VIEWPOINT
Government health plans always ration care

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CONFERENCE NEWS
Coverage of the 34th Annual ONS Congress continues

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JULY/AUGUST 2009 • VOL. 2, NO. 5 www.theoncologynurse.com

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SUPPORTIVE CARE

Extravasation: Assessment and Treatment

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Oncology Clinical Nurse Specialist, Contra Costa Regional Medical Center, Martinez, California

"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 is and the preventive measures undertaken, however, the potential for infiltration and extravasation exists. Dexrazoxane for injection (Totect®) is a rela-

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ASCO ANNUAL MEETING 2009

Photo courtesy of American Society of Clinical Oncology.

More than 4000 studies were presented at oral and poster sessions during the 45th annual meeting of the American Society of Clinical Oncology. Personalized medicine was the theme of the meeting, held May 29-June 2, 2009, in Orlando, Florida.

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THE PATIENT'S VOICE

Long-term Survivors of Myeloma Discuss the Roles of Nurses During Their Diagnosis and Treatment

Six long-term survivors of multiple myeloma attended the 50th annual meeting of the American Society of Hematology in San Francisco, which was held December 6 through 9, 2008. Their attendance was supported by the International Myeloma Foundation (IMF). After the

Continued on page 14

CONFERENCE NEWS

Nurse Support Program Helps Manage Iron Overload

SAN ANTONIO—Researchers reported that a nurse support program can boost adherence to iron chelation therapy in patients with chronic anemias.

Joan Latsko, MSN, CRNP, OCN, AOCNP, with Western Pennsylvania Cancer Institute in Pittsburgh, Pennsylvania, described results using a nurse support program aimed at improving adherence in patients undergoing treatment with the oral iron chelator deferasirox for iron overload.

"While adherence initially increased with only minor

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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

Genentech BIOONCOLOGY

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 multimodality 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 pretreatment 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

Study	Regimen	Incidence of CHF	
		Herceptin	Control
1 & 2[a]	AC[b]→Paclitaxel+ Herceptin	2% (32/1677)	0.4% (7/1600)
3	Chemo→Herceptin	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

Study	Event	Incidence			
		NYHA I-IV		NYHA III-IV	
		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 (5.2)*]. 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 (.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.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)

	Herceptin				
	Single Agent[a] n = 352	+ 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

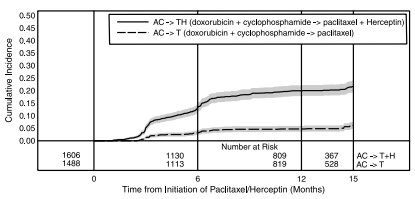
the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF <50% or ≥15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the 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	22.8%	18.3%	11.7%	33.4%	9.2%
(n=1606)	(366)	(294)	(188)	(536)	(148)
AC→T	9.1%	5.4%	2.2%	18.3%	2.4%
(n=1488)	(136)	(81)	(33)	(272)	(36)
Study 3					
Herceptin	8.6%	7.0%	3.8%	22.4%	3.5%
(n=1678)	(144)	(118)	(64)	(376)	(59)
Observation	2.7%	2.0%	1.2%	11.9%	1.2%
(n=1708)	(46)	(35)	(20)	(204)	(21)
Study 4[c]					
TCH	8.5%	5.9%	3.3%	34.5%	6.3%
(n=1056)	(90)	(62)	(35)	(364)	(67)
AC→TH	17%	13.3%	9.8%	44.3%	13.2%
(n=1068)	(182)	(142)	(105)	(473)	(141)
AC→T	9.5%	6.6%	3.3%	34%	5.5%
(n=1050)	(100)	(69)	(35)	(357)	(58)

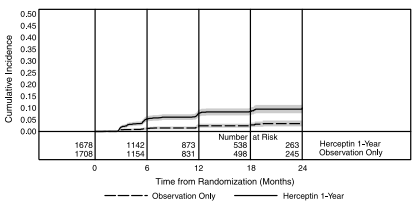
[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization. [b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[c] Study 4 regimens: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



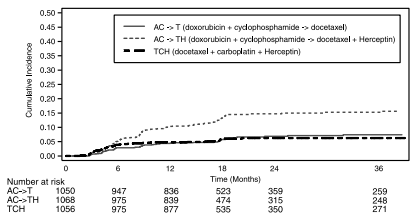
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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 postmarketing 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 postmarketing 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. *Registry* Pregnant women with breast cancer who are using Herceptin are encouraged to enroll in MotHER- the Herceptin Pregnancy Registry: phone 1-800-690-6720. **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 MotHER- the Herceptin Pregnancy Registry [*see Pregnancy*].

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News Notes

News Updates of Relevance to Everyday Oncology Practice

Paying for Cancer Care a Top Fear about the Disease

In a survey commissioned by the Community Oncology Alliance, Americans cited the inability to pay for cancer care among their fears regarding cancer. Sixty-nine percent of Americans fear paying for cancer, the same percent that fears dying of the disease. Only poor quality of life and being in pain are greater fears, with 75% and 72% of Americans, respectively. Other top concerns include being unable to work (61%) and leaving their families in debt (59%). The survey found that to pay for care, 66% of Americans would accept government assistance, 48% would sell their cars, 38% would sell their homes, 44% would borrow the money, 40% would declare bankruptcy, and most disturbing, 33% would discontinue treatment (Community Oncology Alliance. July 8, 2009). Another recent survey found that more than 60% of personal bankruptcies in the United States are related to medical bills (Himmelstein DU, et al. *Am J Med*. 2009 Jun 4. Epub ahead of print). To address patients' financial concerns, the Wellness Community has launched a national education program "Frankly Speaking about Cancer: Coping with the Cost of Care" (www.thewellnesscommunity.org).

Idiopathic Erythroderma Associated with Undiagnosed Cancer

Unexplained erythema may signal possible underlying malignancies, according to a study presented at the International Congress of Dermatology. Thng and colleagues reviewed records of 218 patients evaluated for erythroderma from 2001 to 2005 in Singapore. They found cancer in more than 20% of cases of idiopathic erythroderma: 18% with visceral malignancies and 4.6% who developed cutaneous T-cell lymphoma later in the course of follow-up. The researchers found that compared with age-standardized cases in the Singapore Cancer Registry, patients with idiopathic erythroderma had more than triple the risk of visceral malignancy, and they therefore recommend that patients be closely followed and reevaluated for malignancy even if the initial investigation is negative (ICD 2009; Abstract 195).

New Biomarker for Ovarian Cancer

Brown University researchers have identified a novel diagnostic biomarker—human epididymal protein 4 (HE4)—that can be used to monitor for early-stage ovarian cancer. Data presented by Richard Moore, MD, at the annual meeting of the American Association for Clinical Chemistry indicates that combining the HE4 test with the CA125 test can increase sensitivity for detecting early-stage epithelial ovarian cancer.

A Letter from the Editor

BETH FAIMAN, RN, MSN, APRN, BC, AOCN

EDITOR-IN-CHIEF

Personalized medicine was the theme of the 2009 annual meeting of the American Society of Clinical Oncology (and the topic of the presidential address by Richard Schilsky, MD). He said, "delivering the right care to the right patient at the right time is becoming a universal and realizable goal." Another major theme discussed at numerous sessions was the cost of healthcare and how proposed healthcare reforms might affect oncology practices and patients with cancer.

The two themes are interrelated. Using genetic and other information to identify patients most likely to benefit from certain therapies will not only lead to better clinical outcomes but also to more judicious use of limited resources, which can help contain costs. For example, testing for *KRAS* mutations in patients with metastatic colorectal cancer to select candidates for anti–epidermal growth factor monoclonal antibody treatment will save patients and the healthcare system from paying for drugs that will not be effective for their particular type of cancer.

When it comes to making decisions about costly cancer care, Schilsky said, "Oncologists need to be part of the conversation and the solution." Another speaker, Eric Winer, MD, of Dana-Farber Cancer Institute, said, "We have to pay more attention to the cost of care…. If we don't police ourselves, then we are going to be told how to do it by external sources."

What all this means for nurses is that now, in addition to our clinical responsibilities, we have to think about the cost of cancer treatments, be prepared to talk to our patients about the financial aspects of their care, and participate in the discussion about how shortcomings in the current healthcare system can be remedied without adversely affecting the quality of cancer care. To play an active role in continuing discussions about healthcare reform, oncology nurses and our fellow healthcare providers need more than ever to have a thorough understanding of all the issues—clinical, economic, regulatory—involved in cancer treatment.

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PhaSeal®

Vol. 2, No. 5 July/August 2009

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REFERENCES: 1. The Italian Group for Antiemetic Research. Dexamethasone alone or in combination with ondansetron for the prevention of delayed nausea and vomiting induced by chemotherapy. *N Engl J Med*. 2000;342:1554-1559. 2. Hickok JT, Roscoe JA, Morrow GR, et al. 5-Hydroxytryptamine-receptor antagonists versus prochlorperazine for control of delayed nausea caused by doxorubicin: a URCC CCOP randomised controlled trial. *Lancet Oncol*. 2005;6:765-772. Epub September 13, 2005. 3. Cohen L, de Moor CA, Eisenburg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer*. 2007;15:497-503. Epub November 14, 2006. 4. Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. *Ann Oncol*. 2003;14:1570-1577. 5. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved Prevention of Moderately Emetogenic Chemotherapy-induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel 5-HT_3 Receptor Antagonist: Results of a Phase III, Single-Dose Trial Versus Dolasetron. *Cancer*. 2003;98:2473-2482. 6. ALOXI® (palonosetron HCl) injection full prescribing information.

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Viewpoint

Government Health Plans Always Ration Care

Europe offers a glimpse of the future if President Obama and congressional Democrats have their way.

Only by expanding government control of health care can we bring down its cost. That's the faulty premise of the various proposals for health reform now being batted around Washington. The claimed cost control depends on politically safe ideas such as preventive care or the adoption of electronic health records. And neither—even according to the Congressional Budget Office—will do much to reduce spending.

If these proposals are implemented and fail to produce savings, government will turn to a less appealing but more familiar tool to cut costs: the regulation of access to drugs and medical services. Medicare is already going down this path. What will be new about government-run health care is the instrument of regulatory control. There will be an omnipotent federal health board. Buried in current reform proposals, this board deserves closer scrutiny.

Our best look at this construct comes from a bill released by the Senate Health, Education, Labor and Pensions (HELP) Committee. The bill calls for a "Medical Advisory Council" to determine what medical products and services are "essential benefits" and those that shouldn't be covered by a public insurance plan.

The Senate Finance Committee turns to a "Federal Health Board" to compare similar medical treatments in order to steer reimbursement to lower-cost options. Senate Finance also proposes a "sustainability commission" charged with finding automatic cuts to Medicare spending that would then pass Congress by a simple up or down vote.

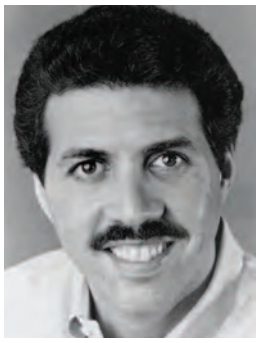
Meanwhile, a draft health-care reform proposal introduced last week in the House of Representatives by the three committees with jurisdiction over health policy set up an independent "advisory committee" that will "recommend a benefit package based on standards set in the law." It also proposes a new "commission" that may, among other things, help develop treatment protocols based on government-directed research.

Congress, of course, can authorize the creation of panels and commissions to provide expert advice to the executive branch. But such bodies are typically advisory, and their advice is free to be rejected or modified by the president. Under the HELP committee's plan, the health board's recommendations would be binding unless Congress acts within a brief period to pass a "joint resolution disapproving such report in its entirety."

President Obama objects when people use the word "rationing" in regards to government-run health care. But rationing is inevitable if we simply expand government control without fixing the way health care is reimbursed so that doctors and patients become sensitive to issues of price and quality.

Like Medicare's recent decisions to curtail the use of virtual colonoscopies, certain wound-healing devices, and

Continued on page 12



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Medical Minutes

BY **JOHN SCHIESZER**

Dealing with Compassion Fatigue

Compassion fatigue in nurses and other frontline cancer care providers can significantly impact how they interact with patients, with patients' families, with other healthcare workers, and with their own families, according to an analysis by researchers at Indiana University School of Medicine. They have been investigating how prevalent this problem is and what needs to be done to help oncology nurses who suffer from compassion fatigue.

The researchers reviewed 57 studies to identify the prevalence of compassion fatigue among cancer care providers, how to detect it, and means of prevention and treatment (Doebbeling C, et al. *J Health Psychol*. 2009;14:267-277).

The term "compassion fatigue" was first coined in the 1990s to describe a syndrome experienced by a healthcare provider caring for individuals facing dire consequences as a result of their disease. Going beyond empathy or "feeling bad" for the person, it affects the nurse, doctor, or other member of the healthcare team in a way that he or she often develops a distance from the patient as a form of self-protection.

"Individuals who are drawn into healthcare careers may be more likely to develop compassion fatigue, based on their drive for perfection and to do their best for their patients. If you work in an environment where despite your very best efforts, patients for whom you provide care will not survive, there is a setup for developing a sense of 'there is nothing I can do anymore,'" said study principal investigator Caroline Carney Doebbeling, MD, associate professor of medicine and psychiatry, Indiana University School of Medicine, Indianapolis.

Symptoms of compassion fatigue include chronic tiredness and irritability, lack of joy in life, and engagement in behaviors such as drinking at a destructive level. Like individuals with posttraumatic stress disorder, those with compassion fatigue often re-experience the deaths of their patients. Compassion fatigue can lead individuals to protect or insulate themselves by loss of compassion, cynicism, decreased productivity, more sick days, and, ultimately, to switch jobs. Although compassion fatigue has not been labeled a psychiatric disorder, it can lead to depression and anxiety disorders.

"How do you deal with compassion fatigue if you see patients every single day?" asks Carney Doebbeling. "To provide the best care to patients, the system, beginning with training in nursing and medical schools and residency, has to do a better job of helping those who go into cancer care learn what to expect and how to deal with it. On the job, we need to create supportive work environments where supervisors and colleagues are aware that those who care for the sickest of the sick may be vulnerable to the triggers that could bring about compassion fatigue."

New Biodegradable Gel for Esophageal Cancer Patients

Researchers at Rush University Medical Center in Chicago are evaluating a new system for delivering chemotherapy to patients with esophageal cancer. The unique drug therapy delivers a highly concentrated dose of chemotherapy injected directly into the tumors in the esophagus nonsurgically.

The investigational drug, OncoGel, is made of two major components: the ReGel drug delivery system, which is made of the same ingredients used in biodegradable stitches, and paclitaxel. The patients receive a one-time injection of the gel during an endoscopy.

"In pilot studies, OncoGel has been shown to continuously release paclitaxel in concentrated doses at a higher magnitude than when delivered through the blood for up to 6 weeks," said Sohrab Mobarhan, MD, the principal study investigator for this drug at Rush Medical Center.

In an earlier phase of the study in patients with late-stage inoperable esophageal cancer, 70% of patients had a reduction in tumor volume when the gel was used in combination with radiotherapy. In addition, posttreatment biopsy samples did not contain tumor cells in almost 40% of patients.

"Patients with esophageal cancer are usually diagnosed at very advanced stages and life expectancy can be less than 2 years from first diagnosis," Mobarhan said. "This [OncoGel] also could potentially be a viable treatment option for patients who have inoperable tumors located in their esophagus."

Combined PET/CT Imaging May Indicate Whether Chemotherapy Is Working

It often takes months before it is possible to determine whether a chemotherapy treatment is working. Researchers at the University of California at Los Angeles (UCLA) now report that it may be possible to determine whether chemotherapy is killing the cancer after just one cycle.

Using a combination positron-emission tomography (PET) and computed tomography (CT) scanner, researchers monitored 50 patients undergoing treatment for high-grade soft-tissue sarcomas (Benz MR, et al. *Clin Cancer Res*. 2009; 15:2856-2863). The patients were receiving neoadjuvant chemotherapy treatments to shrink their tumors before surgery. The study found that response could be determined about 1 week after the first dose of chemotherapy drugs. Typically, patients are scanned at about 3 months into chemotherapy to determine whether there has been a beneficial effect.

PET scanning shows biochemical functions in real time, acting as a sort of molecular camera.

PET scanning shows biochemical functions in real time, acting as a sort of molecular camera. For this study, the researchers monitored the tumor's metabolic function. Because they are growing out of control, cancer cells use much more sugar than do normal cells, making them light up under PET scanning with the glucose analog fluorodeoxyglucose. An effective response to treatment was defined as a 35% decrease in the tumor's metabolic activity.

Of the 50 patients in the study, 28 did not respond to chemotherapy, and the investigators knew that within 1 week of their initial treatment. This allowed the treatment course to be discontinued or changed to another more effective treatment, getting the patient to surgery more quickly.

"The significance of this study was that it identified people, more than half of those in the study, who were not going to benefit from the treatment early in the course of their therapy," said Fritz Eilber, MD, assistant professor of surgical oncology, UCLA Jonsson Cancer Center, Los Angeles. "This information significantly helps guide patient care. Although this study was performed in patients scheduled for surgery, I think these findings will have an even greater impact on patients with inoperable tumors or metastatic disease as you get a much quicker evaluation of treatment effectiveness and can make decisions that will hugely impact quality of life."

Eilber and his colleagues are continuing to follow these patients, and a clinical trial currently is under way based on results from this study. Eilber said this approach may help personalize treatment for each patient and may one day become the standard of care.

Conference News

Richard Schilsky, MD, ASCO President: "Personalizing Cancer Care" Is Everyone's Mission

Photo courtesy of American Society of Clinical Oncology.

Richard Schilsky, MD

ORLANDO—The "personalization of cancer care"—delivering the right care to the right patient at the right time—is becoming a universal and realizable goal, said American Society of Clinical Oncology (ASCO) president Richard Schilsky, MD, professor of medicine and associate dean of clinical research, University of Chicago.

The challenges of the past year have been many: the global economic recession, high unemployment, declining physician workforce, and lack of universal access to optimal care. "But it has also been a year of great hope, as we have a new administration that is committed to curing cancer," Schilsky told annual meeting attendees, in his presidential address.

"We hear much about personalized medicine. It is the new buzzword in healthcare and health policy. But what does it mean to patients and oncologists?" he asked.

Both patient and tumor are unique

Personalized medicine begins with a concept that cancer specialists have long recognized: that each patient is unique in his or her clinical presentation, treatment response, and supportive care needs. But it also includes the growing recognition that tumors are also unique; therefore, personalized treatment plans should address both the patient and the tumor, he said.

Among more than 100 drugs approved for more than 170 cancer indications, a growing number target specific abnormalities of the cancer. Molecular diagnostics are beginning to guide prescribing practice, based on germline variations in the patient and somatic mutations in the tumor.

For example, Kirsten rat sarcoma (*KRAS*) mutations have become established as biomarkers for the lack of efficacy of epidermal growth factor receptor–targeted monoclonal antibodies, and ASCO has issued a provisional clinical opinion calling for *KRAS* testing in patients with metastatic colorectal carcinoma.

"Personalizing cancer care is all about bringing our insights and skills from biology, medicine, engineering, informatics, social sciences, and other disciplines to solving the enormous problem of cancer," he said. "We will increasingly be able to design optimal treatment strategies that offer the best hope of controlling cancer with the least toxicity. And with sophisticated imaging techniques, such as volumetric computed tomography, we can more quickly assess treatment efficacy. This all has the potential to substantially reduce the cost of care."

We will increasingly be able to design optimal treatment strategies that offer the best hope of controlling cancer with the least toxicity.

Personalized cancer care does not cease at the end of treatment, but extends to end-of-life care and survivorship, he added, encouraging oncologists to personalize survivorship plans for their patients, and to communicate with survivors "as an individual and not a statistic, as a person with an illness within a social network."

"As oncologists, our focus has been and must remain treating the person, not the disease," Schilsky reiterated. "We must acquire the skills and devote the time and receive compensation for doing so in an optimal way."

Meeting the growing needs

By 2030 the global cancer burden will triple and cancer will be the leading cause of death. Because this will be coupled with a 30% shortfall in oncologists, new approaches are greatly needed to meet these needs, he said.

One part of the solution is the use of multidisciplinary care teams, the aim being to "extend the reach of oncology services" through mid-level providers. Primary care providers, if oncologists "better engage" them, can also help lighten the workload, he said.

With regard to the increasing cost of care, "oncologists need to be part of the conversation and the solution," he maintained. A new ASCO task force is developing a plan of action on cost of care. Among the recommendations will be greater emphasis on discussions with patients, uniform definitions of "value," examination of factors that underlie cost, and advancement of steps related to comparative effectiveness.

Finally, clinical trial obstacles must be overcome, he said. The US research infrastructure is "the best in the world" but is underfunded and "mired in a regulatory matrix that slows our progress and saps our energy," Schilsky noted.

In 2009, more than 700 drugs are in development for cancer, but fewer than 10% of these will probably be approved, he predicted. "There are not enough patients, dollars, and time," he said, "to test all these within our conventional clinical trial paradigm."

ASCO has convened an expert group to tackle some of the key aspects of the clinical trials problem and to produce a white paper for the US Food and Drug Administration.

Meanwhile, Schilsky advocated for the use of biomarkers to streamline patient selection, preliminary marketing approval based on randomized phase 2 (rather than phase 3) trials, removal of barriers to the completion of confirmatory trials, and streamlining of the processes that support the filing of supplemental new drug applications for new indications.

Such changes would require the willingness of pharmaceutical companies to trade the rewards they reap from short-term widespread use of a drug in large populations to long-term use of a drug in more limited populations, and will necessitate much greater participation in trials on the part of oncologists and patients alike.

Most important, the clinical trials process must be revamped for greater efficiency. Currently, a phase 3 cooperative group trial requires close to 400 steps and 2 years to launch because of a bureaucratic process that involves a multitude of review loops, regulatory requirements, and contract negotiations.

"We must fix this problem now," Schilsky concluded, "because our patients cannot wait."

—Caroline Helwick

Trastuzumab Improves Survival in Gastric Cancer

Photo courtesy of American Society of Clinical Oncology.

Eric Van Cutsem, MD, PhD

ORLANDO—Although trastuzumab is thought of as a breast cancer drug, when it is added to chemotherapy for gastric cancer, it outperformed the standard treatment for this tumor in patients overexpressing human epidermal growth factor receptor 2 (HER2), according to the results of an international, randomized, phase 3 trial reported at the annual meeting of the American Society of Clinical Oncology (ASCO).

In the first large phase 3 study of trastuzumab in patients with gastric cancer, patients receiving trastuzumab had a 26% reduction in the risk of death, compared with chemotherapy with cisplatin and capecitabine or 5-fluorouracil (5-FU), reported Eric Van Cutsem, MD, PhD, University Hospital Gasthuisberg, Leuven, Belgium.

"This is the first phase 3 study to report improved overall survival with a personalized, targeted treatment for gastric cancer."

"This is the first phase 3 study to report improved overall survival with a personalized, targeted treatment for gastric cancer," Van Cutsem said, adding that it is the first time trastuzumab has been shown to improve survival in a tumor other than breast cancer.

David Cunningham, MD, consultant, Royal Marsden Hospital, United Kingdom, who discussed the study at the oral session, commented, "This is an absolutely excellent study. It was a major undertaking to screen nearly 4000 patients for the presence of HER2 expression, and to recruit them for treatment in a timely fashion. All the end points were positive."

HER2 overexpression found in 22% of patients

Similar to what is seen in breast cancer, HER2 overexpression is often found in gastric cancers. Investigators from the ToGA study, which involved sites in Europe, Latin America, and Asia, tested 3807 patients with advanced gastric cancer for overexpression of HER2, which they found in 810 patients (22%).

The study then randomized 594

Continued on page 14

New Study Suggests New Standard of Care for Patients with Advanced Biliary Tract Cancer

ORLANDO—Two agents may be better than one when it comes to advanced biliary tract cancer. In the largest study of its kind, researchers have found that a combination of gemcitabine and cisplatin may reduce the risk of death by 32% and the risk of cancer progression by 30% in patients with inoperable advanced cancers of the biliary tract (gallbladder and bile duct) compared with gemcitabine treatment alone. Until now, advanced biliary tract cancer had no scientifically proven effective treatment.

Photo courtesy of American Society of Clinical Oncology

Juan Valle, MD

"Based on these findings, we can now establish the first-ever standard of care for advanced biliary tract cancers. We found that adding cisplatin to gemcitabine therapy significantly slowed cancer progression and extended survival for these rare but hard-to-treat cancers," said lead study author Juan Valle, MD, senior lecturer and medical oncologist at the University of Manchester, England. "Previous smaller studies supported these findings, but our study is the largest and most reliable study of patients with this cancer to ever be reported."

In this phase 3 National Cancer Research Network study, investigators randomized 410 patients in the United Kingdom with inoperable metastatic biliary tract cancers to receive either a combination of gemcitabine and cisplatin (n = 206) or gemcitabine alone (n = 204). The study was funded by the Cancer Research UK Foundation and conducted by the UCL Cancer Trials Centre.

Valle, who presented the study findings at the annual meeting of the American Society of Clinical Oncology, said the median age of the patients was 64 years (range, 23-85 years) and 47% were men. Patients had a variety of tumor types: gallbladder (36%), bile duct (59%), and ampulla (5%). Disease stage was either metastatic (75%) or locally advanced (25%).

The researchers found that progression-free survival was longer among patients who received gemcitabine plus cisplatin (8.5 months) compared with those who received gemcitabine alone (6.5 months). The patients who received both drugs also lived significantly longer (11.7 vs 8.2 months) than patients on gemcitabine alone.

"One of the problems with biliary tract cancers is that the numbers are small and there are a lot of small series and lots of small studies with just four or five patients," Valle said in an interview with *The Oncology Nurse*. "So until now, there had been no consensus. One of the biggest advantages is that this puts to bed some of the questions about whether chemotherapy has any benefit at all. We know it is now an option. In the past that was in question."

He said gemcitabine plus cisplatin was generally well tolerated. The most common side effect was moderate neutropenia, occurring in 22.6% of patients receiving both drugs and 17.9% of those receiving gemcitabine alone. However, most of the patients who suffered from neutropenia were asymptomatic.

"The most important message is that chemotherapy should be considered as an option with patients with biliary tract cancer, and combination therapy appears to offer an advantage over monotherapy and it appears to be well tolerated," Valle said.

—John Schieszer

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VIEWPOINT

Government Health Plans

Continued from page 8

even a branded asthma drug, the board's decisions will be one-size-fits-all restrictions. Such restrictions don't respect variation in preferences and disease, which make costly products suitable for some even if they are wasteful when prescribed to everyone.

Moreover, these health boards prove that policy makers know they'll need to ration care but want to absolve themselves of responsibility. Some in Congress and the Obama administration recently tipped their hand on this goal by proposing to make recommendations of the current Medicare Payment Advisory Committee (MedPAC) legally binding rather than mere advice to Congress. Any new health board's mission will also expand over time, just as MedPAC's mandate grew to encompass medical practice issues not envisioned when it was created.

The idea of an omnipotent board that makes unpopular decisions on access and price isn't a new construct. It's a European import. In countries such as France and Germany, layers of bureaucracy like health boards have been specifically engineered to delay the adoption of new medical products and services, thus lowering spending.

In France, assessment of medical products is done by the Committee for the Evaluation of Medicines. Reimbursement rates are set by the National Union of Sickness Insurance Funds, a group that also negotiates pay to doctors.

In Germany, the Federal Joint Committee regulates reimbursement and restrictions on prescribing, while the Institute for Quality and Efficiency in Healthcare does formal cost-effectiveness analysis. The Social Insurance Organization, technically a part of the Federal Joint Committee, is in charge of setting prices through a defined formula that monitors doctors' prescribing behavior and sets their practice budgets. In the past 12 months, the 15 medical products and services that cleared this process spent an average 35 months under review. (The shortest review was 19 months, the longest 51.)

In short, other countries where government plays a large role in health care aren't shy about rationing. Mr. Obama's budget director has acknowledged that rationing reduces costs. Peter Orszag told Congress last year when he headed the Congressional Budget Office that spending can be "moderated" if "diffusion of existing costly services were slowed."

Medicare can already be painstakingly slow. Appealing to it takes patients an average 21 months according to a 2003 Government Accountability Office report (17 months involve administrative processing). Layers of commissions and health boards would delay access still further.

When asked to judge the constitutionality of the Senate HELP committee proposal, there's a reason why the nonpartisan Congressional Research Service said that the proposed Medical Advisory Council "raises potentially significant constitutional concerns." Our Founders thought politicians should be accountable when it comes to citizens' right to life, liberty and the pursuit of heart surgery.

—Scott Gottlieb

Dr. Gottlieb, a physician and resident fellow at the American Enterprise Institute, is a former senior official at the Centers for Medicare & Medicaid Services. He is partner to a firm that invests in health-care companies.

Nurse Support Program

Continued from cover

improvement documented at follow-up 1 year later, adherence rates will hopefully increase over the long term, and we are encouraged by our initial findings," Latsko commented at the 34th annual meeting of the Oncology Nursing Society.

Patients with chronic anemias such as sickle cell disease (SCD), myelodysplastic syndromes (MDS), and beta-thalassemia receive red blood cell transfusions as supportive care, she said. Iron chelation therapy is essential in these patients to treat the iron overload that eventually develops.

Until recently, standard treatment involved deferoxamine, which is administered as an 8- to 12-hour infusion, usually 5 to 7 days a week, Latsko added. Treatment is thus cumbersome, especially in young patients, such as those with SCD, as well as patients with MDS, who are usually elderly. As a result, quality of life and treatment adherence are decreased.

Although deferasirox is administered once daily and has been shown to produce higher rates of patient satisfaction than deferoxamine, the treatment nonetheless has notable shortcomings, she said. For example, because iron overload initially produces no symptoms, it is difficult to ensure that patients remain compliant. In addition, older patients with MDS may have comorbidities that complicate management.

Working with pharmacies, Latsko and colleagues provided nursing support through regular proactive calls to patients taking deferasirox. Nurses explained to patients the rationale for their treatment, the importance of adherence, proper use of the therapy, and the management of side effects.

Overall, the treatment adherence rate increased from 58% at 3 months, 42% at 6 months, and 31% at 12 months before the nursing program was initiated to 62%, 46%, and 33%, respectively, afterwards. The persistence rate improved from 71% at 3 months and 50% at 6 months before the program was implemented to 74% and 56%, respectively, afterwards.

Latsko said that the program probably initially improved adherence and persistence because patients were switching from a more burdensome treatment option requiring multiple weekly infusions to a once-daily oral therapy. Also, the inclusion of a nurse support component meant that nurses had the opportunity to manage patients' expectations and provide effective coping strategies, which should translate into improved persistence and adherence, according to Latsko.

The nurse support program not only includes the patient but also the ordering physician's office, she added. The coordinated calls and communication enhance a more collaborative flow of accurate information between all parties. Also, patients can discuss treatment issues or concerns directly with their specialist pharmacist or office practice nurse, improving their adherence, persistence, and compliance rates, she said.

While Latsko and colleagues continue to gather data about the nurse support program, the results thus far highlight the important role nurses play in providing "continuous education" to their patients, she observed. "Nurses should be aware of the value that this education provides in supplementing patient understanding about their iron chelation therapy and, ultimately, enhancing favorable treatment outcomes," she said.

—Jill Stein

Obesity Prevention Is an Important Goal for Childhood Cancer Survivors

SAN ANTONIO—Researchers are calling for rigorous follow-up of childhood cancer survivors that aims to help them avoid becoming significantly overweight or obese.

The recommendation was made at the 34th annual meeting of the Oncology Nursing Society by a group from the Center for Cancer Survivorship in Duarte, California.

Being overweight or obese can be especially insidious in childhood cancer survivors because they may have received treatments for their cancer that increase their risk of a range of conditions linked with excess weight, Karla Wilson, RN, MSN, FNP-C, and her colleagues cautioned. These conditions include dyslipidemia, type 2 diabetes, hypertension, and cardiovascular disease, all of which are worsened by excess weight coupled with a sedentary lifestyle.

Treatments that increase the risk of conditions linked to excess weight or obesity include cranial/head irradiation and a higher radiation dose.

Treatments that increase the risk of conditions linked to excess weight or obesity include cranial/head irradiation (especially if combined with corticosteroids) and a higher radiation dose (with a hypothalamic radiation dose ≥20 Gy conferring the highest risk).

Additional risk factors include female sex, a diagnosis of acute lymphoblastic leukemia, and being younger than 4 years at the start of treatment.

Wilson and her colleagues calculated body mass index (BMI) in 321 childhood cancer survivors enrolled in her facility's program using a formula available on the Centers for Disease Control and Prevention web site. BMI 25 kg/m^2 was considered normal, 25 kg/m^2 to 30 kg/m^2 was considered overweight, and ≥30 kg/m^2 was considered obese. Calculations were adjusted for survivors younger than 18 years.

Of 225 evaluable patients who were between 15 and 39 years of age at their initial visit, 120 (53%) were either overweight or obese.

The researchers advocate "tailored" education to teach childhood cancer survivors about specific therapy-related risks for metabolic and cardiovascular diseases, as well as appropriate dietary and exercise habits. Written materials may be particularly helpful in this population, they said.

—Jill Stein

Oncology Nurses Key to Diagnosis and Management of Fournier's Gangrene in Immunocompromised Cancer Patients

SAN ANTONIO—Fournier's gangrene is a rare but lethal infectious complication that may occur as a result of immunosuppression following chemotherapy in patients with acute myeloid leukemia. Oncology nurses may play an invaluable role in its diagnosis and management, investigators reported at the 34th annual meeting of the Oncology Nursing Society.

Fournier's gangrene is a necrotizing infection of the skin and subcutaneous soft tissue of the external genitalia and perineum, Suzanne Carroll, RN, MS, AOCN, with The Comprehensive Cancer Center of Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina, explained. The infection results from a combination of anaerobic microorganisms that spread quickly and lead to necrosis of skin, subcutaneous tissue, and muscle. The infection is 10 times more likely in men.

Risk factors for Fournier's gangrene include a history of diabetes, alcoholism, malnutrition, morbid obesity, and immunosuppression resulting from chemotherapy. The infection may also develop as a complication of surgery.

Clinical manifestations include the following: advancing erythema and ulcers in the genital area; crepitant skin at the affected areas; severe genital pain and erythema; odor; swelling of the genitals and scrotal area; necrotic tissue of the affected area, which may be discolored; and septicemia leading to systemic toxicity and death.

Treatment typically involves intravenous double- or triple-drug antibiotic therapy and surgical debridement of necrotic tissue and may also include hyperbaric oxygen (HBO_2) therapy, which inhibits the growth and kills anaerobic bacteria. Even when patients are treated with surgical and HBO_2 intervention, the overall mortality rate is 40%, which increases to 78% if the patient has sepsis at the time of diagnosis.

At Carroll's institution, Fournier's gangrene developed in a 37-year-old man with persistent leukemia, prolonged neutropenia, thrombocytopenia, and disseminated fungal infection. The patient, who was not a candidate for conventional surgical or HBO_2 therapy, died within 24 hours of the onset of a rash in his scrotal area.

Oncology nurses should be especially vigilant when assessing immunocompromised cancer patients, Carroll said. Complaints of new-onset rash or pain in the genital area may be clues to the presence of Fournier's gangrene. In addition, although the condition is more common in men, oncology nurses should be aware that it may occur in women in the vaginal and perineal area.

Complaints of new-onset rash or pain in the genital area may be clues to the presence of Fournier's gangrene.

Perineal inspection should be routine with all immunocompromised patients, and any complaint of new-onset or painful rash in the perineal area should be assessed promptly, Carroll advised. Oncology nurses should support patients with a diagnosis of Fournier's gangrene through timely antibiotic administration and close observation for septicemia (hyper- or hypothermia, increased heart rate, and decreased blood pressure).

If patients develop systemic toxicity, a palliative care plan should be initiated, including aggressive pain management and effective communication with the patient and his/her family that incorporates psychosocial, spiritual, and existential support at the end of life, she added. The patient's family and caregivers should also be well supported through the end-of-life experience and provided with psychosocial assistance when needed.

—Jill Stein

Photo by American Photography and Video.

Kathleen McCue of The Gathering Place, author of *Someone I Love is Sick*.

Photo by American Photography and Video.

Visitors to the Green Hill Healthcare Communications booth in San Antonio.

Quiet Time in a Cancer Center Confers Multiple Benefits

SAN ANTONIO—Imposing a designated quiet time in a comprehensive cancer center significantly lowers noise levels, thereby benefiting both patients and nurses, according to research described at the 34th annual meeting of the Oncology Nursing Society.

Yvette Ong, MS, BSN, RN, OCN, with the University of Texas M.D. Anderson Cancer Center in Houston, described the details of a 1-hour quiet time in a cancer unit, during which the level of noise is reduced to a minimum. During this time, lights are also dimmed and activities are decreased. The facility where the quiet time intervention is being tested is a 32-bed medical unit within a comprehensive cancer center.

Ong said that the average noise level in medication areas decreased from 63 dB to 73 dB during normal operations to 53 dB to 57 dB during quiet time. The average noise level in patients' rooms was reduced from 54 dB to 69 dB during normal operations to 42 dB to 44 dB during quiet time. Also, the noise level in the perimeter between the nurses' stations and patients' rooms was lowered from 54 dB to 66 dB during normal operations to 48 dB to 52 dB during quiet time.

Patients in the unit have said that they love the solitude quiet time provides. In addition, nurses reported that the downtime gives them an opportunity to take a break or catch up with documentation.

Excessive noise has been shown to worsen patient outcomes, Ong said. The adverse effects of noise on patient outcomes include sleep deprivation, anxiety, stress, cardiovascular stimulation, decreased pain threshold, emotional and mental disturbances, altered immune function, decreased wound healing, delayed recovery, and higher readmission rates.

The World Health Organization has recommended that noise levels in hospitals not exceed 45 dB during the day and 35 dB at night.

The quiet time currently being tested is set at 12 PM to 1 PM. A device that indicates noise levels is placed in a highly visible area in the nurses station to alert the staff if noise levels exceed 40 dB. Additional measures that decrease noise levels include lowering the ringer volume on telephones and reducing overhead paging. Also, all members of the multidisciplinary team are urged to avoid doing patient rounds during quiet time.

Finally, Ong said that there is a large variety of so-called noise culprits. These include staff and caregiver conversations, multidisciplinary team and ancillary staff rounds, vital signs equipment in rolling cars, industrial floor cleaners, pneumatic tube systems, ventilation systems, computer keyboards and printers, ice machines, paper towel dispensers, patient and bed turnover, and footsteps, among others.

—Jill Stein

Long-term Survivors of Myeloma

Continued from cover

meeting, five of these patients discussed the roles of nurses during their diagnosis and treatment.

Nurse becomes a patient

Marion State of Toronto, Canada, who is herself a nurse, was diagnosed with myeloma about 12 years ago. She says she specialized in mental health and did counseling, and did not remember what multiple myeloma was. "That sent me off to the computer even though I wasn't that computer literate." The nurses where she is being treated, are "always rushed off their feet and have very little time to educate/teach." State founded the Toronto and District Multiple Myeloma Support Group in 1997. "I could see a nurse could play a wonderful role since a nurse presented to our group," she says. State says she's been very proactive in her treatment, partly because of personality and partly because of training. "Since I am a nurse and know how to advocate for myself, I have just gone ahead 'solo.'" She also observes that there are not enough nurses to educate patients, and she's not sure that many nurses knew about myeloma in 1996-1997, when she was in the process of being diagnosed.

"A nurse could come in handy when a patient is booked for a bone marrow biopsy or aspiration. The nurse could sit with the patient and explain the procedure," she says. Where she had her procedure, "there are no standard premedications, and people don't know what to expect. It would be nice if a nurse could explain why they are doing the procedure and the associated tests, such as fluorescent in situ hybridization and cytogenetics."

Finding support

Another patient involved with support groups is Michael Tuohy of Connecticut, who was diagnosed in 2000. His wife Robin, who is now regional director, support groups, Northeast, for the IMF, began the first support group for patients with multiple myeloma in Connecticut with the help of the IMF. He says that when he was diagnosed, he did not have much communication with nurses but when he began treatment with a local oncologist, he found nurses to be a "great deal of comfort to me." Nurses, he found, "are very good at what they do, very supportive, and very outgoing."

A nurse could explain why they are doing the procedure and the associated tests.

"When I had my transplant, the nurse played a huge role. The transplant was done by a nurse. In the hospital, they were fantastic. They were there for moral support and very educated and knew what to do." He acknowledges, however, that at the local oncology office level, nurses deal with a lot of different kinds of cancer, so it is difficult for them to know a lot about myeloma. "The oncology nurses are wonderful and know what they are doing, but don't know the diseases. I think it's great to get out and educate nurses who are willing to take the time. Most people haven't heard of myeloma until they are diagnosed," Tuohy observes. He also suggests that because they are so busy, nurses may not have the time to research this disease on their own, but can focus on learning where to refer patients, for example, the IMF for myeloma (http://myeloma.org), or other patient advocate and information sites for other types of tumors, for example, the American Society of Clinical Oncology's patient site (www.cancer.net/portal/site/patient).

A role for nurses

Aldo Del Col of Montreal, Canada, is cofounder and vice president of Myeloma Canada (www.myelomacanada.ca), an affiliate of the IMF. He was diagnosed in 2002. He says he was not informed about the side effects of the steroid he took as part of his treatment. "These were not shared with patients. Doctors don't have the time. In my opinion, this is the nurses' role, not just the physiologic side effects, but the emotional aspects. They could refer to appropriate professionals for treatment."

Del Col notes that in Quebec each hospital now has an oncology pivot nurse. However, there may be only one in oncology or hematology. "Unless nurses are patients with myeloma, they can't know what the patient is going through, even if they are empathetic," so support groups play an important role in conveying information, he says. "We need to get patients involved at every level."

Playing an active role

Terry Barter of Massachusetts was diagnosed about 10 years ago, and calls the nurses at the cancer center where he was treated "nothing but fantastic." He recalls that for his first bone marrow biopsy, a nurse took him into the room but he had no idea what was going on or what to expect. "Sometimes they can only do what the doctor wants. Nurses are the one that have the compassion and see what happens to you." Barter says his nurse asks what is going on in his life, explains and follows up on side effects, keeps track of his medications, and suggests dietary modifications. Nonetheless, like State, he believes, "You are the only person who can advocate for you."

Hardy Jones of Florida, a 5-year survivor, says his oncology nurse is indispensable in keeping things going for him, including appointments and blood tests. "When I have questions I send them to her between appointments and she gets answers from the doctor and e-mails me. She keeps a running tally of when I am due for medications, when I don't order refills. She is a tremendous facilitator."

Gaps to fill

These long-term survivors mentioned not having much contact with nurses before their diagnosis, or receiving limited information before connecting with an oncology nurse specifically trained in myeloma. Patient support groups can benefit from presentations from nurses, particularly on drug side effects and their management. Patients having procedures such as bone marrow aspirations would benefit from more information about those procedures. Although multiple myeloma is the second most common hematologic malignancy, State recalls patients with malignant melanoma being referred to her myeloma support group, indicating that both patients and nurses can benefit from more education about myeloma.

—Lynne Lederman

CONFERENCE NEWS

Trastuzumab Improves Survival

Continued from page 10

HER2-positive patients to standard chemotherapy or chemotherapy plus trastuzumab, given every 3 weeks for six cycles, with trastuzumab continued until disease progression.

Trastuzumab produced a modest but clinically meaningful improvement in outcome.

Median overall survival was significantly greater with the addition of trastuzumab, 13.8 versus 11.1 months with standard chemotherapy (*P* = .0048), Van Cutsem reported.

After a median of 17 months of follow-up, mortality was reduced by 26% with the combination. The overall response rate with the combination was 47.3% versus 34.5% with chemotherapy alone, again a highly significant difference (*P* = .0017).

In a preplanned subgroup analysis, patients with the highest degree of HER2 overexpression (fluorescence in situ hybridization–positive/3+ by immunohistochemistry) had even greater benefit from trastuzumab, overall survival being 17.8 months versus 12.3 months for chemotherapy alone. This represented a 42% reduction in the risk of death.

The combination was well tolerated, with no significant increase in the occurrence of symptomatic congestive heart failure; as expected, however, asymptomatic left ventricular ejection fraction decreases were reported more frequently with the combination (4.6%-5.9%, depending on the criteria) than with chemotherapy alone (1.1%), he reported.

In his discussion of the study, Cunningham maintained, "Trastuzumab produced a modest but clinically meaningful improvement in outcome for patients who have a relatively poor prognosis with conventional therapies. It is a safe and effective option and should be considered for all patients with advanced gastric cancer who test HER2-positive."

"The magnitude of benefit may be even greater than observed in ToGA," he predicted, "if we apply the definition of overexpression that is used in selecting breast cancer patients for trastuzumab treatment, that is, if patients are more highly selected."

ASCO President Richard Schilsky, MD, University of Chicago Medical Center, called the study "a great example of the concept of personalized medicine." He said that for the first time, there is an indication that "we need to think about two different molecular subtypes of stomach cancer—HER2-positive and HER2-negative."

—CH

ASCO Conference News continued on page 21

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Program #09CE038 • RELEASE DATE: August 15, 2009 • EXPIRATION DATE: August 14, 2010

Follow-up Care in Medicare Beneficiaries with Colorectal Cancer

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LEARNING OBJECTIVES

After completing this activity, the reader should be better able to:

- Describe current guidelines for follow-up care of colorectal cancer survivors.
- Discuss how these guidelines are applied in clinical management of elderly patients.
- Explain reasons for disparities between recommended care and that received by elderly patients.

TARGET AUDIENCE

Advanced practice nurses, registered nurses, and other interested healthcare professionals, especially those caring for cancer patients.

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Routine postoperative surveillance is recommended for patients with colorectal cancer who undergo potentially curative resection.[1-8] The goals of surveillance are to detect recurrent cancer in the colon or metastatic sites before the onset of other symptoms or signs, as well as to screen for cancers and polyps. Most guidelines recommend a combination of regularly scheduled office visits, colonoscopy, and carcinoembryonic antigen (CEA) testing, and two meta-analyses have reported improved long-term survival compared with minimal follow-up.[9,10] However, there are no national, population-based studies on the actual adherence to published comprehensive guidelines, as well as on the potential use of excessive testing. We therefore conducted the present study to determine compliance with guideline-based surveillance recommendations as well as to describe the potential overuse of follow-up testing in colorectal cancer survivors.

Methods

The cohort was identified from a database that included tumor registry data from the Surveillance, Epidemiology, and End Results (SEER) Program and Medicare claims data.[11,12] SEER consists of a series of population-based registries that capture approximately 25% of the US population, and for patients who are age-eligible (65 years and older) Medicare beneficiaries, inpatient, outpatient, and physician-supplier Medicare claims are linked. Patients were included if they were diagnosed with adenocarcinoma of colon or rectum during years in which oncology society guidelines were continuously available, 2000 through June 2001.

The follow-up period of interest was from 6 months after diagnosis through 42 months after diagnosis. Procedures within 6 months were excluded to avoid including tests to evaluate possible postoperative complications and routine postoperative visits. Procedures were identified through billing codes and included office visits, CEA testing, colonoscopy, computed tomography (CT) scan, and positron emission tomography (PET) scan.

The primary outcome of interest was adherence to professional society guidelines for routine surveillance, such as those of the American Society of Clinical Oncology (ASCO)[2,3] and the National Comprehensive Care Network (NCCN)[6] (Table). Because we could not ascertain which individual set of guidelines was most likely referenced in

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The following author has stated that she has the following financial relationships:

- Betty M. Chan, PharmD, BCOP, has received research/grant support from Merck & Co.
- Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP, is a speaker for Amgen, Bristol-Myers Squibb, Merck & Co, and Novartis. She also is on the advisory board for Bristol-Myers Squibb.
- Harry L. Reynolds, Jr., MD, is a course instructor for Covidien.

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Certain cancer-specific characteristics were associated with greater use of CEA testing (ie, regional- vs local-stage, poorly differentiated vs others), but no more than 63.5% of a specific subgroup fulfilled the testing criteria.

practice, we selected a composite minimum frequency of service and procedure receipt to measure guideline adherence:

- Guidelines met: two or more office visits per year, two or more CEA tests per year in years 1 and 2, one or more colonoscopies within 3 years
- Excess of guidelines: patient met guidelines and received one or more CT scans for cancers not poorly differentiated and/or one or more PET scans.

All others were considered to have failed to have met guidelines. Differences in the proportion of eligible patients who met guidelines for individual procedures (office visits, CEA testing, colonoscopy) as well as overall guidelines were compared according to patient and clinical characteristics, and a multivariable logistic regression model was used to determine the independent association of factors with receipt of care meeting or exceeding guidelines (vs not meeting guidelines).

The study was approved by the Institutional Review Board at University Hospitals Case Medical Center.

Results

A total of 9426 patients (mean age, 76.9 years; 54.5% women) who met the study eligibility criteria were identified. We found that 92.3% of patients fulfilled surveillance guidelines for office visits, with at least two visits in each year of follow-up. Although statistically significant differences were found across certain patient subgroups, with the exception of age ≥80 years, the differences in general were not of large magnitude.

We found that only 46.7% of patients in the study cohort met the guideline-based recommendations for CEA testing, lower rates being associated with age ≥80 years, African-American race, and increased comorbidity scores. Certain cancer-specific characteristics were associated with greater use of CEA testing (ie, regional- vs local-stage, poorly differentiated vs others), but no more than 63.5% of a specific subgroup fulfilled the

Continued on page 18

COMMENTARY

Follow-up Care in Medicare Beneficiaries with Colorectal Cancer: A Nurse's Perspective

BY **PAMELA HALLQUIST VIALE, RN, MS, CS, ANP, AOCNP**

Oncology Nurse Practitioner, Saratoga, California; Department of Physiological Nursing, University of California San Francisco

Although reductions have occurred in the death rate from colorectal cancer, this tumor type remains the third most commonly occurring cancer for both men and women, and the third leading cause of cancer death for both sexes.[1] The majority of these cancers occur in the elderly, with a median age at diagnosis of 71 years. Despite this fact, the elderly do not participate in many clinical trials and may also receive less than standard therapy or guideline-based care compared with their younger counterparts.[2,3]

Recently, a national, retrospective chart review of 520 elderly patients treated in community practices noted that these patients were less likely to receive first-line doublet chemotherapy than younger patients and that the use of targeted therapy agents, such as bevacizumab, was much lower in the elderly population as well.[2] The reasons for the treatment disparity included the presence of comorbidities, which could have prevented elderly patients from being able to receive doublet chemotherapy, and the fact that many of these older patients required hospitalization for their increased adverse side effects, such as gastrointestinal complaints.[2] The literature indicates that the elderly should not be considered for treatment by their chronological age alone, and comprehensive evaluation, including assessment of the preferences of the elderly patients themselves, is essential in determining the appropriate treatment.[4]

The treatment disparities described above are primarily related to concerns regarding the increased adverse events and higher hospitalization rates associated with chemotherapy and targeted therapy agents in the elderly. Cooper and colleagues, however, also noted disparities in the surveillance care of elderly patients after their initial treatment. Surveillance guidelines included recommendations for biomarker testing, visits to clinicians, and radiographic tests or procedures. In their study, elderly patients received carcinoembryonic antigen (CEA) testing below the recommended guidelines and did not undergo the recommended colonoscopy examinations as frequently as recommended either.

Cooper and colleagues note that these results reflect a large population of colorectal cancer survivors who should be receiving adequate surveillance to determine recurrence of disease. In addition, differences in frequency of surveillance testing were noted in certain racial groups, such as African Americans, which could affect overall survival. The authors point out limitations to their data, such as accuracy of procedure coding for Medicare patients and lack of information for the reason procedures were performed. Nonetheless, the observed disparities between the recommended frequency of testing and the actual frequency of testing are disturbing, and the authors recommend further study of the reasons for poor adherence to guidelines in this population as well as its potential effect on patient outcome.

Because colorectal cancer remains a common cancer in the elderly, clinicians, including oncology nurses, should have increased awareness of the specific needs of this population of patients. The National Comprehensive Cancer Network (NCCN) provides specific clinical practice guidelines for the care of the senior adult oncology patient, which call for careful assessment and an individual approach.[5] Assessment tools for geriatric functional assessment are included, and clinicians are cautioned to remain aware of the specific physical needs of the older patient. After active treatment has concluded, surveillance should be conducted to determine whether there are post-treatment complications and to detect recurrence of disease as early as possible, rendering metastatic disease potentially curable.[6]

The 2009 NCCN clinical practice guidelines for colon cancer survivors call for history and physical examination every 3 to 6 months for 2 years, then every 6 months for 3 years, with CEA testing every 3 to 6 months for 2 years, then every 6 months for 3 years.[6] A computed tomography scan of the abdomen and pelvis should be conducted annually for 3 years, with a colonoscopy at 1 year, repeated as clinically indicated.[6] These recommendations apply to all patients, with no differences noted in frequency of surveillance testing for elderly patients. Oncology nurses and clinicians should advocate for compliance with guideline-based treatment and surveillance for elderly patients. Future studies should gather additional information regarding compliance and recommended surveillance for this population.

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Table. Recommended Colorectal Cancer Surveillance Guidelines

Guideline (year)	Office visits	CEA testing	Colonoscopy
American Gastroenterological Association (1989)[a]	Every 3-6 months for 2 years, then 6-12 months for 2 years	Every 2 months for 2 years, then every 4 months for 2 years	1 year, then every 3 years
American Society of Clinical Oncology (1999, 2000)	Every 6 months for 3 years	Every 2-3 months for at least 2 years in stages II and III	Every 3-5 years
American Society of Clinical Oncology (2005)[b]	Every 3-6 months for 3 years	Every 3 months for at least 3 years in stages II and III	3 years; if normal, every 5 years
American Society of Colon and Rectal Surgeons (2004)[c]	At least three times yearly for 2 years	At least three times yearly for 2 years	Every 3 years
National Comprehensive Cancer Network (updated yearly)	Every 3-6 months for 2 years, then every 6 months	Every 3-6 months for 2 years, then every 6 months	1 year, 3 years later, 5 years later

CEA indicates carcinoembryonic antigen; CT, computed tomography; FOBT, fecal occult blood test.

[a]Also recommend FOBT and liver enzymes every 3-6 months for 2 years then every 6-12 months for 2 years, chest x-ray every 6-12 months for 2 years then yearly.
[b]Also recommend annual CT scans for patients at higher risk of recurrence.
[c]Also recommend considering annual CT scans for patients at high risk for recurrence (ie, lymphatic or venous invasion or poorly differentiated tumors).

COMMENTARY

Follow-up Care in Medicare Beneficiaries with Colorectal Cancer: A Pharmacist's Perspective

BY **BETTY M. CHAN, PHARMD, BCOP**
University of Southern California/Norris Comprehensive Cancer Center, Los Angeles

In the article by Cooper and colleagues on follow-up care in Medicare beneficiaries with colorectal cancer, the authors report that the majority of patients (92.3%) fulfilled the surveillance guidelines for physician follow-up office visits, but overall guideline-based recommendations were met in only 17.1% of patients, with 60.2% of patients receiving testing below the minimum frequency. Being aged 70 to 74 years, African-American race, having local-stage, non-poorly differentiated colorectal cancers, and increased comorbidity scores were factors identified by the authors as most strongly associated with lack of guideline adherence.

Since 1998, incidence rates of colorectal cancer have been rapidly declining among both men and women.[1] Between 1996 and 2004, only 40% of patients with colorectal cancer were diagnosed with local-stage disease, for which the 5-year relative survival rate is 90%; for patients diagnosed with regional-stage disease, the 5-year relative survival rate decreases to 68%, and for patients diagnosed with distant-stage disease, the 5-year relative survival rate decreases further to 11%.[2] With the introduction of 5-fluorouracil–based adjuvant chemotherapy for stage III resectable colon cancer in the late 1980s, mortality from colon cancer was further reduced by 30%.[3] These statistics, along with the case study included by Cooper and colleagues, further illustrate the importance of follow-up and surveillance for cancer survivors with early stages of disease.

Posttreatment surveillance of colorectal cancer patients is performed to evaluate for possible therapeutic complications and to discover early recurrence of disease at its early resectable stages, which allows for curative treatment, as well as at its preinvasive stage, which affords for better treatment outcomes. Several meta-analyses of randomized controlled trials have demonstrated the advantages of intensive follow-up surveillance for colorectal cancer patients.[4-7] The National Comprehensive Cancer Network clinical practice guidelines regarding colon cancer patients recommend outlining a prescription plan for survivorship upon transfer of care to a primary care physician, which should include[8]:

- Overall summary of treatment received, including all surgeries, radiation, and chemotherapy
- Description of clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae from treatment
- Recommendations for follow-up surveillance.

Although surveillance guidelines are available for clinicians, adherence to the guidelines can be a challenge and often requires a multidisciplinary approach that involves the patients and their family members or caregivers to ensure patient compliance with follow-up appointments. Oncology nurses and pharmacists can also assist by developing follow-up care plans and a patient-care database to help track and document methods of follow-up and surveillance.

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Case Study

An otherwise healthy 70-year-old African-American man presented for first-time screening colonoscopy and was found to have a nonobstructing mass lesion in the cecum with pathology showing well differentiated adenocarcinoma. In addition, two polyps were removed from the sigmoid colon, each of which was a tubular adenoma. He underwent right hemicolectomy, with the surgical margins free of residual cancer and 14 lymph nodes negative for malignancy. Postresection, his carcinoembryonic antigen level was 1 ng/mL. He was considered to be TNM Stage II, and a medical oncology consultant did not recommend adjuvant chemotherapy. He was seen by the surgeon 2 weeks, 1 month, and 3 months postoperatively and, because he had made a complete recovery, no further surgical follow up was recommended. Approximately 1 year after surgery, he presented to his primary care physician for routine evaluation. The primary care physician assumed that any recommended cancer-related follow up would be coordinated by other specialists and recommended that he return for an annual physical examination in 1 year. When the patient returned at that time, he reported a 3-month history of intermittent rectal bleeding and was referred for an urgent colonoscopy. He was found to have an ulcerated mass in the sigmoid colon, with pathology showing moderately well-differentiated adenocarcinoma, requiring a subtotal colectomy.

testing criteria. Only 73.6% of patients met guideline-specified criteria for colonoscopy (at least one examination within 3 years of diagnosis). Advancing age, especially age 70 to 74 years, African-American race, and increased comorbidity scores were associated with decreased use of colonoscopy. Across the SEER registries, the vast majority of patients in all sites received the requisite number of office visits (range, 86.0%-95.6%), but there was wider variation in adherence with colonoscopy (67.6%-78.8%) and CEA testing (37.2%-49.8%).

When we examined the use of two procedures that are not routinely recommended for cancer surveillance, abdominal/pelvic CT scans and PET scans, we found that 47.7% of patients received at least one CT scan. Although guidelines recommend that CT scanning be considered for poorly differentiated tumors, we found that 51.4% of patients with poorly differentiated cancer compared with 47.1% of others underwent CT scans.

Overall, the findings showed that guideline-based recommendations were met in 17.1% of patients and exceeded in 22.7%, 60.2% receiving testing below the minimum frequency. Among the factors that were most strongly associated with lack of adherence to guidelines were local stage and nonpoorly differentiated cancers. Age 70 to 74 years, African-American race, and increased comorbidity scores were also associated with less than recommended surveillance included.

In a multivariate logistic regression model, the variables that were most strongly associated with meeting or exceeding guidelines for surveillance care were younger age group and regional-stage cancers. Patients who were non–African-American and who had lower inpatient comorbidity scores and poorly differentiated cancers were more likely to undergo testing. Differences were also observed across geographic location, with odds ratios ranging from 0.60 (New Mexico) to 1.57 (Michigan).

Discussion

Approximately three of four patients diagnosed with colorectal cancer have local- or regional-stage tumors, and, assuming that these patients receive treatment with curative intent, the population of survivors in whom routine surveillance testing would be recommended is extremely large. The goals of surveillance testing are to discover a recurrence that is potentially resectable, identify metachronous neoplasms at an early stage, and provide reassurance to the patient.

Professional society practice guidelines include recommendations for routine colorectal cancer surveillance testing (Table).[1-8] The present study of a large cohort of patients treated in routine clinical practice showed that the majority of patients did not receive testing according to practice guidelines for cancer surveillance. Despite including the lowest extreme of the recommended range for testing from these guidelines (two office visits per year, two CEA tests per year in years 1 and 2, one colonoscopy in 3 years), we found that fewer than half the patients achieved compliance. Conversely, a subset of patients received procedures not routinely recommended by guidelines, such as CT and PET scans. Although some of these nonrecommended tests were likely performed because of signs or symptoms and/or abnormal results of routine testing, we suspect that many were obtained for routine follow-up.

Some of the differences in surveillance testing may be explained by clinical factors, such as stage of disease or perceived longevity as measured by age or comorbidity, but we also found important differences across racial groups and geographic sites. The generally lower use of testing in African Americans is likely a contributing factor to their poorer stage-specific survival compared with whites.[13] The results, especially the geographic differences across SEER sites, also suggest that patient and physician preferences may influence choice of testing.

The data used for this study had several inherent limitations. First, the accuracy of procedure coding in the Medicare population has not been formally studied, although we have evaluated its accuracy in a similar population from a large health plan.[14] Second, the study did not measure the indication for procedures, which could have been performed for diagnostic purposes as well as routine surveillance, particularly for procedures such as CEA testing and CT and PET scans, which are used to detect metastatic disease. Third, the database was limited to older patients (≥66 years) with colorectal cancer, and thus adherence in younger individuals could not be assessed. Fourth, because physician identifiers or specialty were not available in this database, we could not measure potential differences in practice according to provider type. Finally, we did not measure other factors that could have an impact on procedure use, such as access to care and socioeconomic status, which could not be ascertained from this database.

Summary

Our study of this population-based cohort of older colorectal cancer survivors showed that most patients underwent colorectal surveillance testing below a minimum frequency specified by clinical practice guidelines. We also found that a significant number of patients underwent procedures not recommended by clinical practice guidelines, suggesting potential overuse of surveillance tests. Further studies should ascertain the reasons for poor compliance with clinical practice guidelines and the effect this may have on patient outcome.

Acknowledgments

This study used the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, the National Center Institute; the Office of Research, Development and Information, Centers for Medicare & Medicaid Services; Information Management Services, Inc; and the SEER Program tumor registries in the creation of the SEER-Medicare database.

This study was supported by a research project grant (RSGT-01-072-03-CPHPC) from the American Cancer Society.

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Oncology Drug Codes

Medications Used for the Treatment of Prostate Cancer

The following sections include:

- Associated *ICD-9-CM* codes used for the classification of prostate cancer
- Drugs that have been FDA-approved in the treatment of prostate cancer. ***Please note:*** if a check mark appears in the FDA column it will NOT appear in the compendia section even if a drug is included in the *NCCN (National Comprehensive Cancer Network) Drugs & Biologics Compendium*
- Drugs included in the *NCCN Drugs & Biologics Compendium* for off-label use in genitourinary cancers. NCCN is recognized by the Centers for Medicare & Medicaid Services (CMS) as a referencing source
- Corresponding HCPCS/CPT codes and code descriptions
- Current Code Price (AWP-based pricing)
- Most recent ASP plus 6% (Medicare allowable)
- Possible CPT Administration Codes for each medication.

The following sections will assist healthcare professionals and payers by providing appropriate coding, billing, and reimbursement information associated with the management of prostate cancer.

Associated *ICD-9-CM* Code Used for Prostate Cancer

185 Malignant neoplasm of prostate

Excludes: *seminal vesicles (187.8)*

Generic (brand) name	HCPCS code: code description	FDA-approved for prostate cancer	*NCCN Drugs & Biologics Compendium* off-label use for prostate cancer	Current code price (AWP-based pricing)	Medicare allowable (ASP + 6%), effective 7/1/09-9/30/09	CPT administration codes
bicalutamide (Casodex)	J8999*: prescription drug, oral, chemotherapeutic, not otherwise specified	✓		NDC level pricing	NDC level pricing	N/A
carboplatin (Paraplatin)	J9045: injection, carboplatin, 50 mg		✓	$85.10	$5.22	96409, 96413, 96415
cisplatin (Platinol AQ)	J9060: cisplatin, powder or solution, per 10 mg		✓	$4.51	$2.32	96409, 96413, 96415
cisplatin (Platinol AQ)	J9062: cisplatin, 50 mg		✓	$22.56	$11.60	96409, 96413, 96415
Degarelix	J9999*: not otherwise classified, antineoplastic drugs *OR* C9399: unclassified drugs or biological	✓		NDC level pricing	NDC level pricing	96402
docetaxel (Taxotere)	J9170: injection, docetaxel, 20 mg		✓	$467.37	$344.65	96413
estradiol (Estrace)	J8499*: prescription drug, oral, nonchemotherapeutic, not otherwise specified	✓		NDC level pricing	NDC level pricing	N/A
estramustine (Emcyt)	J8999*: prescription drug, oral, chemotherapeutic, not otherwise specified	✓		NDC level pricing	NDC level pricing	N/A
etoposide (Etopophos)	J9181: injection, etoposide, 10 mg		✓	$0.55	$0.45	96413, 96415
etoposide (VePesid)	J8560: etoposide, oral, 50 mg		✓	$47.64	$30.35	N/A
flutamide (Eulexin)	J8999*: prescription drug, oral, chemotherapeutic, not otherwise specified	✓		NDC level pricing	NDC level pricing	N/A

Generic (brand) name	HCPCS code: code description	FDA-approved for prostate cancer	*NCCN Drugs & Biologics Compendium* off-label use for prostate cancer	Current code price (AWP-based pricing)	Medicare allowable (ASP + 6%), effective 7/1/09-9/30/09	CPT administration codes
goserelin (Zoladex)	J9202: goserelin acetate implant, per 3.6 mg	✓		$469.99	$196.05	96372, 96402
histrelin (Vantas)	J9225: histrelin implant (Vantas), 50 mg	✓		$6250.00	$1579.32	11981, 11982, 11983
ketoconazole (Nizoral)	J8499*: prescription drug, oral, nonchemotherapeutic, not otherwise specified		✓	NDC level pricing	NDC level pricing	N/A
leuprolide (Lupron Depot, Eligard)	J9217: leuprolide acetate (for depot suspension), 7.5 mg	✓		$367.25	$198.87	96402
mitoxantrone (Novantrone)	J9293: injection, mitoxantrone hydrochloride, per 5 mg	✓		$126.94	$68.36	96409, 96413
nilutamide (Nilandron)	J8999*: prescription drug, oral, chemotherapeutic, not otherwise specified	✓		NDC level pricing	NDC level pricing	N/A
prednisone	J7506: prednisone, oral, per 5 mg		✓	$0.05	$0.04	N/A
triptorelin (Trelstar LA, Trelstar Depot)	J3315: injection, triptorelin pamoate, 3.75 mg	✓		$756.25	$161.82	96372, 96402
zoledronic acid (Zometa)	J3487: injection (Zometa), zoledronic acid, 1 mg		✓	$268.96	$217.37	96365, 96374

*When billing a nonclassified medication using a CMS 1500 claim form you must include both the HCPCS code (ie, J8999 for Degarelix) in column 24D and the drug name, strength, and National Drug Code (NDC) in box 19 to ensure appropriate reimbursement.

References

• *HCPCS Level II Expert, 2009* • *CPT 2009; 2008* • *ICD-9-CM for Professionals Volumes 1 & 2; 2009* • *The Drug Reimbursement Coding and Pricing Guide,* Vol 6, No 3; RJ Health Systems International LLC; 3rd Quarter 2009 • FDA-approved indication (from products' prescribing information) • NCCN • National Cancer Institute • www.ReimbursementCodes.com powered by RJ Health Systems International, LLC, Wethersfield, Connecticut • CMS-Medicare allowable 3rd Quarter 2009 (effective dates 7/1/09-9/30/09).

Prices listed herein are effective as of July 1, 2009.

ASP indicates average sales price; AWP, average wholesale price; CMS, Centers for Medicare & Medicaid Services; CPT, Current Procedural Terminology; FDA, US Food and Drug Administration; HCPCS, Healthcare Common Procedure Coding System; NCCN, National Comprehensive Cancer Network.

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Novel Agent Omacetaxine Active in *T315I*-Positive CML

ORLANDO—In patients with a challenging form of chronic myeloid leukemia (CML), a first-in-class agent may prove to be an effective treatment option.

Tyrosine kinase inhibitors (TKIs) have significantly improved the outcomes of patients with CML; currently available TKIs, however, have no activity against the type of CML associated with the *T315I*-mutant form of *BCR-ABL*. This mutation renders patients insensitive to TKIs, and is responsible for up to 20% of the point mutations that develop with imatinib resistance.

Results from a phase 2/3 study presented at the annual meeting of the American Society of Clinical Oncology indicate that the novel agent omacetaxine, the first agent in the cetaxine class, has clinical activity in this subtype.

"Omacetaxine may offer a new therapy for patients with *T315I*-positive CML, where we have no other options except allogeneic transplantation," said lead author Jorge Cortes, MD, University of Texas, M.D. Anderson Cancer Center, Houston, in his oral presentation.

Omacetaxine is a semisynthetic formulation of the natural alkaloid homoharringtonine, a compound that was used to treat CML until the advent of imatinib. The mechanism of action of omacetaxine is independent of tyrosine kinase inhibition. Instead, it inhibits protein synthesis and induces apoptosis, Cortes explained.

The open-label study included 66 patients with imatinib-resistant *T315I*-positive CML who were in chronic, accelerated, or blast phase of disease. Eighty percent of the patients had received two or more prior treatments.

Induction therapy was with 1.25 mg/m^2 of omacetaxine, self-administered daily for 14 days on a 28-day cycle. After one or more induction cycles, and on achievement of hematologic response, patients received maintenance therapy with the same dose for 7 days of every cycle.

Treatment with omacetaxine led to a complete hematologic response in 85% of the 40 patients with chronic-phase CML, in 50% of the 16 patients with accelerated-phase CML, and in 50% of the 10 patients with blast-phase CML, Cortes reported.

The median duration of complete hematologic response was 8.9 months (range, 1.7-23.9 months) for patients in chronic phase, and 4.1 months and 3.3 months for accelerated and blast phases, respectively.

A cytogenetic response was achieved in 28% of patients in chronic phase and 6% of those in accelerated phase. For six (15%) of the 40 chronic-phase patients, this was a major cytogenetic response lasting a median of 6.1 months.

For the chronic-phase patients, overall survival was nearly 90% after more than 2 years, and the median survival time had not been reached. Median survival was almost 19 months for accelerated-phase patients but less than 2 months for blast-phase patients. "In many patients there was a disappearance of the *T315I* clone," Cortes added.

Omacetaxine was generally well tolerated, the primary toxicity being myelosuppression that was usually transient and manageable with dose reductions. "We can adjust the dose to minimize myelosuppression over time," Cortes noted.

Thrombocytopenia occurred in 58%, anemia in 41%, neutropenia in 36%, and febrile neutropenia in 15% of patients. Diarrhea and fatigue affected <3% of patients.

—*CH*

Coverage of the 2009 Annual Meeting of ASCO continues in the September/October issue of *The Oncology Nurse*.

Extravasation: Assessment and Treatment

Continued from cover

tively new treatment for anthracycline extravasations, and comes packaged in an emergency toolkit.[1] It has been added to the 2009 ONS guidelines as the only US Food and Drug Administration (FDA)-approved treatment for anthracycline extravasations.

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 of practice define infiltration and extravasation as[2]:

- **Infiltration**—inadvertent administration of nonvesicant medication or 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 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. Nonantineoplastic 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 resicants 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 are 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.

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.

Totect® has been added to the new 2009 ONS guidelines as the only US Food and Drug Administration–approved treatment for anthracycline extravasations.

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 of the agent.

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.

Recent FDA Approvals

- **Pemetrexed for Maintenance Therapy in Advanced Nonsquamous NSCLC**

The US Food and Drug Administration (FDA) has approved pemetrexed (Alimta, Eli Lilly) for intravenous use, 100-mg and 500-mg vials, in maintenance treatment in patients with advanced or metastatic nonsquamous non–small-cell lung cancer (NSCLC) whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Pemetrexed is not indicated for treatment of patients with squamous cell NSCLC.

- **Mylan's Generic Bicalutamide for Prostate Cancer**

The FDA has approved Mylan's version of bicalutamide tablets, 50 mg, a generic version of Casodex (AstraZeneca). Bicalutamide is indicated for use in combination therapy with a leutinizing hormone-releasing hormone analog for the treatment of stage D_2 metastatic carcinoma of the prostate. It is not approved for use alone or with other treatments. Mylan has begun to ship this product.

Treatment of extravasation

Data on treatment of vesicant anticancer drug extravasations have been largely empirically based, have shown an inconsistent frequency of 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 FDA for the treatment of vesicant extravasations. Sodium thiosulfate/mechlorethamine and Totect® extravasation emergency toolkit.

Sodium thiosulfate has been shown to have efficacy in mechlorethamine extravasations. In limited clinical data and one preclinical animal study,[4] sodium thiosulfate has been shown to neutralize mechlorethamine through alkalinization and formation of thioesters to reduce toxicity. On preparing a 1/6 molar solution, 2 mL of the sodium thiosulfate solution are injected with a 25-gauge needle subcutaneously into the affected area for each milligram of mechlorethamine that has extravasated, changing the needle with each injection.[7]

The second FDA-approved agent for vesicant extravasations is Totect®, which 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. The agent Totect® also acts as an iron chelator and minimizes oxidative damage caused by formation of anthracycline–iron complexes.[19,20] Totect® is then rapidly metabolized within the cell to chelate iron and limit anthracycline-mediated oxidative injury.

Table 2. Examples of DNA-binding Capacity of Selected Intravenous Medications

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

[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.

Several clinical trials have been performed to determine the safety and efficacy of Totect®. Two international, 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 Totect® 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 Totect® to have 98% overall efficacy in preventing necrosis that required surgery.[21]

Totect® 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 Totect® 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]

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. Totect®, 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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International Oncology News

Reports from International Meetings and Researchers

Everolimus Shows Potential in Non-Hodgkin's and Hodgkin's Lymphoma

BERLIN—Treatment with the mammalian target of rapamycin inhibitor everolimus seems to produce significant tumor shrinkage in patients with relapsed non-Hodgkin's lymphoma (NHL) and Hodgkin's disease, according to phase 2 data released at the 14th Congress of the European Hematology Association.

Thomas Witzig, MD, with the Mayo Clinic in Rochester, Minnesota, and his associates tested the efficacy and safety of everolimus, 10 mg/day, in 146 patients with relapsed/refractory aggressive or indolent NHL or Hodgkin's disease whose disease had progressed despite prior treatment.

Results showed that 33% of patients experienced a 50% or greater decrease in tumor size. The median time to disease progression for the entire study population was 4.3 months, and the median duration of response for the 48 responders was 6.8 months. Of the initial responders, 19 remained progression-free at 6 months.

Everolimus showed anticancer activity in a broad range of lymphoma types. The overall response rate was 63% for T-cell NHL, 53% for Hodgkin's disease, 50% for follicular lymphoma, 32% for mantle cell lymphoma, 30% for diffuse large B-cell lymphoma, and 18% for small lymphocytic lymphoma. Treatment was well tolerated.

A phase 3 trial is being planned that will study the efficacy and safety of everolimus in preventing relapse in patients with diffuse large B-cell lymphoma.

Oral Bisphosphonates Do Not Increase Esophageal Cancer Risk

VIENNA—New research appears to undermine the notion of a possible link between oral bisphosphonate treatment and esophageal cancer.

Bo Abrahamsen, MD, with Copenhagen University Hospital in Gentofle, Denmark, and associates examined the risk of esophageal cancer using recent 10-year data from a national registry.

Earlier this year, the US Food and Drug Administration reported 23 cases of esophageal cancer in patients who had been prescribed oral bisphosphonates for osteoporosis and called for studies to determine if these agents increase esophageal cancer risk.

The analysis included 15,795 patients with fractures starting oral bisphoshonate therapy and 31,590 fracture patients who were not starting bisphosphonate therapy. The two groups were matched for age, sex, and fracture type.

The investigators identified 45 cases of esophageal cancer over 132,000 patient-years. Patients who refilled their oral bisphosphonate prescription actually had a significantly lower risk of esophageal cancer compared with untreated matched controls.

The lower esophageal cancer rates in bisphosphonate users who refilled their prescriptions may suggest that oral bisphosphonates are preferentially targeted to and accepted by patients without upper gastrointestinal complaints, Abrahamsen said.

He reported the findings at the 36th European Symposium on Calcified Tissues.

—Jill Stein

In the Literature

Concise Reviews of Studies Relevant to Cancer Care

Weekly Topotecan and Docetaxel in Heavily Pretreated Patients with Recurrent Uterine and Ovarian Cancers

Background: Recurrent gynecologic cancers tend to be difficult to treat, and although topotecan and docetaxel are commonly used agents, they are not always used in combination.

Design: Patients with epidermal growth factor receptor–positive colorectal cancer with unresectable metastases were randomized to receive FOLFIRI either alone or in combination with cetuximab.

Design: In a phase 2 trial without a comparison group, researchers evaluated the efficacy and safety of weekly topotecan (3.5 mg/m^2) and docetaxel (30 mg/mg/m^2) for 3 consecutive weeks in heavily pretreated patients with recurrent uterine or epithelial ovarian cancers. Cycles were repeated every 4 weeks for six cycles. Response was assessed as per RECIST. Time to best response and overall survival were calculated using Kaplan-Meier statistical methods.

Summary: Of the 24 patients evaluable for response, the majority had received two prior chemotherapy regimens. Patients experienced three grade 4 neutropenias and 10 grade 3 toxicities, six of which were not related to treatment. Overall response rate was 25% (95% CI, 7.7%-42.3%; 8% CR; 17% PR). Thirty-eight percent had clinical benefit (95% CI, 18.1%-56.9%; CR+PR+13% SD). Median duration of response was 8.5 months; median overall survival was 18.5 months.

Takeaway: Weekly combination therapy with topotecan plus docetaxel has clinical benefit for and is well tolerated by heavily pretreated patients with recurrent uterine or epithelial ovarian cancers.

Gupta D, et al. Gynecol Oncol. *2009;113:327-330.*

Insulin Resistance and Risk Factors for Cardiovascular Disease in Young Adult ALL Survivors

Background: Long-term survivors of childhood acute lymphoblastic leukemia (ALL) have been found to have a significantly elevated risk of premature mortality and serious morbidity. With the number of survivors increasing and entering middle-age, further study is needed to determine whether the risk of cardiovascular disease (CVD) is increased.

Design: The researchers estimated insulin resistance in 118 survivors of childhood ALL (median age, 23 years; range, 18-37 years) using the homeostasis model for assessment of insulin resistance (HOMA-IR). Sex-specific comparisons were made with a cohort of 30- to 37-year-old patients from the Dallas Heart Study (DHS, N = 782). Survivors were stratified by treatment with/without cranial radiotherapy (CRT).

Summary: Using the DHS participants as controls (female: mean, 2.4; 95% CI, 2.2-2.7; male: mean, 2.3; 95% CI, 2.1-2.6), female survivors had a significantly higher HOMA-IR (CRT: mean, 4.6; 95% CI, 3.6-5.7; no CRT: mean, 3.3; 95% CI, 2.8-3.8) as did male survivors (CRT: mean, 4.0; 95% CI, 2.8-5.6; no CRT: mean, 3.4; 95% CI 2.9-3.9). Of women treated with CRT, 80% had at least three of six CVD risk factors and were significantly more likely to have these risk factors than controls (OR = 5.96; 95% CI, 2.15-16.47). Male survivors were no more likely to have multiple CVD risk factors than the controls.

Takeaway: ALL survivors, regardless of sex and therapy, have an increased prevalence of insulin resistance. Women treated with CRT have a substantially increased prevalence of various CVD risk factors, and thus close monitoring and risk-reduction strategies are warranted.

Oeffinger KC, et al. J Clin Oncol. *June 29, 2009. Epub ahead of print.*

Leading patients toward improved outcomes

You help patients reach their treatment goals

RITUXAN is a proven path for many patients battling non-Hodgkin's lymphoma (NHL), but they can't complete the journey alone.

Oncology nurses are central members of a cancer care team—working together to achieve improved outcomes. Your guidance and leadership help patients reach their treatment goals. We recognize your commitment and support your continued efforts with innovative patient-education materials and services.

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RITUXAN is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

Reference: 1. RITUXAN® (Rituximab) full prescribing information, Genentech, Inc., 2008.

Please see brief summary of prescribing information on adjacent page.

Attention Healthcare Provider: Provide Medication Guide to patient prior to RITUXAN infusion.

BOXED WARNINGS and Additional Important Safety Information

The most important serious adverse reactions of RITUXAN are **fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions, progressive multifocal leukoencephalopathy (PML)**, hepatitis B reactivation with fulminant hepatitis, other viral infections, cardiovascular events, renal toxicity, and bowel obstruction and perforation. The most common adverse reactions of RITUXAN (incidence ≥25%) observed in patients with NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia.[1]

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