall incidence of extravasation injuries from vesicant chemotherapy administration has been reported to range from 1% to approximately 6%. Local symptoms (eg, pain, erythema, swelling) are usual, but it is difficult to differentiate these symptoms as a flare reaction or a vesicant extravasation. Extravasation can be extremely debilitating and disabling and requires immediate attention. If the extravasation is significant, necrosis may occur. A lesion can heal slowly, or not at all, and possibly result in a long-term or permanent disability. Increasing awareness of the complications of extravasation and improved infusion techniques among the healthcare community may lead to a lower incidence.

The Infusion Nurses Society standards define infiltration and extravasation as[2]:

- **Infiltration**—inadvertent administration of nonvesicant medication of solution into the surrounding tissue
- **Extravasation**—inadvertent administration of vesicant medication or solution into the surrounding tissue.

Extravasation injuries have been described frequently in the oncology literature, and education on how to prevent and treat cancer chemotherapy extravasation is common among oncology staff. It is important to note, however, that injury can also occur in the nononcology setting. Reports of significant patient morbidity have been related to extravasation of a variety of vasoconstrictive substances and hyperosmolar and/or concentrated electrolyte solutions, such as potassium chloride, parenteral nutrition, sodium bicarbonate, norepinephrine, and phenytoin.[2]

In a review of systemic infusion chemotherapeutic agents, extravasations were reported in 0.1% to 6.5% of cases.[2] Extravasation may or may not lead to tissue injury, and the potential for tissue injury is related to the vesicant/irritant properties of the solution (eg, cytotoxicity, pH, and osmolality), concentration of the drug, volume extravasated, and the affected tissue/anatomical structure location. The classification of nonvesicant, irritant, or vesicant is based on the drug's potential to cause local tissue injury (Table 1).

The potential for chemotherapeutic drugs to cause tissue damage can be classified further according to whether the agents bind to the nucleic acids in DNA. For example, vinca alkaloids or epipodophylotoxins do not bind to DNA, allowing these agents to be metabolized and more easily neutralized. The degree of tissue damage will be determined by the ability of the patient to clear the agent metabolically, which depends on the concentration and volume. In general, extravasations of these drugs can be mildly to moderately painful, tend to remain localized, and improve over time. Conversely, anthracyclines bind to the nucleic acids in DNA. Upon initial absorption into local tissue cells, direct cell death and endocytolysis is induced. The released cellular contents allow surrounding cells to uptake the anthracycline, leading to progressive tissue destruction through a cycle of cellular destruction and surrounding cell drug uptake. Therefore, anthracyclines can remain in the surrounding tissue for months.[2-5]

Table 1. Infiltration and Extravasation Drug Classifications

Classification of nonvesicant, irritant, or vesicant is based on potential to cause local tissue injury.

- **Nonvesicant drugs**—If extravasated, these drugs will rarely produce tissue necrosis.
- **Irritant drugs**—These drugs can cause pain at the injection site or along the vein tract, with or without inflammation. Local tissue injury can occur with large amounts of extravasated, concentrated drug solution.
- **Vesicant drugs**—On inadvertent extravasation, these drugs can cause the formation of blisters, tissue destruction, and necrosis.

Source: Reference 2.

"No matter how careful the nurse and the preventive measures undertaken, however, the potential for infiltration and extravasation exists."

Table 2 lists some of the agents commonly used for chemotherapy. As mentioned previously, chemotherapy agents are categorized into three categories: vesicants, irritants, and nonvesicants. In addition, these agents can be classified according to their DNA- or non-DNA–binding properties. Nonneoplastic solutions are listed as irritants, but these solutions have vesicant potential depending on their chemical properties, concentration, and volume of extravasation. Vesicants or irritants manifest as local signs and symptoms, but these agents may cause local tissue death or necrosis while irritants do not.

Location of the access device, drug concentration, and amount of vesicant leaking into the local area play factors in the severity of the extravasation.[5,6] Functional muscle damage and changes can occur within a few hours, and nerve damage can take place within 24 hours.[7] Anthracyclines, mechlorethamine, and vinca alkaloids usually cause immediate pain. Pain from other agents (eg, mitomycin C) may not become apparent until a few days or a week later. Other examples of problematic agents are oxaliplatin (reported to have vesicant properties), cisplatin (vesicant potential if greater than 20 mL of 0.5 mg/mL concentration extravasates), and mitroxantrone.

Prevention of extravasation

Prevention of extravasation is always the goal. Peripheral intravenous (IV) catheters should be established in smooth pliable veins, preferably in the forearm, taking care to avoid areas of flexion or apparent injury, small fragile veins, areas of altered venous return, and lower extremities. After the venous access is established peripherally or centrally, blood return and patency should be verified before and during administration.

Signs and symptoms of extravasation

Little or no blood return from the IV device being used for chemotherapy is one possible indication of infiltration/extravasation. Others are if the IV fluid rate decreases or stops completely, or a pump alarm sounds, indicating an occlusion. These signs should be taken seriously, and the peripheral or central chemotherapy-infusion site should be checked for symptoms. Swelling at the site is a very common symptom and usually the first to be observed. Other signs and symptoms of a vesicant extravasation are redness and discomfort. However, not all patients experience symptoms, and loss of blood return may be the only indication.

In the case of central venous access, further evaluation using radiographs with dye studies may be indicated to determine line placement and integrity before further use. Upon determination of an extravasation, the infusion should be discontinued, and the catheter disconnected. Aspiration of residual solution at the site should be attempted, the peripheral IV or port needle should be removed, the symptoms assessed, the physician or advanced practice nurse notified, and appropriate management measures initiated.[5] Blistering, ulceration, and tissue necrosis may appear quickly or within a few days to a week after the extravasation.[5,8] Ultraviolet light and fluorescein may help define necrotic tissue with doxorubicin extravasation.[9] Doxorubicin extravasation

tissue injury has been specifically noted to progress slowly, with increasing severity over several weeks but without the typical healing pattern.[10] Early surgery with debridement followed by skin grafts for significant vesicant extravasation has been recommended to remove necrosis, but can cause permanent disfiguration.

Treatment of extravasation

Data on treatment of vesicant anticancer drug extravasations have been largely empirically based, have shown an inconsistent frequency in clinical events, and have been based mainly on animal models. Conventional nonpharmacologic and pharmacologic therapies have had limited efficacy. Nonpharmacologic therapies include topical cooling, saline lavage and suction, hyperbaric oxygen, and topical negative pressure. ONS guidelines recommend stopping the infusion and applying warm or cold compresses, depending on the type of medication that has escaped into the subcutaneous tissue.[11] For example, cold compresses or ice packs are appropriate for anthracycline, whereas heated compresses are appropriate for plant alkaloids. The application of heat is believed to increase drug distribution through vasodilation, thereby decreasing the accumulation of the drug in the local tissue. The vasoconstriction associated with the application of cold limits the spread of the drug by localizing it.[11]

Pharmacologic therapies reported in the literature include the administration/application of growth factors, dimethyl sulfoxide (DMSO), hydrocortisone, hyaluronidase, ginkgo biloba extract, alpha-tocopherol (vitamin E), cimetidine, diphenhydramine, heparin, lidocaine, and N-acetylcysteine. DMSO has only shown to be effective in a 99% medical grade, which is unavailable in the United States. Corticosteroids, initially thought to be effective against tissue injury by decreasing inflammatory effects, have not been shown to be beneficial in most circumstances and may actually be harmful. However, some studies have reported a benefit in oxaliplatin extravasation. Sodium bicarbonate was thought to neutralize the agent but has been shown not to be active and may, in fact, be a vesicant.[4,12-15] Only two compounds have been approved by the US Food and Drug Administration (FDA) for the treatment of vesicant extravasations. Sodium thiosulfate/mechlorethamine and dexrazoxane.

Dexrazoxane has a unique dual mechanism of action. It inhibits DNA topoisomerase II, the target of anthracycline chemotherapy, and binds to DNA topoisomerase II at a different step in the catalytic cycle.[16-18] This locks the enzyme in a form that is no longer affected by the anthracycline. Dexrazoxane also acts as an iron chelator and minimizes oxidative damage caused by formation of anthracycline–iron complexes.[19,20] Dexrazoxane is then rapidly metabolized within the cell to chelate iron and limits anthracycline-mediated oxidative injury.

Several clinical trials have been performed to determine the safety and efficacy of dexrazoxane. Two internantional, single-arm, multicenter clinical studies were performed.[21] In the TT01 study, none of the 19 patients required surgical intervention nor had serious late conditions as a result of the extravasation. In the TT02 study, one of the 38 patients required surgery for removal of dead tissue. Thirteen patients were treated for other conditions as a result of the extravasation, including pain and atrophy. The anthracyclines extravasated included epirubicin, doxorubicin, daunorubicin, and pegylated liposomal doxorubicin. The sites of extravasation included the forearm (63%), hand (21%), antecubital area (11%), and central venous access device (5%). Patients were administered dexrazoxane IV infusions of 1000 mg/m^2 or 500 mg/m^2 for 1 to 2 hours once daily for 3 days, at 24 and 48 hours. Primary efficacy was defined as debridement surgery not required. Local aspiration of extravasation was recommended. Cooling was permitted 15 minutes before treatment. No steroid or DMSO treatment was permitted. These studies showed dexrazoxane to have 98% overall efficacy in preventing necrosis that required surgery.[21]

Dexrazoxane for injection is currently the only FDA-approved treatment specifically for anthracycline extravasations. Treatment should be initiated within 6 hours of the extravasation and continued daily around the same time of day for a total of 3 days. The product is sold in an emergency toolkit that contains everything needed for the complete 3-day treatment: 10 vials of dexrazoxane powder (500 mg of dexrazoxane hydrochloride/vial) and 10 vials of dexrazoxane diluent solution. Upon reconstitution, each vial contains a concentration of 10 mg/mL dexrazoxane, which should be infused immediately. Dosage is determined by the patient's body surface area. On days 1 and 2, the patient should receive 1000 mg/m^2, and on day 3 a dose of 500 mg/m^2. The daily dose should not exceed 2000 mg/m^2, and the dose should be reduced by 50% if the creatinine clearance is less than 40 mL/min. After the IV catheter is inserted into a large vein located in the opposite extremity, the infusion is administered over 1 to 2 hours. Topical cooling should be removed at least 15 minutes before and during the infusion to enhance perfusion of the affected area.

The most common side effects of dexrazoxane are neutropenia, thrombocytopenia, fever, infusion site pain/phlebitis, and nausea and vomiting. The patient's complete blood count and liver enzyme levels should be monitored because of the potential for transient liver enzyme increases, neutropenia, and thrombocytopenia.[1]

Table 2. Categories of Chemotherapeutic Agents

DNA-binding agents (vesicants)	Non-DNA–binding agents (vesicants)	Nonneoplastic agents (irritants[a])
Anthracycline agents	**Vinca alkaloids**	• Hyperosmotic solutions (eg, parenteral nutrition)
• Doxorubicin[b]	• Vincristine[b]	• Concentrated electrolyte solutions (eg, calcium gluconate)
• Daunorubicin[b]	• Vinblastine[b]	• Agents altering intracellular pH (eg, sodium bicarbonate)
• Epirubicin[b]	• Vindesine[b]	
• Idarubicin[b]	• Vinorelbine[b]	
• Mitoxantrone[b]		
Antitumor antibiotics	**Taxane agents**	• Agents inducing severe vasoconstriction and ischemia
• Mitomycin C[b]	• Paclitaxel	
• Liposomal doxorubicin	• Docetaxel	
• Bleomycin		
Alkylating agents	**Alkylators**	
• Mechlorethamine	• Amsacrine	• Etoposide (VP-16)[b]
• Platinum analogs		• Oxaliplatin[b]
Other anticancer antibiotics		• Cisplatin[b]
• Dactinomycin		
• Mitoxantrone		

[a]Have vesicant potential depending on their chemical properties, concentration, and volume of extravasation.
[b]Has been shown to evoke extravasation more frequently than the other agents listed.
Sources: References 3 and 4.

Conclusion

The oncology infusion nurse is responsible for the safe administration of irritant and vesicant infusates. Prevention of extravasations is always the goal but is not always possible. Extravasations can be managed by a variety of pharmacologic and nonpharmacologic methods. Clinical trial data support the use of some agents but not others. Anthracycline extravasations have been particularly difficult to manage because of the drug's DNA-binding capacity. Dexrazoxane, however, has been shown to be highly effective in preventing tissue injury due to anthracycline extravasation. By following the national guidelines for safe administration,[2,7] nurses will be able to minimize potential tissue injury related to extravasations.

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Recent Advances in Diagnosis and Treatment of Breast Cancer

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Fortunately, there continues to be a great deal of ongoing research related to breast cancer; however, keeping up with the latest data can be challenging. At recent annual meetings of the American Society of Clinical Oncology (ASCO), the American Society for Therapeutic Radiation and Oncology (ASTRO), and the Oncology Nursing Society (ONS), as well as the ASCO Breast Cancer Symposium, advances were presented in various areas of breast cancer research, including risk factors, diagnostics, new drugs/regimens, and quality of life/symptom management issues. Some of these newer studies are discussed in this article.

Ongoing research

Breast cancer continues to be the most common cancer (excluding skin cancer) in women and the second leading cause of cancer death in this group. Although final numbers are not yet available for 2008, it was estimated that 182,460 women in the United States would be diagnosed with breast cancer and 40,480 would die of the disease.[1] A disappointing and surprising fact revealed at the ASCO Breast Cancer Symposium was that despite the many advances in the treatment of metastatic breast cancer, there has been no significant improvement in median survival. A retrospective review done at a National Cancer Institute comprehensive cancer center looked at the decades 1985-1994 and 1995-2005. Although median overall survival (OS) tended to improve from 2.4 years to 3.1 years, this improvement was not statistically significant. No advantage in survival regardless of hormone-receptor status was evident.[2]

A large retrospective review of 82,759 patients with breast cancer presented at the ASCO Breast Cancer Symposium suggested that contralateral prophylactic mastectomy in women who are younger (18-49 years of age) and have early-stage estrogen-receptor–negative breast cancer appears to improve breast cancer survival. Older patients, those with advanced disease, and those with hormone-receptor–positive cancer did not receive a significant survival benefit from the surgery.[3] Although prophylactic mastectomy may not improve survival in these women, they still may choose this option to avoid the anxiety of yet another cancer diagnosis and the morbidity and life disruption that accompanies such a diagnosis.

An interesting study presented at ASCO's annual meeting revealed that vitamin D deficiency is common at the time of diagnosis of breast cancer and is associated with higher grade tumors and an increased risk of distant recurrence and death.[4] Thus, testing vitamin D levels in the blood should be considered to ensure a healthy range. More research is needed in this area, including a study to evaluate whether vitamin D repletion would make a difference. Vitamin D supplementation should be done only if levels are low, and patients should be instructed about the dangers of exceeding the recommended dose.

"Vitamin D deficiency is common at the time of diagnosis of breast cancer and is associated with higher grade tumors and an increased risk of distant recurrence and death."

Diagnostics and tumor markers

The use of magnetic resonance imaging (MRI) in women with a diagnosis of breast cancer remains controversial. One study examined trends in mastectomy rates at the Mayo Clinic in Rochester, Minnesota, from 2003 to 2006. During this time period, the researchers found that women who had a preoperative MRI after being diagnosed with breast cancer were more likely to undergo a mastectomy than those who did not. It also was discovered that in the same time period, mastectomy rates increased 12% in women who did not have a preoperative MRI. No other factors, such as the influence of MRI findings, role of family history or genetic testing, and patient or physician preference on decision to have an MRI, were considered.[5] Another retrospective review of 577 patient records showed that women who had a pretreatment MRI had treatment delay and an increased likelihood of mastectomy without improving outcomes. The time from diagnosis to first therapeutic surgery averaged 38 days without MRI and 57 days with MRI (P = .010). Mastectomy was the initial surgical procedure in 19.5% of patients who did not have MRI compared with 27.7% of those who did (P = .024).[6] In a study of 159 women aged 70 years or older, 5.7% were found to have an occult contralateral cancer identified by MRI. This suggests that age should not be a deterrent to MRI, but rather this modality should be a prime consideration for diagnostics in the older population.[7]

"Women who had a pretreatment MRI had treatment delay and an increased likelihood of mastectomy without improving outcomes."

A prospective study evaluating positron-emission tomography used to assess axillary lymph nodes in women having sentinel lymph node biopsy (SLNB) showed that the imaging technique was not sufficiently sensitive to detect positive lymph nodes. Its high positive predictive value in the trial, however, suggests that it could be used in women with large primary tumors to identify those in whom an SLNB could be omitted prior to therapeutic axillary lymph node dissection.[8]

Molecular breast imaging (MBI) gained much attention at the ASCO Breast Cancer Symposium. This technique proved better than mammography in women at high risk for breast cancer who had dense breast tissue. With this imaging device, a radiotracer is administered followed by imaging that requires approximately 10 minutes per view. Only light compression of the breast is needed. Among 940 patients screened with mammography and MBI, cancers were detected in 10 of 13 who had MBI compared with three of 13 for mammography. The recall rate was 7.7% for MBI and 9.4% with mammography. Currently the molecular imaging machine is not commercially available. Future research will focus on comparing it with MRI.[9]

A retrospective review of more than 3100 patients showed that those with triple-negative breast cancer (TN-BC) have a higher risk of developing cerebral metastases (CM) compared with other types of breast cancer. CM occurred earlier in those with TN-BC and displayed a trend for poorer outcome. Oncologists might consider routine central nervous system MRI in TN-BC patients.[10]

The German SUCCESS trial of more than 1500 node-positive and high-risk node-negative patients analyzed the peripheral blood for circulating tumor cells (CTCs) before and after adjuvant taxane-based chemotherapy. The presence of CTCs did not correlate with tumor size, grading, hormonal status, or ERBB2 (formerly HER2 or HER2/*neu*) status of the primary tumor, but with the presence of lymph node metastases (P = .003). Although the presence of CTCs before systemic treatment did not have prognostic relevance for disease-free survival (DFS) or OS, persistence of CTCs after chemotherapy was a significant predictor for both reduced DFS (P = .04) and OS (P = .03). These results suggest a potential role for CTC monitoring in the future. Long-term follow-up is needed as the median follow-up time in this study was only 12 months.[11]

Treatments

Several studies have been investigating the optimal method and duration of radiation therapy to the breast. In women with early-stage breast cancer, partial breast irradiation, using the MammoSite Targeted Radiation Therapy System for 1 week, has proved as effective as standard whole breast radiation in preventing recurrence. These results, based on data from 1400 women with a median follow-up time of 36 months, may prompt more women, who otherwise were unable or unwilling to undergo 5 to 6 weeks of standard radiation therapy, to undergo breast conservation therapy (BCT). Some clinicians, however, may believe more follow-up data are needed before

it becomes standard care.[12]

A study presented at the ONS Annual Congress showed the MammoSite system to be well tolerated with minimal adverse effects. Overall, patients were satisfied with the treatment regimen and cosmetic result. Patients were likely to recommend this treatment to others. Satisfaction remained high at 1 year or longer post-treatment. As expected, the shorter treatment regimen was the determining factor in the patients' selection.[13]

A study from Canada randomized more than 1200 women with node-negative invasive breast cancer to a 3-week course of radiation treatment or the standard 5 weeks. Results after 10 years of follow-up showed that the shorter duration was as effective as the standard course. Although the shorter course has become standard of care in Canada, currently, the course remains 5 to 6 weeks in the United States.[14]

In a 14-year follow-up of more than 1800 patients with ductal carcinoma in situ, it was shown there was no value in the addition of boost radiation therapy in reducing the recurrence of invasive or noninvasive breast cancers for patients with this cancer.[15]

Older women are underrepresented in clinical trials and, therefore, minimal data are available for this population. The CALGB/CTSU 49907 study was designed to compare the efficacy of capecitabine with standard treatment in breast cancer patients aged 65 years or older. Patients (n = 633) were randomized to receive standard treatment doxorubicin/cyclophosphamide; cyclophosphamide, methotrexate, fluorouracil; or capecitabine. The primary end point was relapse-free survival (RFS), defined as locoregional, distant relapse, or death. Median follow-up was 2.4 years. Results showed that standard treatment was superior to capecitabine for both RFS and OS, especially in patients with hormone-receptor–negative tumors.[16]

Women with *ERBB2*-positive metastatic breast cancer that had progressed while on trastuzumab did benefit when trastuzumab was used in conjunction with other agents. In a randomized study, 296 heavily pretreated women with *ERBB2*-positive metastatic breast cancer whose cancer progressed on trastuzumab received either lapatinib alone or in combination with trastuzumab. Results indicated that the combination regimen brought improvement in progression-free survival (PFS), doubled clinical benefit rate, and displayed a trend toward improved OS as compared with lapatinib alone.[17]

A study of 736 women with metastatic breast cancer who were randomized to receive docetaxel and bevacizumab at either 7.5 mg/kg or 15 mg/kg or docetaxel alone showed that both doses of bevacizumab in combination with docetaxel significantly improved PFS and response rate compared with docetaxel alone.[18]

A prospective study examined outcomes in women with *BRCA1/2*-associated breast cancer. They were treated locally with mastectomy versus breast-conserving surgery and radiotherapy. Fifteen-year rates of contralateral breast cancer (CBC) were comparable with and without radiotherapy, suggesting no detectable increase in CBC from scatter radiation therapy. These results are important for *BRCA1/2* carriers with breast cancer when considering options.[19]

Large clinical trials

The Austrian Breast and Colorectal Cancer Study Group examined the efficacy of ovarian suppression using goserelin in combination with anastrozole or tamoxifen with or without zoledronic acid in premenopausal women (n = 1800) with hormone-responsive breast cancer. The addition of zoledronic acid (4 mg every 6 months) to adjuvant endocrine therapy significantly prolonged DFS (by 36%) and RFS (by 35%) compared with adjuvant endocrine therapy alone. There was no significant difference in DFS between tamoxifen and anastrozole. There was a nonsignificant trend favoring the zoledronic acid arm for OS. This large clinical trial demonstrates that the antitumor activity of adjuvant zoledronic acid improves outcomes beyond the effect of endocrine therapy alone.[20]

"Antitumor activity of adjuvant zoledronic acid improves outcomes beyond the effect of endocrine therapy alone."

A study of 236 women with locally advanced breast cancer who received neoadjuvant chemotherapy compared the incidence of locoregional recurrence rate between those undergoing BCT and those receiving mastectomy. Results showed that at a median follow-up time of 58 months, the rate of locoregional recurrence was low and similar for both groups: 5% in the BCT group and 9% in the mastectomy group (P = .32). Overall 5-year survival rates, however, were 90% in the BCT group and 69% in the mastectomy group (P = .01).[21]

Quality of life/symptom management

Many women with breast cancer experience hot flashes as a result of hormonal therapies used in treatment or early menopause due to chemotherapy. Although some medications (eg, venlafaxine, gabapentin, and captopril) may help to reduce hot flashes, alternatives are being studied. One small (n = 47) study randomized patients to receive venlafaxine or acupuncture treatments. Results showed that the two treatments were equally effective for reducing hot flashes, night sweats, and other effects of antiestrogen therapy. Women in the venlafaxine group reported a variety of side effects, including nausea, dry mouth, headache, sleep disturbance, dizziness, vision disturbance, increased blood pressure, fatigue, and anxiety, whereas the acupuncture group reported no treatment-related effects. The acupuncture group stated that they had improvement in energy, clarity of thought, sexual desire, and overall sense of well-being. Women who took venlafaxine had an increase in the number and intensity of hot flashes within 2 weeks of discontinuing drug therapy, whereas women receiving acupuncture did not begin to have an increase in the number or severity of hot flashes for 14 or 15 weeks after treatment.[22]

In premenopausal women who developed osteoporotic fractures due to chemotherapy-induced menopause, zoledronic acid has been shown to increase bone mineral density.[23]

Fertility preservation is another important area being studied in premenopausal women with breast cancer. There is conflicting evidence on the use of gonadotropin-releasing hormone (GnRH) analogs to preserve fertility in women undergoing adjuvant chemotherapy. A study presented at the ASCO annual meeting was the first randomized clinical trial designed to evaluate the benefit of GnRH use during chemotherapy. The results of this small study indicated that the use of GnRH analogs does not appear to preserve menstrual status. Follicular-stimulating hormone levels in patients in whom menstruation has returned was not significantly different in the GnRH arm versus the control arm.[24]

Additional information on the latest in breast cancer diagnostics and treatment options can be found by accessing the web sites of ASCO, ASTRO, and ONS.

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Meetings

MAY 2009

3-6 TEL AVIV, ISRAEL
12th World Congress on Cancer of the Skin 2009
Wccs2009@kenes.com

13-14 WASHINGTON, DC
4th Annual Oncology Economics Forum: Access to Innovative Cancer Therapies in 2009
www.conferagroup.com

May 29-June 2
ORLANDO, FL
2009 ASCO Annual Meeting
www.cancerlearning.com

JUNE 2009

17-20 MIAMI, FL
HOPA 2009: Hematology/Oncology Pharmacy Association 5th Annual Conference
www.hoparx.org

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22-26 KOHALA COAST, HI
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24-26 MADRID, SPAIN
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Reference: 1. RITUXAN® (Rituximab) full prescribing information, Genentech, Inc., 2008.

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