BREAST CANCER
New technologies in HER2 testing. Part 2

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CANCER CLINICAL TRIALS
Coalition of Cancer Cooperative Groups works to increase clinical trial participation

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NURSING PRACTICE

New ACCC President Seeks to Shine a Light on Oncology Workforce Shortage

An interview with Luana Lamkin, RN, MPH

Luana Lamkin, RN, MPH, became president of the Association of Community Cancer Centers (ACCC) at its 35th annual meeting in March. Lamkin is the administrator for St. Luke's Mountain States Tumor Institute at St. Luke's Boise Medical Center, Idaho. In this interview, she discusses her goals for her year as president.

Are you the first nurse to serve as ACCC president?

No, actually I'm the fifth nurse to serve as ACCC president. The presidency reflects the diverse membership of the organization. Of the people who attend meetings, about 50% are physicians and about 50% are nurses and other members of the

Continued on page 40

PROSTATE CANCER

AUA Counters Mainstream Recommendations with New Prostate Cancer Guidelines

CHICAGO—The American Urological Association (AUA) is lowering the recommended age for prostate-specific antigen (PSA) testing by 10 years, from age 50 years to age 40 years. The AUA issued new clinical guidance, which directly contrasts with recent recommendations by other major groups, at its 104th Annual Scientific Meeting in April. The new recommendation by the AUA is that PSA testing should be offered to

Continued on page 30

CONFERENCE NEWS

PARP Inhibitors Show Promise in Various Forms of Advanced Breast Cancer

ORLANDO—Inhibitors of poly (ADP-ribose) polymerase (PARP) show significant activity in triple-negative and *BRCA*-deficient advanced breast cancer, said researchers at the 2009 annual meeting of the American Society of Clinical Oncology.

In the treatment of triple-negative breast cancer, the PARP-1 inhibitor BSI-201 on top of standard chemotherapy significantly improved progression-free

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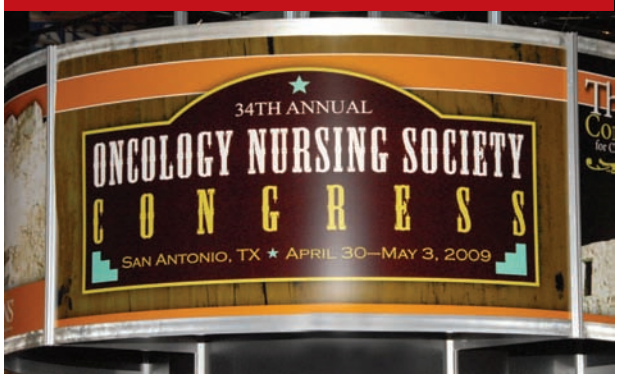
34TH ANNUAL ONS CONGRESS



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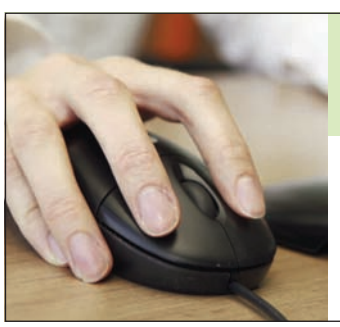
Faces at the Congress: page 13



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:

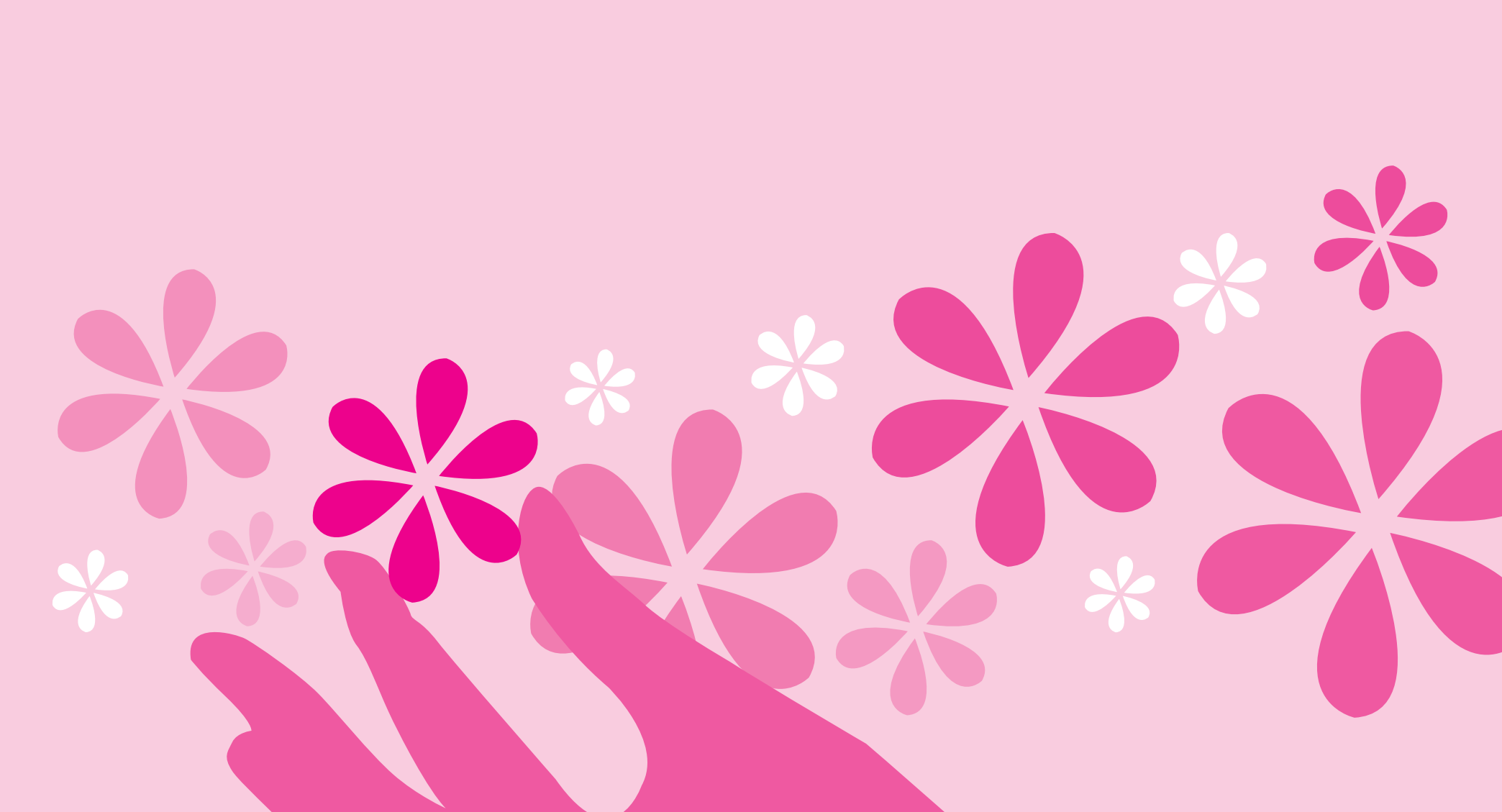
- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

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

		Incidence of CHF	
Study	Regimen	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

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

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

Infusion Reactions Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [*see Adverse Reactions*]. In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction. Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications. **Exacerbation of Chemotherapy-Induced Neutropenia** In randomized, controlled clinical trials in women with metastatic breast cancer, the per-patient incidences of NCI CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was not significantly increased. [*see Adverse Reactions*]. **Pulmonary Toxicity** Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and Precautions (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)

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

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

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast, metastatic breast cancer, or post-marketing experience. *Cardiomyopathy* Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year Herceptin arm); and in Studies 1 and 2, 23 months in

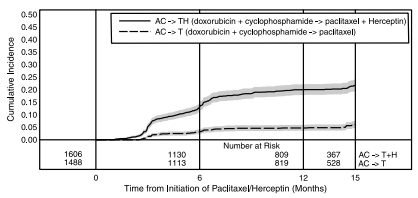
the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF <50% or ≥15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving Herceptin and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving Herceptin monotherapy compared to observation in Study 3 (see Table 5, Figures 1 and 2).

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

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF <50%	≥10% decrease	≥16% decrease	<20% and ≥10%	≥20%
Studies 1 & 2[a]					
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)

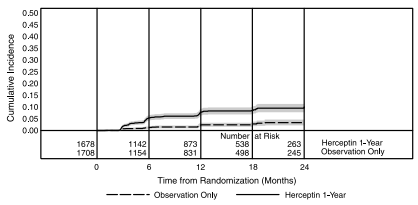
[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization. [b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[c] Study 4 regimens: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



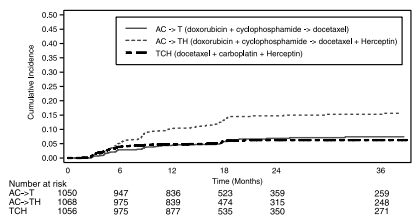
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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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4839803
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Revision Date: March 2009
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News Notes

News Updates of Relevance to Everyday Oncology Practice

BRCA1 and *BRCA2* Patents Challenged

A potential landmark lawsuit was filed on May 12, 2009, in the federal court of New York against Myriad Genetics Laboratories, the manufacturer of BRAC *Analysis*, and the US Patent Office. The suit challenges the decision to grant a patent on a gene to a single company. Plaintiffs argue that *BRCA* testing would improve if market forces were allowed to work, and that the restriction on competition blocks other companies to develop alternatives, as well as to interpret or compare gene sequences that involve the patented genes. Myriad has not yet responded publicly to the suit. The American Civil Liberties Union, which organized the lawsuit, pointed out that the problem is with the US Patent Office, not Myriad specifically. Single companies also hold patents on the *HFE* gene, which is linked to hereditary hemochromatosis, the *CFTR* gene, which is linked to cystic fibrosis, and a genetic test on long QT syndrome, which can lead to heart arrhythmias and sudden death (*New York Times*. May 12, 2009).

Sleep Problems May Lead to Increased Cancer Pain

Pain and fatigue may be reduced by interventions to help patients with cancer deal with sleep problems and depressed mood. Further, pain management may help alleviate trouble sleeping. Stepanski and colleagues analyzed demographic, clinical, and patient-reported outcomes data from 11,445 cancer patients undergoing treatment in a large community oncology practice using structural equation modeling. The data were split so that a model was constructed using half of the patients; this model was then cross-validated on the remaining patients. Although fatigue was best represented as a latent variable, significant direct effects were found for trouble sleeping, depressed mood, and pain (*J Sleep Med*. April 15, 2009).

Risk for False-positive Findings with Multiple Cancer Screenings

As the number of cancer screening tests increases, the likelihood for false-positives may also increase, along with diagnostic interventions. Researchers examined this cumulative risk by analyzing data from patients participating in the ongoing Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Croswell and colleagues found that after 14 tests, the cumulative risk of having at least one false-positive is 60.4% and the cumulative risk of undergoing an invasive diagnostic procedure prompted by a false-positive result is 28.5% for men and 22.1% for women. Based on this likelihood, physicians should educate their patients about these risks during cancer screening discussions (*Ann Fam Med*. 2009;7:212-222).

Continued on page 8

A Letter from the Editor

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

EDITOR-IN-CHIEF

As this issue goes to press, news from the annual meeting of the American Society of Clinical Oncology is being widely reported to both healthcare professionals and the general public. Although no major breakthroughs were reported, many smaller studies showed advances that may lead to new treatment options and new hope for patients with advanced cancers and hard-to-treat cancers like melanoma and ovarian cancer. The latest cancer statistics reported this week by the American Cancer Society also attest to the progress being made in the fight against cancer. In 2006 (the latest year for which statistics are available), there were 181 cancer deaths per 100,000 people, down from 184 in 2005. Although modest, these changes show a continuing downward trend in cancer deaths, attributed to earlier detection and improved treatment.

Not only are new treatments emerging for cancers such as advanced melanoma, but new research is leading to reevaluation of older agents, such as gefitinib for non–small-cell lung cancer, as discussed in the continuing education article by Edward S. Kim, MD, and his colleagues. But, as their study shows, cancer therapies not only have to be compared in terms of safety and efficacy but also in terms on their impact on quality of life. As Karen Oishi points out in her commentary, patients and their families must be informed about the available treatment options, and their preferences regarding treatments and their potential side effects must be considered.

The recent news reports of a mother and her 13-year-old son who fled after a court-ordered treatment for the son's lymphoma illustrate how complex these decisions may be and how important it is to establish good communication with patients and their families.

The theme of the ASCO meeting this year was personalized medicine. Advances in understanding of the genetics and biology of cancer and identification of biomarkers have made it possible to tailor cancer treatments to the biologic characteristics of the individual patient. But beyond this, the patient's values, beliefs, preferences, and lifestyle must be taken into account as well, and treatment options must be clearly communicated to the patient and his or her family. As nurses, we will have to educate ourselves about new therapies so that we can discuss them with our patients and help them make informed decisions about which options are best for them and how to use them properly to optimize outcomes and minimize adverse effects.

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News Notes

Continued from page 3

FDA Invests in Product Safety

The US Food and Drug Administration (FDA) has requested a budget of $3.2 billion to protect and promote the public health—a 19% increase over the current year's budget. The 2010 request proposes two major initiatives: protecting America's food supply and safer medical products. The safer medical products effort ($166.4 million) provides resources to improve the safety of human and animal drugs, medical devices, vaccines, blood, and other medical products by strengthening the safety and security of the supply chain for medical products. Included in this effort is the follow-on biologics and drug importation initiative ($5 million), which proposes a new authority for the FDA to approve follow-on biologics and provides funding for the FDA to develop policies to allow Americans to buy drugs approved in other countries (www.fda.gov/bbs/topics/NEWS/2009/NEW02013.html).

Stimulus Package Increases Cancer Research Funding

With the American Recovery and Reinvestment Act of 2009, the National Cancer Institute (NCI) will receive $1.3 billion during 2009 and 2010. This increase in available financing for research allows the NCI to support the best 25% of grant applications that pass peer review. This is almost double the amount of applications approved for funding last year. The stimulus money, however, will not go into the NCI's general budget, leaving some applications to receive only 4 years of funding instead of the standard 5 years (www.cancer.gov/ncicancerbulletin/042109/page4).

Updated Medicare Hospice Referral Process

Beginning in 2010, hospice physicians who certify or recertify a beneficiary as terminally ill will need to write a short narrative on the certification form that briefly describes the clinical evidence supporting a life expectancy of <6 months, according to a proposed rule to update the Medicare Hospice Wage Index for fiscal year 2010 issued by the Centers for Medicare & Medicaid Services. This proposed regulation would bring the Medicare Hospice Wage Index more in line with the index now used for home health agencies, while maintaining the fiscal integrity of Medicare and allowing continued access to hospice services for its beneficiaries.

This requirement will be in addition to a planned 1.1% cut in hospice care reimbursement rates, by eliminating the temporary adjustment (with a 2-year phase-out) used in calculating the wage index, partially offset by the estimated increase in the hospital market-basket indicator of costs (www.cms.hhs.gov/apps/media/press/factsheet.asp?Counter=3441).

In the Literature

Concise Reviews of Studies Relevant to Cancer Care

Cetuximab plus FOLFIRI Reduces Risk of Progression of Metastatic Colorectal Cancer

Background: Researchers investigated the efficacy of cetuximab plus FOLFIRI (irinotecan, fluorouracil, and leucovorin) as first-line treatment for metastatic colorectal cancer. The researchers also sought to find associations between the mutation status of the Kirsten rat sarcoma (*KRAS*) gene and clinical response to cetuximab.

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.

Summary: This study adds to the growing number of reports showing the significant association between *KRAS* mutation status and tumor response. The researchers found that cetuximab benefit was limited to patients with wild-type *KRAS* tumors. However, they found no significant difference in overall survival. Grade 3/4 adverse events, which were more frequent with the combination therapy, included skin reactions, infusion-related reactions, and diarrhea.

Takeaway: Cetuximab plus FOLFIRI increased progression-free survival by 1.2 months in patients with metastatic colorectal cancer wild-type *KRAS* tumors.

Van Custem E, et al. N Engl J Med. *2009;360:1408-1417.*

Addition of Casopitant Mesylate Reduces CINV

Background: Management of chemotherapy-induced nausea and vomiting (CINV) remains an issue for patients receiving highly emetogenic chemotherapy. The addition of casopitant mesylate to a regimen of dexamethasone and ondansetron may help prevent delayed-phase CINV.

Design: In a multicenter, randomized, double-blind, placebo-controlled trial, chemo-naïve patients with malignant solid tumors were randomized to receive placebo, single oral dose (150 mg) of casopitant mesylate, or 3-day intravenous (90 mg on day 1) plus oral (50 mg on days 2 and 3) casopitant mesylate. The primary end point was the proportion of patients without vomiting, retching, or use of rescue medications in the first 120 hours.

Summary: More patients in the casopitant groups achieved complete response after cycle 1 (66% in the placebo group, 86% in the oral casopitant group, and 80% in the intravenous plus oral casopitant group). This improvement was sustained over multiple cycles. Adverse events included neutropenia, febrile neutropenia, and dehydration.

Takeaway: The three-drug regimen (casopitant mesylate, dexamethasone, ondansetron) significantly reduces CINV in patients receiving highly emetogenic chemotherapy compared with the two-drug regimen (dexamethasone, ondansetron). This study was funded by GlaxoSmithKline.

Grunberg SM, et al. Lancet Oncol. *May 8, 2009. Epub ahead of print.*

Cancer Survivors More Likely to Be Unemployed

Background: Almost half of all cancer survivors are younger than 65 years, a group for which cancer and its treatment could alter employment opportunities. However, the association between survivorship and employment status is unknown.

Design: Researchers performed a meta-analysis using data found through a systematic search of studies published between 1966 and June 2008 from the MEDLINE, CINAHL, PsycINFO, and OSH-ROM databases. Meta-regression analysis was performed to assess associations of unemployment with cancer type, country of origin, average age at diagnosis, and background unemployment rate.

Summary: Cancer survivors were 1.37 times more likely to be unemployed than healthy controls. Survivors of breast cancer, gastrointestinal cancers, and cancer of the female reproductive organs were at an increased risk for unemployment.

Takeaway: To improve employment outcomes, clinical and supportive services should be aimed at better management of symptoms, rehabilitation, and workplace accommodation for disabled survivors.

De Boer AGEM, et al. JAMA. *2009;301:753-762.*

Gemcitabine and Vinorelbine Effective in Children with Hodgkin's Disease

Background: Both gemcitabine and vinorelbine have significant single-agent response rates in pediatric patients with heavily pretreated relapsed/refractory Hodgkin's disease. The efficacy and toxicity of a combination of these two agents (ie, GV) were assessed for this population by the Children's Oncology Group.

Design: In a phase 2 trial, patients received, on days 1 and 8 of each 21-day cycle, vinorelbine 25 mg/m^2/dose via intravenous (IV) push before gemcitabine 25 mg/m^2/dose IV over 100 minutes. Response (including complete response, very good partial response, partial response) was evaluated every two cycles.

Summary: In patients aged 10.7 to 29.4 years who had received at least two prior chemotherapy regimens, some having undergone prior autologous stem-cell transplantation, measurable responses were seen in 76% of assessable patients. Hematologic toxicity was prominent in all treatment cycles. Nonhematologic grade 3 and 4 toxicity was less common.

Takeaway: GV is an effective and well-tolerated reinduction regimen for children with relapsed or refractory Hodgkin's disease. Further evaluation of GV in this population is warranted.

Cole PD, et al; for the Children's Oncology Group. J Clin Oncol. *2009;27:1456-1461.*

Adjuvant Chemotherapy Improves Survival in Older Women with Early-Stage Breast Cancer

Background: In the United States, the average age at diagnosis of breast cancer is approximately 63 years, and most deaths occur in women 65 years or older. However, older women are underrepresented in clinical trials.

Design: Patients with stage I, II, IIIA, or IIIB breast cancer were randomized to receive either standard chemotherapy or capecitabine. Endocrine therapy was recommended when applicable. A Bayesian statistical design was used to test the noninferiority of capecitabine as compared with standard chemotherapy. The primary end point was relapse-free survival.

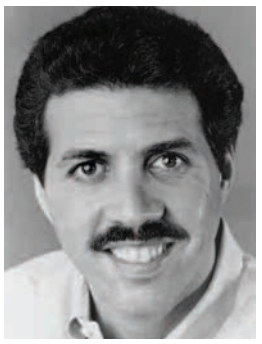
Summary: At 2 years, patients who received capecitabine were twice as likely to have a relapse and almost twice as likely to die as patients who received standard chemotherapy. At 3 years, the rate of relapse-free survival was 68% for patients who received capecitabine and 85% in those who received standard chemotherapy.

Takeaway: Standard adjuvant chemotherapy is superior to capecitabine in patients with early-stage breast cancer who are 65 years of age or older.

Muss HB, et al; for the CALB Investigators. N Engl J Med. *2009; 360:2005-2065.*

Did you Know?

According to new American Cancer Society statistics, about 562,340 American men and women will die of cancer in 2009. The most common fatal cancers are cancers of the lung and bronchus, prostate, and colorectum in men and cancers of the lung and bronchus, breast, and colorectum in women.



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Medical Minutes

BY **JOHN SCHIESZER**

A Speedier and More Precise Radiotherapy

Cancer specialists at the University of Alabama at Birmingham (UAB) say they have now become among the first in the United States to adopt a speedier cancer radiation therapy. The new technique can turn a 20-minute radiotherapy session into a 90-second session for selected patients. Additionally, the new therapy reportedly saves healthy human tissue from unwanted radiation exposure at rates that are the same or better than other radiotherapy techniques.

The new therapy is called RapidArc (Varian Medical Systems), which is the next generation of intensity-modulated radiation therapy (IMRT). Conventional IMRT was introduced in the 1990s as a way to deliver multiple beams of radiation to a tumor, and minimize damage to nearby healthy tissues. RapidArc advances the early technology, with radiation delivery duration up to eight times faster than conventional IMRT.

"RapidArc is an important advance for us and our patients," said John Fiveash, MD, who is an associate professor of radiation oncology at UAB. "Knowing that we can reduce delivery times to less than 2 minutes per day is important, considering what cancer care involves emotionally and physically."

He and his colleagues say faster radiation delivery times reduce the chances that a slight move will affect the accuracy of the radiotherapy targeting. In addition, it means that patients can spend less time and feel less discomfort in the treatment position.

"We presently treat many patients with very complex treatment plans," said John Brinkhoff, RPh, who is part of the UAB cancer team. "We have a head and neck cancer plan that would normally require patients to lie still for 20 minutes with their face in a cushioned stability mask. With RapidArc, they are required to remain still for only 90 seconds."

The new system incorporates powerful computers to help clinicians arrive at a radiotherapy treatment strategy after pouring over thousands of biological and mathematical variables, including medical scans of each patient's tumor.

Eating Soy Early in Life May Reduce Breast Cancer Risk

Eating tofu and other soy foods as a child may help protect some girls from developing breast cancer later in life. A new study by researchers at the National Cancer Institute (NCI) has found that Asian-American women who ate higher amounts of soy during childhood had a 58% reduced risk of breast cancer.

"Historically, breast cancer incidence rates have been four to seven times higher among white women in the United States than in women in China or Japan. However, when Asian women migrate to the United States, their breast cancer risk rises over several generations and reaches that of US white women, suggesting that modifiable risk factors, rather than genetics, are responsible for the international differences. These lifestyle or environmental factors remain elusive. Our study was designed to identify them," said study investigator Regina Ziegler, PhD, MPH, who is in the Division of Cancer Epidemiology and Genetics at the NCI.

The current study focused on women of Chinese, Japanese, and Filipino descent who were living in San Francisco, Oakland, Los Angeles, or Hawaii. The researchers interviewed 597 women with breast cancer and 966 healthy women. If the women had mothers living in the United States, the researchers interviewed those mothers to determine the frequency of soy consumption in childhood.

The researchers divided soy intake into thirds and compared the highest and the lowest groups. High intake of soy in childhood was associated with a 58% reduction in breast cancer. A high level of soy intake in the adolescent and adult years was associated with a 20% to 25% reduction. The childhood relationship held in all three ethnicities and all the study sites, and in women with and without a family history of breast cancer.

"Since the effects of childhood soy intake could not be explained by measures other than Asian lifestyle during childhood or adult life, early soy intake might itself be protective," said lead study investigator Larissa Korde, MD, MPH, who is a clinician at the NCI's Clinical Genetics Branch. "Childhood soy intake was significantly associated with reduced breast cancer risk in our study, suggesting that the time of soy intake may be especially critical."

The underlying mechanism is not known. However, early soy intake may have a biological role in breast cancer prevention. Korde said soy isoflavones have estrogenic properties that may cause changes in breast tissue. She noted that animal models have suggested that ingestion of soy may result in earlier maturation of breast tissue and increase resistance to carcinogens.

Folic Acid Fortification May Be Associated with Heightened Colon Cancer Risk

There may be a rather significant downside to folic acid fortification. According to a newly released study, the rate of colorectal cancer in Chile may have increased since that country began fortifying wheat flour with folic acid.

Researchers at the University of Chile in Santiago analyzed changes in colon cancer rates since the Chilean government introduced a mandatory program of folic acid fortification of wheat flour in 2000. Several countries have implemented similar policies in recent years, with the goal of preventing spina bifida and other neural tube defects. In Chile, the rate of neural tube defects decreased by 40% in the first year after the start of folic acid fortification. However, there now appears to be a possible caveat.

The researchers compared hospital discharge data on colon cancer rates in Chile in 4-year periods before and after folic acid fortification: 1992 to 1996 versus 2001 to 2004. Although no causative relationship can be proved, the data suggested a significant relationship between folic acid supplementation and colorectal cancer. Reported cases of colon cancer increased by 162% in people aged 45 to 64 and by 190% in people aged 65 to 79.

After adjustment for other factors, discharge diagnoses of colon cancer in these age groups were two to three times more frequent after the start of folic acid fortification. Most other disease diagnoses showed no consistent pattern of changes. There was a small increase in breast cancer, which may have been related to early detection and universal treatment programs for that disease.

Chile is the third country to report an apparent increase in colorectal cancer after introducing a national folic acid fortification program. A 2007 report suggested increases in colorectal cancer after folic acid fortification was introduced in the United States and Canada in the mid-1990s. Chile uses a higher "dose" of folic acid than the two North American countries. Folic acid fortification has not yet been introduced in Europe.

For patients 55 years and older with acute myelogenous leukemia (AML) following induction chemotherapy...

Go Beyond Neutrophil Recovery With LEUKINE

LEUKINE is a multilineage colony-stimulating factor that stimulates the production and activity of monocytes/macrophages and dendritic cells, as well as neutrophils[1]

Significantly fewer deaths due to serious infections in patients treated with LEUKINE versus placebo*[2]

75% DECREASE	90% DECREASE	83% DECREASE	73% DECREASE
LEUKINE, 3/52 (5.8%) vs placebo, 11/47 (23.4%)	LEUKINE, 1/52 (1.9%) vs placebo, 9/47 (19.1%)	LEUKINE, 1/8 (12.5%) vs placebo, 9/12 (75%)	LEUKINE, 2/14 (14.3%) vs placebo, 7/13 (53.8%)
P=.019 Fatal infections during and within 30 days of study completion	*P*=.006 Death from fungal infections in all patients	*P*=.02 Fatal fungal infections in patients with grade 3/4 fungal infections	*P*=.046 Death from pneumonias in patients with pneumonia

*In a phase III, multicenter, randomized, double-blind, placebo-controlled trial of 99 newly diagnosed adult patients, 55 to 70 years of age, receiving induction chemotherapy with or without consolidation therapy.[2]

References: 1. LEUKINE® (sargramostim) [package insert]. Bayer HealthCare Pharmaceuticals Inc.; April 2008. **2.** Rowe JM, Rubin A, Mazza JJ, et al. Incidence of infections in adult patients (> 55 years) with acute myeloid leukemia treated with yeast-derived GM-CSF (sargramostim): results of a double-blind prospective study by the Eastern Cooperative Oncology Group. In: Hiddemann W, et al, eds. *Acute Leukemias V: Experimental Approaches and Management of Refractory Diseases.* Berlin, Germany: Springer-Verlag; 1996:178-184.

Bayer HealthCare Pharmaceuticals

Drug Interactions

Drugs that can increase white blood cells (WBCs), such as lithium and corticosteroids, should be used with caution while receiving LEUKINE. Also, LEUKINE should not be used 24 hours before through 24 hours after any chemotherapy or radiation therapy. Interactions between LEUKINE and other drugs have not been fully evaluated.

Important Safety Considerations

LEUKINE is contraindicated in patients with excessive leukemic blasts in bone marrow or peripheral blood (≥10%); in patients with known hypersensitivity to GM-CSF, yeast-derived products, or any component of LEUKINE; and for concomitant use with chemotherapy and radiotherapy.

Serious allergic or anaphylactic reactions have been reported with LEUKINE. If any serious or anaphylactic reactions occur, LEUKINE therapy should immediately be discontinued and appropriate therapy initiated.

Liquid solutions containing benzyl alcohol (including liquid LEUKINE) or lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates.

LEUKINE should be used with caution and monitored in patients with preexisting fluid retention, pulmonary infiltrates, or CHF; respiratory symptoms or disease; cardiac symptoms or disease; and renal or hepatic dysfunction.

Edema, capillary leak syndrome, pleural and/or pericardial effusion, supraventricular tachycardia, sequestration of granulocytes in the pulmonary circulation, and dyspnea have been reported in patients after LEUKINE administration. LEUKINE has induced the elevation of serum creatinine or bilirubin and hepatic enzymes in some patients. Monitoring of renal and hepatic function in patients with preexisting renal or hepatic dysfunction is recommended at least every other week during LEUKINE administration.

Nearly all patients reported leukopenia, thrombocytopenia, and anemia. Adverse events occurring in >10% of AML patients receiving LEUKINE in controlled clinical trials and reported in a higher frequency than placebo were: fever, skin reactions, metabolic disturbances, nausea, vomiting, weight-loss, edema, and anorexia.

If ANC >20,000 cells/mm^3 or if platelet counts >500,000/mm^3, LEUKINE administration should be interrupted or the dose reduced by half. Twice weekly monitoring of CBC with differential should be performed.

LEUKINE therapy should be discontinued if disease progression is detected during treatment.

Please see brief summary of full Prescribing Information on adjacent pages.

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BRIEF SUMMARY
CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Use Following Induction Chemotherapy in Acute Myelogenous Leukemia LEUKINE is indicated for use following induction chemotherapy in older adult patients with acute myelogenous leukemia (AML) to shorten time to neutrophil recovery and to reduce the incidence of severe and life-threatening infections and infections resulting in death. The safety and efficacy of LEUKINE have not been assessed in patients with AML under 55 years of age.

The term acute myelogenous leukemia, also referred to as acute non-lymphocytic leukemia (ANLL), encompasses a heterogeneous group of leukemias arising from various non-lymphoid cell lines which have been defined morphologically by the French-American-British (FAB) system of classification.

Use in Mobilization and Following Transplantation of Autologous Peripheral Blood Progenitor Cells LEUKINE is indicated for the mobilization of hematopoietic progenitor cells into peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment as compared with collection without mobilization. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care. Myeloid reconstitution is further accelerated by administration of LEUKINE following peripheral blood progenitor cell transplantation.

Use in Myeloid Reconstitution After Autologous Bone Marrow Transplantation LEUKINE is indicated for acceleration of myeloid recovery in patients with non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukemia (ALL) and Hodgkin's disease undergoing autologous bone marrow transplantation (BMT). After autologous BMT in patients with NHL, ALL, or Hodgkin's disease, LEUKINE has been found to be safe and effective in accelerating myeloid engraftment, decreasing median duration of antibiotic administration, reducing the median duration of infectious episodes and shortening the median duration of hospitalization. Hematologic response to LEUKINE can be detected by complete blood count (CBC) with differential cell counts performed twice per week.

Use in Myeloid Reconstitution After Allogeneic Bone Marrow Transplantation LEUKINE is indicated for acceleration of myeloid recovery in patients undergoing allogeneic BMT from HLA-matched related donors. LEUKINE has been found to be safe and effective in accelerating myeloid engraftment, reducing the incidence of bacteremia and other culture positive infections, and shortening the median duration of hospitalization.

Use in Bone Marrow Transplantation Failure or Engraftment Delay LEUKINE is indicated in patients who have undergone allogeneic or autologous bone marrow transplantation (BMT) in whom engraftment is delayed or has failed. LEUKINE has been found to be safe and effective in prolonging survival of patients who are experiencing graft failure or engraftment delay, in the presence or absence of infection, following autologous or allogeneic BMT. Survival benefit may be relatively greater in those patients who demonstrate one or more of the following characteristics: autologous BMT failure or engraftment delay, no previous total body irradiation, malignancy other than leukemia or a multiple organ failure (MOF) score ≤ two (see CLINICAL EXPERIENCE). Hematologic response to LEUKINE can be detected by complete blood count (CBC) with differential performed twice per week.

CONTRAINDICATIONS

LEUKINE is contraindicated:

1) in patients with excessive leukemic myeloid blasts in the bone marrow or peripheral blood (≥ 10%);
2) in patients with known hypersensitivity to GM-CSF, yeast-derived products or any component of the product;
3) for concomitant use with chemotherapy and radiotherapy.

Due to the potential sensitivity of rapidly dividing hematopoietic progenitor cells, LEUKINE should not be administered simultaneously with cytotoxic chemotherapy or radiotherapy or within 24 hours preceding or following chemotherapy or radiotherapy. In one controlled study, patients with small cell lung cancer received LEUKINE and concurrent thoracic radiotherapy and chemotherapy or the identical radiotherapy and chemotherapy without LEUKINE. The patients randomized to LEUKINE had significantly higher incidence of adverse events, including higher mortality and a higher incidence of grade 3 and 4 infections and grade 3 and 4 thrombocytopenia.[11]

WARNINGS

Pediatric Use Benzyl alcohol is a constituent of liquid LEUKINE and Bacteriostatic Water for Injection diluent. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. **Liquid solutions containing benzyl alcohol (including liquid LEUKINE) or lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates** (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Fluid Retention Edema, capillary leak syndrome, pleural and/or pericardial effusion have been reported in patients after LEUKINE administration. In 156 patients enrolled in placebo-controlled studies using LEUKINE at a dose of 250 mcg/m²/day by 2-hour IV infusion, the reported incidences of fluid retention (LEUKINE vs. placebo) were as follows: peripheral edema, 11% vs. 7%; pleural effusion, 1% vs. 0%; and pericardial effusion, 4% vs. 1%. Capillary leak syndrome was not observed in this limited number of studies; based on other uncontrolled studies and reports from users of marketed LEUKINE, the incidence is estimated to be less than 1%. In patients with preexisting pleural and pericardial effusions, administration of LEUKINE may aggravate fluid retention; however, fluid retention associated with or worsened by LEUKINE has been reversible after interruption or dose reduction of LEUKINE with or without diuretic therapy. LEUKINE should be used with caution in patients with preexisting fluid retention, pulmonary infiltrates or congestive heart failure.

Respiratory Symptoms Sequestration of granulocytes in the pulmonary circulation has been documented following LEUKINE infusion[12] and dyspnea has been reported occasionally in patients treated with LEUKINE. Special attention should be given to respiratory symptoms during or immediately following LEUKINE infusion, especially in patients with preexisting lung disease. In patients displaying dyspnea during LEUKINE administration, the rate of infusion should be reduced by half. If respiratory symptoms worsen despite infusion rate reduction, the infusion should be discontinued. Subsequent IV infusions may be administered following the standard dose schedule with careful monitoring. LEUKINE should be administered with caution in patients with hypoxia.

Cardiovascular Symptoms Occasional transient supraventricular arrhythmia has been reported in uncontrolled studies during LEUKINE administration, particularly in patients with a previous history of cardiac arrhythmia. However, these arrhythmias have been reversible after discontinuation of LEUKINE. LEUKINE should be used with caution in patients with preexisting cardiac disease.

Renal and Hepatic Dysfunction In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of LEUKINE has induced elevation of serum creatinine or bilirubin and hepatic enzymes. Dose reduction or interruption of LEUKINE administration has resulted in a decrease to pretreatment values. However, in controlled clinical trials the incidences of renal and hepatic dysfunction were comparable between LEUKINE (250 mcg/m²/day by 2-hour IV infusion) and placebo-treated patients. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least every other week during LEUKINE administration.

PRECAUTIONS

General Parenteral administration of recombinant proteins should be attended by appropriate precautions in case an allergic or untoward reaction occurs. Serious allergic or anaphylactic reactions have been reported. If any serious allergic or anaphylactic reaction occurs, LEUKINE therapy should immediately be discontinued and appropriate therapy initiated.

A syndrome characterized by respiratory distress, hypoxia, flushing, hypotension, syncope, and/or tachycardia has been reported following the first administration of LEUKINE in a particular cycle. These signs have resolved with symptomatic treatment and usually do not recur with subsequent doses in the same cycle of treatment.

Stimulation of marrow precursors with LEUKINE may result in a rapid rise in white blood cell (WBC) count. If the ANC exceeds 20,000 cells/mm³ or if the platelet count exceeds 500,000/mm³, LEUKINE administration should be interrupted or the dose reduced by half. The decision to reduce the dose or interrupt treatment should be based on the clinical condition of the patient. Excessive blood counts have returned to normal or baseline levels within three to seven days following cessation of LEUKINE therapy. Twice weekly monitoring of CBC with differential (including examination for the presence of blast cells) should be performed to preclude development of excessive counts.

Growth Factor Potential LEUKINE is a growth factor that primarily stimulates normal myeloid precursors. However, the possibility that LEUKINE can act as a growth factor for any tumor type, particularly myeloid malignancies, cannot be excluded. Because of the possibility of tumor growth potentiation, precaution should be exercised when using this drug in any malignancy with myeloid characteristics.

Should disease progression be detected during LEUKINE treatment, LEUKINE therapy should be discontinued.

LEUKINE has been administered to patients with myelodysplastic syndromes (MDS) in uncontrolled studies without evidence of increased relapse rates.[13, 14, 15] Controlled studies have not been performed in patients with MDS.

Use in Patients Receiving Purged Bone Marrow LEUKINE is effective in accelerating myeloid recovery in patients receiving bone marrow purged by anti-B lymphocyte monoclonal antibodies. Data obtained from uncontrolled studies suggest that if *in vitro* marrow purging with chemical agents causes a significant decrease in the number of responsive hematopoietic progenitors, the patient may not respond to LEUKINE. When the bone marrow purging process preserves a sufficient number of progenitors (>1.2 x 10^4/kg), a beneficial effect of LEUKINE on myeloid engraftment has been reported.[16]

Use in Patients Previously Exposed to Intensive Chemotherapy/Radiotherapy In patients who before autologous BMT, have received extensive radiotherapy to hematopoietic sites for the treatment of primary disease in the abdomen or chest, or have been exposed to multiple myelotoxic agents (alkylating agents, anthracycline antibiotics and antimetabolites), the effect of LEUKINE on myeloid reconstitution may be limited.

Use in Patients with Malignancy Undergoing LEUKINE-Mobilized PBPC Collection When using LEUKINE to mobilize PBPC, the limited *in vitro* data suggest that tumor cells may be released and reinfused into the patient in the leukapheresis product. The effect of reinfusion of tumor cells has not been well studied and the data are inconclusive.

Information for Patients LEUKINE should be used under the guidance and supervision of a health care professional. However, when the physician determines that LEUKINE may be used outside of the hospital or office setting, persons who will be administering LEUKINE should be instructed as to the proper dose, and the method of reconstituting and administering LEUKINE (see **DOSAGE AND ADMINISTRATION**). If home use is prescribed, patients should be instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, drug product, and diluent. A puncture resistant container should be used by the patient for the disposal of used needles.

Patients should be informed of the serious and most common adverse reactions associated with LEUKINE administration (see **ADVERSE REACTIONS**). Female patients of childbearing potential should be advised of the possible risks to the fetus of LEUKINE (see **PRECAUTIONS, Pregnancy Category C**).

Laboratory Monitoring LEUKINE can induce variable increases in WBC and/or platelet counts. In order to avoid potential complications of excessive leukocytosis (WBC >50,000 cells/mm³; ANC >20,000 cells/mm³), a CBC is recommended twice per week during LEUKINE therapy. Monitoring of renal and hepatic function in patients displaying renal or hepatic dysfunction prior to initiation of treatment is recommended at least biweekly during LEUKINE administration. Body weight and hydration status should be carefully monitored during LEUKINE administration.

Drug Interaction Interactions between LEUKINE and other drugs have not been fully evaluated. Drugs which may potentiate the myeloproliferative effects of LEUKINE, such as lithium and corticosteroids, should be used with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility Animal studies have not been conducted with LEUKINE to evaluate the carcinogenic potential or the effect on fertility.

Pregnancy (Category C) Animal reproduction studies have not been conducted with LEUKINE. It is not known whether LEUKINE can cause fetal harm when administered to a pregnant woman or can affect reproductive capability. LEUKINE should be given to a pregnant woman only if clearly needed.

Nursing Mothers It is not known whether LEUKINE is excreted in human milk. Because many drugs are excreted in human milk, LEUKINE should be administered to a nursing woman only if clearly needed.

Pediatric Use Safety and effectiveness in pediatric patients have not been established; however, available safety data indicate that LEUKINE does not exhibit any greater toxicity in pediatric patients than in adults. A total of 124 pediatric subjects between the ages of 4 months and 18 years have been treated with LEUKINE in clinical trials at doses ranging from 60-1,000 mcg/m²/day intravenously and 4-1,500 mcg/m²/day subcutaneously. In 53 pediatric patients enrolled in controlled studies at a dose of 250 mcg/m²/day by 2-hour IV infusion, the type and frequency of adverse events were comparable to those reported for the adult population. **Liquid solutions containing benzyl alcohol (including liquid LEUKINE) or lyophilized LEUKINE reconstituted with Bacteriostatic Water for Injection, USP (0.9% benzyl alcohol) should not be administered to neonates** (see **WARNINGS**).

Geriatric Use In the clinical trials, experience in older patients (age ≥65 years), was limited to the acute myelogenous leukemia (AML) study. Of the 52 patients treated with LEUKINE in this randomized study, 22 patients were age 65-70 years and 30 patients were age 55-64 years. The number of placebo patients in each age group were 13 and 33 patients respectively. This was not an adequate database from which determination of differences in efficacy endpoints or safety assessments could be reliably made and this clinical study was not designed to evaluate difference between these two age groups. Analyses of general trends in safety and efficacy were undertaken and demonstrate similar patterns for older (65-70 yrs) vs younger patients (55-64 yrs). Greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Autologous and Allogeneic Bone Marrow Transplantation LEUKINE is generally well tolerated. In three placebo-controlled studies enrolling a total of 156 patients after autologous BMT or peripheral blood progenitor cell transplantation, events reported in at least 10% of patients who received IV LEUKINE or placebo were as reported in Table 6.

No significant differences were observed between LEUKINE and placebo-treated patients in the type or frequency of laboratory abnormalities, including renal and hepatic parameters. In some patients with preexisting renal or hepatic dysfunction enrolled in uncontrolled clinical trials, administration of LEUKINE has induced elevation of serum creatinine or bilirubin and hepatic enzymes (see **WARNINGS**). In addition, there was no significant difference in relapse rate and 24 month survival between the LEUKINE and placebo-treated patients.

In the placebo-controlled trial of 109 patients after allogeneic BMT, events reported in at least 10% of patients who received IV LEUKINE or placebo were as reported in Table 7.

There were no significant differences in the incidence or severity of GVHD, relapse rates and survival between the LEUKINE and placebo-treated patients.

Adverse events observed for the patients treated with LEUKINE in the historically-controlled BMT failure study were similar to those reported in the placebo-controlled studies. In addition, headache (26%), pericardial effusion (25%), arthralgia (21%) and myalgia (18%) were also reported in patients treated with LEUKINE in the graft failure study.

In uncontrolled Phase I/II studies with LEUKINE in 215 patients, the most frequent adverse events were fever, asthenia, headache, bone pain, chills and myalgia. These systemic events were generally mild or moderate and were usually prevented or reversed by the administration of analgesics and antipyretics such as acetaminophen. In these uncontrolled trials, other infrequent events reported were dyspnea, peripheral edema, and rash.

Reports of events occurring with marketed LEUKINE include arrhythmia, fainting, eosinophilia, dizziness, hypotension, injection site reactions, pain (including abdominal, back, chest, and joint pain), tachycardia, thrombosis, and transient liver function abnormalities.

In patients with preexisting edema, capillary leak syndrome, pleural and/or pericardial effusion, administration of LEUKINE may aggravate fluid retention (see **WARNINGS**). Body weight and hydration status should be carefully monitored during LEUKINE administration.

Adverse events observed in pediatric patients in controlled studies were comparable to those observed in adult patients.

Acute Myelogenous Leukemia Adverse events reported in at least 10% of patients who received LEUKINE or placebo were as reported in Table 8.

Nearly all patients reported leukopenia, thrombocytopenia and anemia. The frequency and type of adverse events observed following induction were similar between LEUKINE and placebo groups. The only significant difference in the rates of these adverse events was an increase in skin associated events in the LEUKINE group (p=0.002). No significant differences were observed in laboratory results, renal or hepatic toxicity. No significant differences were observed between the LEUKINE and placebo-treated patients for adverse events following consolidation. There was no significant difference in response rate or relapse rate.

In a historically-controlled study of 86 patients with acute myelogenous leukemia (AML), the LEUKINE treated group exhibited an increased incidence of weight gain (p=0.007), low serum proteins and prolonged prothrombin time (p=0.02) when compared to the control group. Two LEUKINE treated patients had progressive increase in circulating monocytes and promonocytes and blasts in the marrow which reversed when LEUKINE was discontinued. The historical control group exhibited an increased incidence of cardiac events (p=0.018), liver function abnormalities (p=0.008), and neurocortical hemorrhagic events (p=0.025).[15]

Antibody Formation Serum samples collected before and after LEUKINE treatment from 214 patients with a variety of underlying diseases have been examined for immunogenicity based on the presence of antibodies. Neutralizing antibodies were detected in five of 214 patients (2.3%) after receiving LEUKINE by continuous IV infusion (three patients) or subcutaneous injection (SC)(two patients) for 28 to 84 days in multiple courses. All five patients had impaired hematopoiesis before the administration of LEUKINE and consequently the effect of the development of anti-GM-CSF antibodies on normal hematopoiesis could not be assessed. Antibody studies of 75 patients with Crohn's disease receiving LEUKINE by subcutaneous injection with normal hematopoiesis and no other immunosuppressive drugs showed one patient (1.3%) with detectable neutralizing antibodies. The clinical relevance of the presence of these antibodies are unknown. Drug-induced neutropenia, neutralization of endogenous GM-CSF activity and diminution of the therapeutic effect of LEUKINE secondary to formation of neutralizing antibody remain a theoretical possibility. Serious allergic and anaphylactoid reactions have been reported with LEUKINE but the rate of occurrence of antibodies in such patients has not been assessed.

Overdosage The maximum amount of LEUKINE that can be safely administered in single or multiple doses has not been determined. Doses up to 100 mcg/kg/day (4,000 mcg/m²/day or 16 times the recommended dose) were administered to four patients in a Phase I uncontrolled clinical study by continuous IV infusion for 7 to 18 days. Increases in WBC up to 200,000 cells/mm³ were observed. Adverse events reported were dyspnea, malaise, nausea, fever, rash, sinus tachycardia, headache and chills. All these events were reversible after discontinuation of LEUKINE.

In case of overdosage, LEUKINE therapy should be discontinued and the patient carefully monitored for WBC increase and respiratory symptoms.

Table 6

Percent of AuBMT Patients Reporting Events

Events by Body System	LEUKINE (n=79)	Placebo (n=77)	Events by Body System	LEUKINE (n=79)	Placebo (n=77)
Body, General			**Metabolic, Nutritional Disorder**		
Fever	95	96	Edema	34	35
Mucous membrane disorder	75	78	Peripheral edema	11	7
Asthenia	66	51	**Respiratory System**		
Malaise	57	51	Dyspnea	28	31
Sepsis	11	14	Lung disorder	20	23
Digestive System			**Hemic and Lymphatic System**		
Nausea	90	96	Blood dyscrasia	25	27
Diarrhea	89	82	**Cardiovascular System**		
Vomiting	85	90	Hemorrhage	23	30
Anorexia	54	58	**Urogenital System**		
GI disorder	37	47	Urinary tract disorder	14	13
GI hemorrhage	27	33	Kidney function abnormal	8	10
Stomatitis	24	29	**Nervous System**		
Liver damage	13	14	CNS disorder	11	16
Skin and Appendages					
Alopecia	73	74			
Rash	44	38			

Table 7

Percent of Allogeneic BMT Patients Reporting Events

Events by Body System	LEUKINE (n=53)	Placebo (n=56)	Events by Body System	LEUKINE (n=53)	Placebo (n=56)
Body, General			**Metabolic/Nutritional Disorders**		
Fever	77	80	Bilirubinemia	30	27
Abdominal pain	38	23	Hyperglycemia	25	23
Headache	36	36	Peripheral edema	15	21
Chills	25	20	Increased creatinine	15	14
Pain	17	36	Hypomagnesemia	15	9
Asthenia	17	20	Increased SGPT	13	16
Chest pain	15	9	Edema	13	11
Back pain	9	18	Increased alk. phosphatase	8	14
Digestive System			**Respiratory System**		
Diarrhea	81	66	Pharyngitis	23	13
Nausea	70	66	Epistaxis	17	16
Vomiting	70	57	Dyspnea	15	14
Stomatitis	62	63	Rhinitis	11	14
Anorexia	51	57	**Hemic and Lymphatic System**		
Dyspepsia	17	20	Thrombocytopenia	19	34
Hematemesis	13	7	Leukopenia	17	29
Dysphagia	11	7	Petechia	6	11
GI hemorrhage	11	5	Agranulocytosis	6	11
Constipation	8	11	**Urogenital System**		
Skin and Appendages			Hematuria	9	21
Rash	70	73	**Nervous System**		
Alopecia	45	45	Paresthesia	11	13
Pruritis	23	13	Insomnia	11	9
Musculo-skeletal System			Anxiety	11	2
Bone pain	21	5	**Laboratory Abnormalities***		
Arthralgia	11	4	High glucose	41	49
Special Senses			Low albumin	27	36
Eye hemorrhage	11	0	High BUN	23	17
Cardiovascular System			Low calcium	2	7
Hypertension	34	32	High cholesterol	17	8
Tachycardia	11	9			

**Grade 3 and 4 laboratory abnormalities only. Denominators may vary due to missing laboratory measurements.*

Table 8

Percent of AML Patients Reporting Events

Events by Body System	LEUKINE (n=52)	Placebo (n=47)	Events by Body System	LEUKINE (n=52)	Placebo (n=47)
Body, General			**Metabolic/Nutritional Disorder**		
Fever (no infection)	81	74	Metabolic	58	49
Infection	65	68	Edema	25	23
Weight loss	37	28	**Respiratory System**		
Weight gain	8	21	Pulmonary	48	64
Chills	19	26	**Hemic and Lymphatic System**		
Allergy	12	15	Coagulation	19	21
Sweats	6	13	**Cardiovascular System**		
Digestive System			Hemorrhage	29	43
Nausea	58	55	Hypertension	25	32
Liver	77	83	Cardiac	23	32
Diarrhea	52	53	Hypotension	13	26
Vomiting	46	34	**Urogenital System**		
Stomatitis	42	43	GU	50	57
Anorexia	13	11	**Nervous System**		
Abdominal distention	4	13	Neuro-clinical	42	53
Skin and Appendages			Neuro-motor	25	26
Skin	77	45	Neuro-psych	15	26
Alopecia	37	51	Neuro-sensory	6	11

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Faces at the Congress

APRIL 30–MAY 3, 2009, SAN ANTONIO, TEXAS

FOR MORE PICTURES, VISIT WWW.THEONCOLOGYNURSE.COM AND CLICK FACES AT THE CONGRESS ON THE HOMEPAGE FOR A COMPREHENSIVE COLLAGE.

1 **Michelle Polacelli** of Faxton-St. Luke's Healthcare, Utica, New York, takes a break in the Oncology Nursing Certification Corporation lounge, one of the perks of certification.

2 **Maureen Rigney** of the Lung Cancer Alliance catches up on her reading.

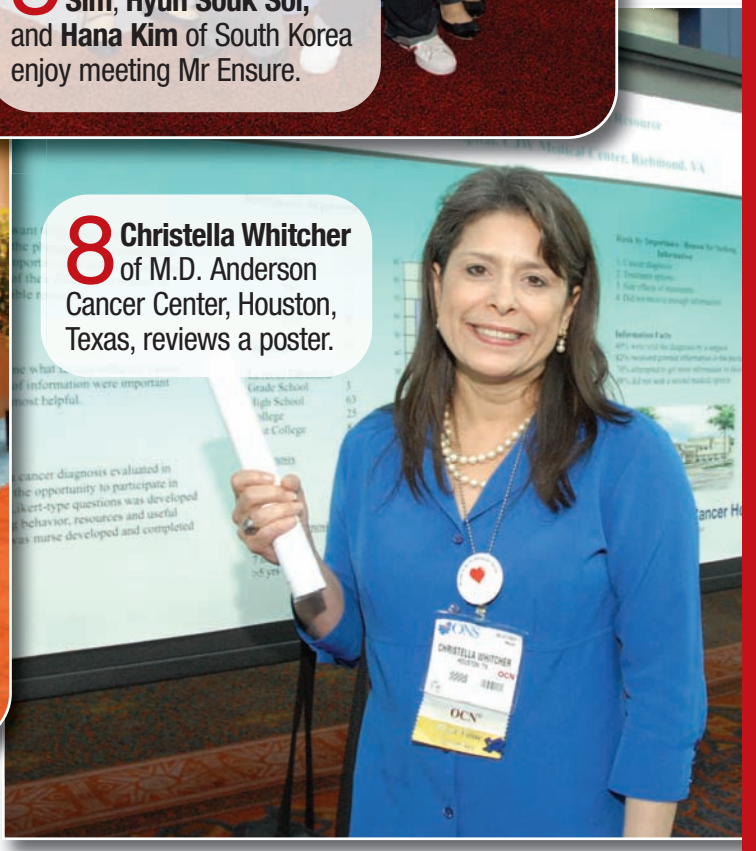
3 **Debra Steverson** promotes the new NCI Ask Me campaign.

4 **Rene Gavin** of Hospira explains the latest technology to **Stephanie Novak** of West Jordan, Utah.

5 **Jeong-Eun Lee**, **Hyungja Sim**, **Hyun Souk Sol,** and **Hana Kim** of South Korea enjoy meeting Mr Ensure.

7 **David Cox** of Eisai Inc. and **Erica Caballero**, **Leticia Cavazos**, and **Marian Barron** of Loredo, Texas, take time out for a group photo.

6 **Peggy Aaron, Carol Duryea,** and **Deborah Murray** greet visitors to the MDS Foundation booth.



8 **Christella Whitcher** of M.D. Anderson Cancer Center, Houston, Texas, reviews a poster.

Photos by American Photography and Video.

Conference News

Continued from cover

Aprepitant Should Be Routinely Included in Antiemetic Regimen in Chemotherapy-treated Breast Cancer Patients

SAN ANTONIO—The neurokinin 1 (NK1)-receptor antagonist aprepitant should be a regular component of an antiemetic regimen in breast cancer patients undergoing chemotherapy in a private practice setting, investigators said at the 34th Annual Congress of the Oncology Nursing Society (ONS).

Patients are often hesitant to report the severity and duration of their symptoms to their oncology physicians and nurses.

James C. Street, PhD, with Reagent in New York, New York, reported the results of a questionnaire completed by 91 women with breast cancer before and after each of three consecutive cycles of chemotherapy administered in a private practice setting. Patients had been prescribed antiemetics at the oncology prescriber's discretion.

Although chemotherapy-induced nausea and vomiting (CINV) remains a significant problem for many women with breast cancer, patients are often hesitant to report the severity and duration of their symptoms to their oncology physicians and nurses, Street pointed out.

Several factors may account for patients' hesitation to share details about their CINV with their clinical care team, he said.

- Patients may be concerned that their dose of chemotherapy will be reduced or postponed.
- Patients may not want to "bother" their oncology care team.
- The most severe nausea and vomiting occur after the patient is at home.
- There is usually a period of 2 to 3 weeks before the patient presents to the clinic for the next infusion, at which time her recollection of CINV may have faded.

As a result, some patients are undermedicated for CINV, Dr Street noted. This is especially problematic given that delayed CINV is now more common than acute CINV and may cause dehydration that aggravates nausea, impairs routine activities, and also promotes anticipatory or intractable CINV.

Of the patients who completed the questionnaires, 50 had received an antiemetic regimen including aprepitant, 33 had received antiemetics without aprepitant, five were not sure if they had received antiemetics, and three got no antiemetic.

Significantly more patients receiving a regimen with aprepitant experienced no vomiting compared with those receiving another antiemetic regimen (96.0% vs 66.7%). Also, 6.1 times as many patients taking a regimen that did not contain aprepitant experienced at least one vomiting episode as those taking a regimen with aprepitant (24.3% vs 4.0%, respectively).

Results also revealed that 88% of patients receiving a regimen that included aprepitant had no nausea or only mild nausea compared with 60.6% of those receiving another antiemetic regimen. In addition, more than three times as many patients taking a nonaprepitant-containing regimen developed moderate to very severe nausea as those taking a regimen with aprepitant (39.4% vs 12%, respectively).

Aprepitant had less of an impact on daily activities than other regimens. In fact, almost twice as many patients receiving a regimen with aprepitant experienced no or only slight interference with daily activities compared with those receiving another antiemetic regimen (83.8% vs 43.5%).

Overall, the data support a role for aprepitant in breast cancer patients undergoing chemotherapy starting at their first treatment cycle in accordance with established guidelines, Dr Street said.

—Jill Stein

Oncology Nurse Navigator May Help Manage Distress in Oncology Inpatients

SAN ANTONIO—An oncology nurse navigator can help reduce cancer-related distress in adult oncology inpatients, according to data from a 3-month pilot trial released at the 34th Annual Congress of the Oncology Nursing Society (ONS). To date, oncology nurse navigators have typically been employed only in an outpatient setting.

Investigators at the St. Elizabeth Cancer Institute in Lincoln, Nebraska, used a Distress Thermometer developed by the National Comprehensive Cancer Network (NCCN) to determine whether oncology nurse navigator visits would reduce cancer-related distress in adult oncology inpatients. The Distress Thermometer is a scale with a symptom checklist that has been validated for use in a clinical setting. The analysis included 55 patients whose distress level was measured on at least two dates during their inpatient visit.

"We found that patient distress tended to be lower when an oncology nurse navigator was part of the healthcare team," said principal investigator Jay Swanson, RN, BSN, OCN.

Jay Swanson, RN, BSN, OCN

The benefits were statistically significant in rural patients, patients who were 65 years of age or younger, and patients who had been visited by an oncology nurse navigator at least three times.

"While most adult oncology patients experience significant levels of distress, only a few are screened for their distress," Swanson pointed out. Predictably, the lack of screening means a lack of intervention, he said.

Patients have been reported to be "strongly satisfied" with the care/treatment provided by the oncology nurse navigator, Swanson noted. "Patients feel that the oncology nurse navigator helps things run more smoothly and makes the whole experience less overwhelming," he said. "While these observations are difficult to capture, most patients would rate their interactions with the oncology nurse navigator as very favorable." The impact of the oncology nurse navigator on clinical outcomes, however, has not been addressed, he added.

Swanson decided to search for a tool that would provide an easy and reliable means of identifying distress at the bedside. The NCCN Distress Thermometer satisfied the criteria. The patient is asked to quantify his/her stress on a scale of 0 to 10, where a score of 4 or more indicates significant distress that, per NCCN guidelines, requires further evaluation. At St. Elizabeth Regional Medical Center, it is the nighttime floor nurse who tests the patients' distress levels using the Distress Thermometer, and all patients —regardless of their distress score—are asked if they would like to see an oncology nurse navigator.

Swanson, the sole oncology nurse navigator at his institution, initially relied on a list of 35 questions that required only a "yes" or "no" response (eg, is transportation a problem?). However, he now favors an informal conversation with patients, which he feels is more effective at uncovering the cause(s) of their distress—be it psychological, spiritual, logistical, or medical. He typically spends about 90 minutes with a patient on his first visit and about 15 to 30 minutes on subsequent visits. Between visits, he works on resolving the sources of distress. "For example, if the patient is distressed about transportation, I will call the American Cancer Society's Road to Recovery program and try to work solutions," he said.

Results of the pilot program showed that oncology nurse navigator visits tended to reduce distress scores, and the change in distress scores were significant in certain subgroups. For example, patients who had three to four oncology nurse navigator visits had a mean 3.88-point decrease in distress scores versus a mean 0.42-point decrease in patients seen less than three times. Rural patients had a significant decrease in distress scores after seeing the oncology nurse navigator (a mean decrease of 3.64 points). Patients who were 65 years of age or younger also had significant improvements when seen by an oncology nurse navigator.

"The distress experienced by adult cancer inpatients is often neglected, and it's not because the floor nurses are incompetent but rather because there are excess demands placed on them," Swanson said. "The oncology nurse navigator can play a pivotal role in screening and treatment of distress in this population."

—Jill Stein

Continued on page 16

Is peripheral neuropathy holding them back?

Intervene early to preserve quality of life

Peripheral neuropathy (PN) can have a devastating effect on patients with multiple myeloma (MM). These patients have an increased risk since both MM and some of its treatments can cause PN.[1-4] Even though PN symptoms are mild at the outset, eventually they can have an impact on patients' lives, limiting their ability to do the activities they enjoy. And these effects may cause permanent damage.[5,6] That is why it is so important to identify symptoms early.[2]

Assessing PN is critical to optimizing myeloma management

A baseline assessment is the first step in preventing or controlling the symptoms of PN.[2] Patients with MM may have pre-existing conditions, such as diabetes, that can lead to PN.[7] By identifying pre-existing PN early on, you can better monitor patients throughout treatment.

Identifying and assessing symptoms can be challenging. The sensations caused by PN are subjective, and patients may be hesitant to share these symptoms since it may lead to changes in their treatment plan.[5,8] Therefore, it is important to encourage your patients to report any symptoms they may be experiencing.[7] Here are some questions to start the dialogue:

- "Do you have any unusual sensations (pins and needles, shooting pain like electric current) in your feet, legs, or hands?"
- "Would you describe these sensations as tingling, numbness, burning, or pain?"
- "Do any of these sensations or feelings keep you from doing things like buttoning your shirt or using a fork and knife?"
- "Have your legs or arms been weak? Does this weakness keep you from taking part in the activities you enjoy, like needlework or golfing?"

Discuss PN with your patients early and often

Multiple myeloma treatments may cause PN symptoms and the damage may be permanent.[3,4] By identifying patients at risk and assessing their symptoms, you can:

- Help them overcome their fears: assure your patients that a change in treatment plan in response to PN does not have to compromise efficacy
- Assess PN at baseline and throughout treatment to help guide treatment decisions[2]

Your intervention can help ensure your patients' treatment allows them to pursue the things they love

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Conference News

Continued from cover

Ellie Flores of the University of California, San Diego, studies a poster.

Easy Measures Curb Falls in Hem/Onc/BMT Unit

SAN ANTONIO—Boston clinicians report favorable results using a program involving hourly nursing rounds to prevent falls and injuries in adult patients in a hematology/oncology/ bone marrow transplant (hem/onc/BMT) unit.

The program, in which pharmacists also reviewed medications daily for patients considered at high risk of falling, was implemented in a 777-bed urban tertiary teaching hospital.

Results showed a 100% reduction in falls with injuries during the 3-month trial period.

Results showed a 100% reduction in falls with injuries during the 3-month trial period, Lana Callahan, RN, OCN, with Brigham and Women's Hospital/ Dana-Farber Cancer Center, announced at the 34th Annual Congress of the Oncology Nursing Society (ONS).

The US Joint Commission National Patient Safety Goal states that hospitals must reduce the risk of patient harm resulting from falls and recommends that a fall-reduction program be implemented, Callahan pointed out. The Commission also recommends that the fall-reduction program be evaluated.

In 2007, the hospital's hem/onc/ BMT unit had a high rate of falls with an injury rate that exceeded national and local benchmarks for an adult medical population.

Callahan and colleagues decided to test an intervention that featured comprehensive daily rounds as one of its key components. The program had been piloted 2 years earlier in a neuroscience unit.

Nursing rounds involved assessing each patient's pain, positioning/comfort, toileting, personal needs, and safety. Each patient's risk of falling was also assessed daily using the Morse Fall Scale, a widely validated tool to identify the fall-prone patient.

A multidisciplinary team consisting of a quality manager, nursing staff, educators, and pharmacists met daily during weekdays to review medications in patients deemed to be at high risk of a fall and injury, and medications were adjusted when indicated.

"We also had daily weekday huddles to evaluate the process and address barriers to the program in real time," Callahan said.

The hem/onc/BMT unit where the intervention was tested averages 12 adult inpatients per day.

In addition to a complete absence of falls during the 3-month study period that was sustained at 9 months, the program provided additional benefits, Callahan said. These included a 1.9% increase in patient satisfaction with nursing care, a 2.0% increase in the amount of attention given to patient needs, a 3.7% increase in teamwork, and a 1.2% increase in pain control. There was also a one-third drop in the number of times patients activated their call lights.

"We believe this program underscores the need to roll out patient comfort rounds in all areas that have high fall rates and to ensure that measures are in place that sustain the positive changes we found in our preliminary evaluation," Callahan said.

—Jill Stein

Coverage of the ONS 34th Annual Congress Continues in the July/August issue of *The Oncology Nurse*.

Oncology Nurses Play Pivotal Role in Ensuring Proper Use of Oral Chemotherapy Medications

SAN ANTONIO—Oncology nurses can help improve patients' knowledge about and adherence to oral chemotherapy medications, a Houston group said at the 34th Annual Congress of the Oncology Nursing Society (ONS).

Mary Vinson, RN, MSN, OCN, with Texas Oncology Simmons Cancer Center in Houston, and colleagues analyzed the results of surveys distributed to 135 cancer patients who had a prescription for an oral anticancer medication. The surveys aimed to determine patients' knowledge about medications, barriers associated with adherence, and their medication-taking behavior.

"In recent years, oral anticancer drugs have been increasingly used for the treatment of a range of cancers," Vinson observed. "Oral medications are primarily self-administered in the community and offer several advantages over intravenous administration. Notably, oral regimens may be more convenient for patients, because patients can take them at home rather than solely at a hospital or infusion clinic."

However, the availability of oral chemotherapy agents has presented new challenges to the healthcare practitioner in managing cancer treatment, she added. Potential limitations include side effects and nonadherence to treatment.

To date, there have been limited data on adherence to oral chemotherapy medications in a real-world setting.

More than 90% of survey respondents indicated that they know why they have been prescribed a particular medicine, how much to take each time, when to take it, where to store their medicine, if and when to obtain a refill, and whom to call with questions, concerns, or side effects.

Likewise, more than 90% of respondents indicated that they do not forget their doctor's instructions, take a lower dose than prescribed, or take a higher dose than prescribed (to see if the higher dose would provide additional benefit).

More than 90% of survey participants also said that they did not stop taking a medication because they felt fine or experienced side effects.

However, 17% of those surveyed said they were not certain they could cite the side effects of the oral chemotherapy drugs they were taking nor were they certain what to do in the event of a side effect. Nearly 40% omitted some doses, and more than 25% took their medication late.

Finally, Vinson noted that the data show that patients consider the oncology nurse as their key source of information. For example, patients said that they were more likely to call an oncology nurse with questions about their medication than their oncologist or pharmacist.

"Nurses can be instrumental in developing interventions that will help increase medication adherence as well as interventions that will help patients better understand and manage treatment-related side effects," she said.

—Jill Stein

Joyce Divanbeigi and **Alicia Carmack** of Siteman Cancer Center, St. Louis, Missouri, discuss their study with **Laura Kobayashi** also of St. Louis.

PARP Inhibitors

Continued from cover

and overall survival compared with chemotherapy alone, reported Joyce O'Shaughnessy, MD.

Triple-negative breast cancer is a highly aggressive cancer (30% of patients develop metastatic disease) for which no targeted therapies exist.

PARP is a nuclear enzyme that is involved in DNA base excision repair and is upregulated in most triple-negative breast cancers, said O'Shaughnessy, co-director of the Breast Cancer Research Program at the Baylor Cancer Center, Dallas, Texas. Similar to *BRCA1*-associated cancers, triple-negative breast cancers "block the ability to repair double-stranded DNA breaks. When they block that ability, they're reliant on single-strand DNA repair, and that's where PARP comes in. Most triple-negative breast cancers have a lot of this PARP enzyme because they block the ability to repair double-stranded breaks," she said.

PARP is a nuclear enzyme that is involved in DNA base excision repair and is upregulated in most triple-negative breast cancers.

BSI-201 is an intravenous PARP-1 inhibitor that potentiates the effects of platinum-based chemotherapy. "Interestingly, and kind of different from what we're used to in the cancer world, BSI-201 does not add any toxicity to chemotherapy," O'Shaughnessy noted. It was tested in a phase 2 trial of 120 women with metastatic triple-negative breast cancer, who were randomized to 21-day cycles of gemcitabine and carboplatin (given on days 1 and 8) alone or in combination with BSI-201 (given on days 1, 4, 8, and 11). Patients were allowed to cross over to the BSI-201 arm at disease progression, and 40% did so.

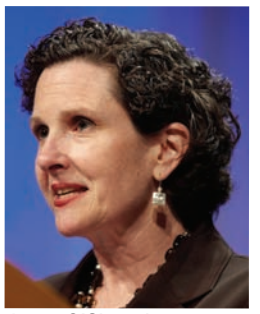
Progression-free survival more than doubled, from a median of 3.3 months to 6.9 months (P <.0001), with the addition of BSI-201. Overall survival increased from a median of 5.7 months with gemcitabine and carboplatin alone to 9.2 months with the addition of BSI-201 (P = .0005). The objective overall tumor response rate increased from 16% to 48% (P = .002) by adding the PARP inhibitor.

There were no additional toxicities by adding BSI-201 to the gemcitabine and carboplatin regimen. A large phase 3 trial will follow, with patient accrual planned to start in late June 2009, she said.

An oral PARP inhibitor, olaparib, also showed significant activity as a single agent in a phase 2 trial of women with *BRCA*-deficient advanced breast cancer, reported Andrew Tutt, MD, PhD, director of the Breakthrough Cancer Research Unit, Kings College, London.

Olaparib targets the DNA repair weakness in *BRCA1/BRCA2* tumors, he said. In an open-label study, olaparib was given either at 100 mg twice daily or 400 mg twice daily to 54 women with advanced breast cancer that was refractory to chemotherapy. The women had been exposed to a median of three prior lines of chemotherapy.

The overall response rate was 22% in the 100-mg twice-daily arm and 41% in the 400-mg twice-daily arm. One patient (400-mg arm) had complete tumor disappearance. The median progression-free survival was 5.7 months.



Joyce O'Shaughnessy, MD

Photo courtesy of American Society of Clinical Oncology

The most common side effects were low-grade nausea (26%), fatigue (33%), and vomiting (15%); grade 3 or 4 fatigue occurred in five patients and grade 3 or 4 nausea occurred in two patients.

—Wayne Kuznar

For complete coverage of the 2009 annual meeting of the American Society of Clinical Oncology, see the July/August issue of *The Oncology Nurse*.

Breast Cancer

New Technologies in HER2 Testing. Part 2

Serum Level and RT-PCR Tests

BY **LORI McMULLEN BSN, RN, OCN**
HUNTERDON REGIONAL BREAST CARE PROGRAM, FLEMINGTON, NEW JERSEY

In patients with breast cancer, an overexpression of human epidermal growth factor receptor 2 (HER2) is associated with tumor aggressiveness and poorer prognosis. Although the American Society of Clinical Oncology (ASCO) has recommended HER2 testing as part of a diagnostic and metastatic evaluation for breast cancer since 2001, there is no test that is recognized as the gold standard. In part 1 (March/April 2009), the foundational tests for determining HER2 overexpression (HER2-positive) and tissue testing by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) were reviewed. Neither IHC nor FISH is considered 100% accurate in determining HER2 overexpression.[1,2]

Two new tests, the HERmark Breast Cancer Assay and the SPOT-Light chromogenic in situ hybridization (CISH) kit, also were discussed in detail in part 1. In brief, these tests were introduced in July 2008; both tests use formalin-fixed, paraffin-embedded tissue tumor samples. The HERmark Breast Cancer Assay is promoted as providing accurate quantitative measurement of HER2 total protein and HER2 homodimer levels rather than the semiquantitative HER2 measurement of conventional testing by IHC and FISH. The SPOT-Light test uses CISH to measure quantitatively the strength of HER2 gene amplification.

This article discusses two additional methods of testing HER2 status. The Serum HER-2/*neu* test (Siemens Healthcare Diagnostics) uses serum to test extracellular HER2 levels. The Oncotype DX Breast Cancer Assay (Genomic Health) uses formalin-fixed, paraffin-embedded tissue.

Serum HER2/*neu* monitoring

Although serum HER2 monitoring is not new (the technology has been available for 20 years), it is a relatively unknown laboratory test for monitoring disease progression in patients with HER2-positive (HER2+) metastatic breast cancer (MCB). The serum test is a quantitative measurement of the serum level changes of the HER2 oncoproteins in contrast to the more commonly used tumor markers (CA 15-3, CEA, and CA 27-29), which measure tumor burden.[3] Normal serum HER2/*neu* levels are below 13 ng/mL; patients with a serum HER2/*neu* level above 15 ng/mL are considered to be HER2+.[3]

The Serum HER-2/*neu* test should be used as a complement to standard FISH and IHC testing, not a replacement. A modified version of the classic HER2 algorithm (Figure 1) illustrates the benefit of serum testing.[4,5] There are several advantages to using the serum test, which has been cleared by the US Food and Drug Adminstration.

One advantage is that approximately 10% to 30% of primary tumors that were negative by IHC and FISH have been shown to overexpress HER2 in the presence of a metastatic tumor when serum HER2 is tested.[6] In addition, a benefit is realized when the biopsy specimen of the primary tumor was not tested for HER2 overexpression or the tissue sample is no longer viable or available for testing.

Another advantage is that the HER2 serum test can predict response to trastuzumab treatment. The objective response rate to trastuzumab therapy is 34%.[7] By monitoring a patient with MBC receiving trastuzumab therapy with serum HER2 tests, prolonged treatment without response can be avoided. MBC patients receiving trastuzumab therapy typically have repeat imaging studies 2 to 3 months after starting treatment, and imaging studies do not always detect small metastasis.[8] Also, not pursuing an ineffective treatment can result in substantial cost savings.[9]

Multiple studies have corroborated the clinical utility of serum testing of HER2. Esteva and colleagues conducted a multicenter, retrospective study of 103 women with MBC who had HER2 overexpression. The patients were followed over a period of 12 to 20 months and monitored using HER2 serum testing and CA 15-3 tumor markers. The results showed a significant difference in progression-free survival between patients whose HER2 serum values 2 to 4 weeks after starting trastuzumab therapy were >77% or ≤ 77% of the baseline value (217 and 587 days, respectively).[10]

A pooled analysis of data on 307 patients showed similar results. Patients who had a ≥20% reduction in serum HER2 levels showed a benefit from trastuzumab, as measured by significantly longer progression-free survival, longer duration of response, and longer overall survival; those with a decline of ≤20% showed less benefit.[11]

The Serum HER-2/*neu* test uses levels of <15 ng/mL as a normal baseline value. The manufacturer recommends that patients with MBC with HER2 values at this level should be monitored periodically to check for progression of disease, and patients with a baseline level >15 ng/mL should be monitored routinely. The manufacturer does not assign specific timeframes to "periodically" or "routinely." Increasing serum HER2 levels indicate disease progression, and falling serum HER2 levels suggest response to trastuzumab-based therapy or stable disease.[4]

The Serum HER-2/*neu* test has been assigned a *Current Procedural Terminology (CPT)* code and is covered by most health insurance programs. The technology is available through many large diagnostic laboratories; however, ASCO guidelines for the use of tumor markers in breast cancer do not recommend serum testing of the extracellular domain of HER2 in clinical settings.[12]

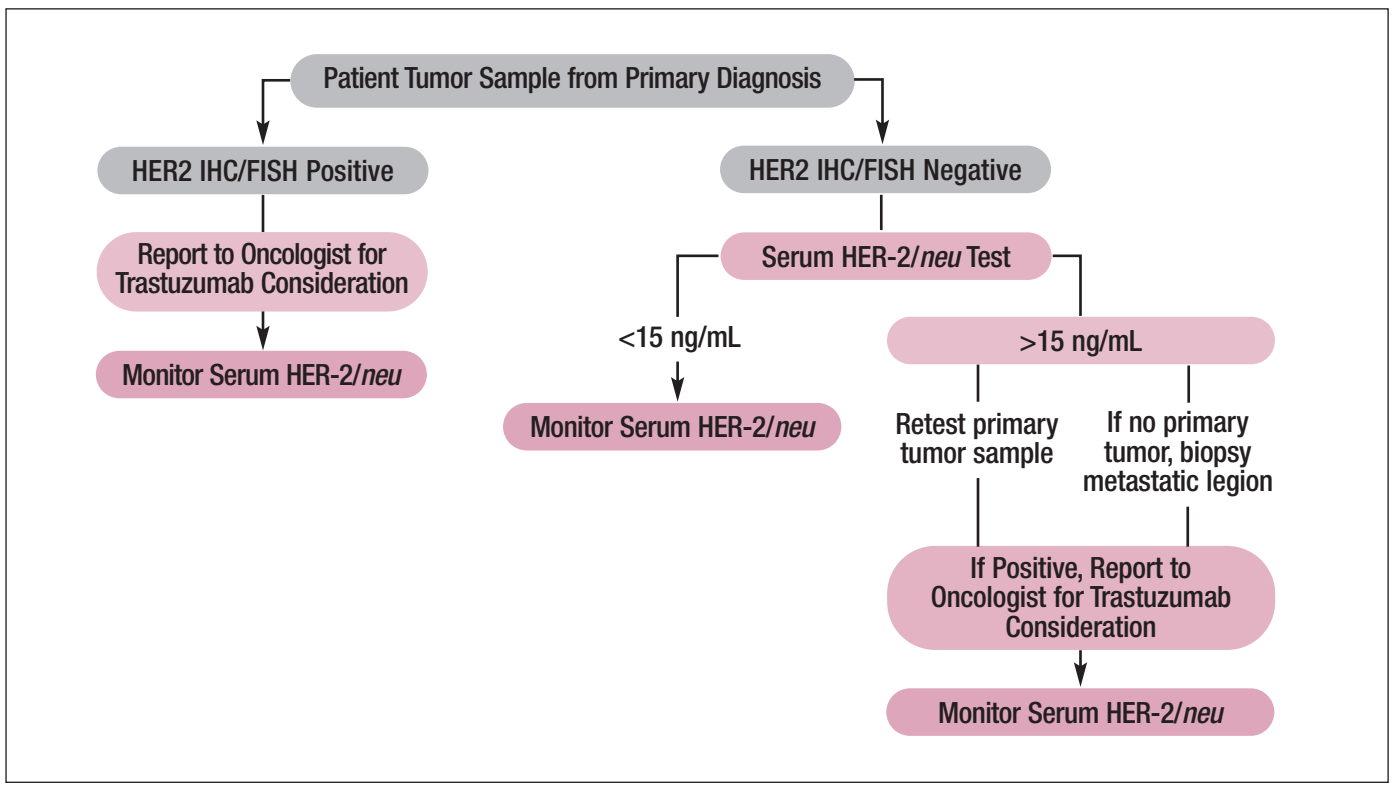


Figure 1. Serum HER2 algorithm.

FISH indicates fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
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Oncotype DX

Available since January 2004, the Oncotype DX Breast Cancer Assay is a tool to assist patients who have early-stage, node-negative, estrogen receptor–positive breast cancer with treatment decisions. This assay uses formalin-fixed, paraffin-embedded tissue from the breast tumor, and reverse transcriptase-polymerase chain reaction (RT-PCR) to provide a 21-gene assay that can predict chemotherapy benefit and distant (10-year) tumor recurrence.

In September 2008, the manufacturer released information, substantiated by recent research, which stated that the Oncotype DX was able to reliably assess quantitative HER2 status. The release of this information coincided with the 2008 ASCO Breast Cancer Symposium. Two studies were presented that demonstrated a high concor-

Continued on page 20

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PhaSeal®

New Technologies in HER2 Testing

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HER2 Central IHC vs Oncotype DX (Current ASCO/CAP Guidelines)

	IHC+	IHC–	Total
RT-PCR by Oncotype DX +	94 (78%)	4 (1%)	98
RT-PCR by Oncotype DX –	27 (22%)	439 (99%)	466
Total	121	443	564

Concordance: 95%
95% CI (92%, 96%)

Figure 2. Intergroup Trial E2197: Concordance in HER2 status between HER2 testing by IHC and quantitative HER2 testing, RT-PCR reported by Oncotype DX.

HER2 indicates human epidermal growth factor receptor 2; IHC, immunohistochemistry; RT-PCR, reverse transcriptase-polymerase chain reaction.

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HER2 Central FISH vs Oncotype DX (Current ASCO/CAP Guidelines)

	FISH+	FISH–	Total
RT-PCR by Oncotype DX +	55 (98%)	11 (3%)	66
RT-PCR by Oncotype DX –	1 (2%)	408 (97%)	409
Total	56	419	475

Concordance: 97%
95% CI (96%, 99%)

Figure 3. Kaiser Permanente Oncotype DX study: FISH HER2 testing by a central laboratory and quantitative HER2 testing, RT-PCR reported by Oncotype DX.

FISH indicates fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; RT-PCR, reverse transcriptase-polymerase chain reaction.

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dance between both IHC and FISH testing for HER2 and the Oncotype DX assay HER2 score.

Sparano and colleagues studied RNA from tumor samples from 755 patients enrolled in Intergroup Trial E2197.[13] Although the purpose of the trial was to compare two different adjuvant chemotherapy regimens in patients with zero to three positive lymph nodes, the data showed a 95% concordance in HER2 status between IHC and quantitative RT-PCR reported by Oncotype DX (Figure 2).

Baehner and colleagues compared central laboratory HER2 testing by FISH and quantitative HER2 testing by RT-PCR.[14] A sample of 568 breast cancer specimens from the Kaiser Permanente Oncotype DX study were used to compare concordance of the testing methods. The results showed a high concordance for HER2 status, 97%, between FISH testing and RT-PCR reported by Oncotype DX (Figure 3).

The Oncotype DX assay is performed only at Genomic Health Laboratory, a Clinical Laboratory Improvement Amendment–certified clinical reference laboratory and is available only for estrogen receptor–positive, lymph node–negative, early-stage I or II patients. The test has been assigned a CPT code for billing purposes. Results are usually available within 10 to 14 days after receipt of the specimen. Many insurance companies cover the cost of testing for patients who fit into the validation criteria.

Conclusion

As technology changes, it is the responsibility of oncology nurses to keep informed of advances that have the potential to change patient treatment options and outcomes. The new technologies available for testing HER2 (Table) offer options for both the diagnosis of HER2 status and monitoring of response to therapy with trastuzumab. Despite the promising data presented in recent studies, the 2007 ASCO guidelines state that the only recommended tests for confirmation of HER2 status in patients with breast cancer are IHC and/or FISH.

Table. New Technology for Testing HER2

Test type (brand name)	Sample type	Measurement	Method of assay	Comments
Immunohistochemistry (IHC) (HercepTest, Pathway HER2 Test)	Formalin-fixed, paraffin-embedded tumor sample	Semiquantitative	Detects antibodies (proteins) on cell surface	No special laboratory equipment needed
Fluorescence in situ hybridization (FISH) (PathVysion)	Formalin-fixed, paraffin-embedded tumor sample	Quantitative	Measures gene amplification by complementary DNA probes	Special laboratory equipment needed
Chromogenic in situ hybridization (CISH) (SPOT-Light CISH kit)	Formalin-fixed, paraffin-embedded tumor sample	Quantitative	Measures strength of gene amplification	Need to purchase SPOT-Light kit; no special laboratory equipment needed
Protein-Protein (HERmark Breast Cancer Assay)	Formalin-fixed, paraffin-embedded tumor sample	Quantitative	Measures HER2 protein and HER2 homodimer levels by electrophoresis	Sample must be sent to Monogram Biosciences Labs
Serum level (Serum HER-2/*neu*)	Serum	Quantitative	Measures serum HER2 protein levels	Special laboratory equipment needed
Reverse transcriptase-polymerase chain reaction (RT-PCR) (Oncotype DX Breast Cancer Assay)	Formalin-fixed, paraffin-embedded tumor sample	Quantitative	Measures HER2 gene overexpression	Sample must be sent to Genomic Health Laboratory

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In the treatment of higher-risk MDS*…

* MDS, myelodysplastic syndromes; higher-risk MDS, Intermediate-2- and High-risk MDS per International Prognostic Scoring System (IPSS).

Please see Important Safety Information and Brief Summary of full Prescribing Information on following pages.

...A Breakthrough in

Vidaza®

azacitidine for injection

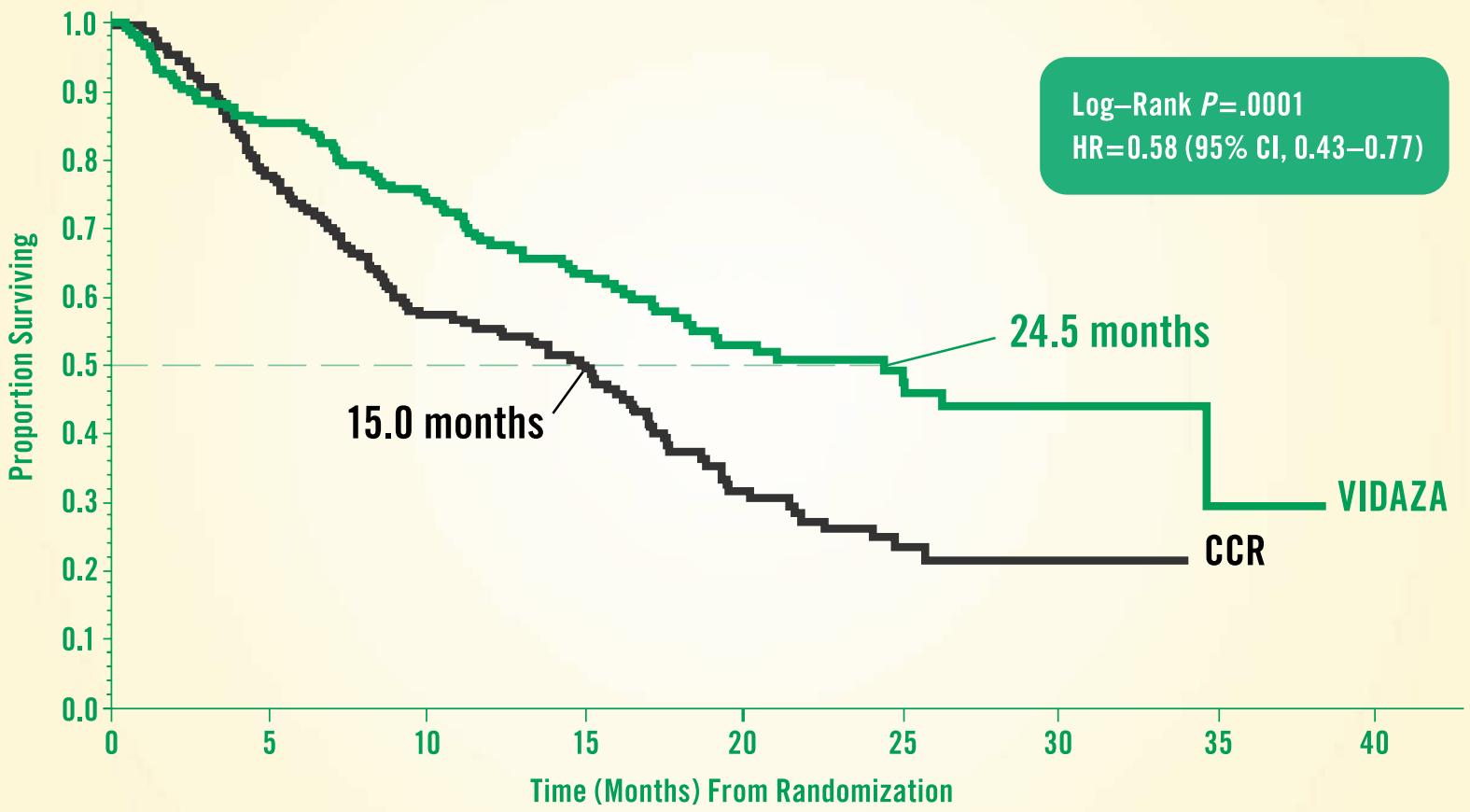
Proven Results. Extended Survival.

S U R V I V A L

VIDAZA is the first and only agent proven to extend overall survival vs conventional care regimens (CCR) in patients with higher-risk MDS

- Monitor liver chemistries and serum creatinine prior to initiation of therapy and with each cycle

VIDAZA nearly doubled the 2-year overall survival rate[1]



Study 4, the Survival Study (AZA-001), was a phase 3, prospective, international, multicenter, randomized, controlled, parallel-group, non-crossover study of 358 adult (≥18 years) patients with higher-risk MDS (IPSS Intermediate-2 or High), and FAB*-defined refractory anemia with excess blasts (RAEB), or RAEB in transformation (RAEB-T†), or dysplastic-type chronic myelomonocytic leukemia (CMMoL), using modified FAB criteria. Patients were randomized to receive either VIDAZA (75 mg/m^2 SC daily for 7 days each 28-day cycle) + best supportive care (BSC; transfusions, antibiotics, G-CSF for neutropenic infection), or 1 of 3 conventional care regimens (CCR). CCR treatments included BSC alone; low-dose cytarabine (L-DAC; 20 mg/m^2 SC daily for 14 days every 28 to 42 days); or 7+3 chemotherapy (induction with cytarabine 100-200 mg/m^2/d by continuous IV infusion over 7 days plus an anthracycline days 1-3 [plus a maximum of 2 consolidation cycles]). CCR were pre-selected by study investigators. The primary end point of the study was overall survival.[1]

* French-American-British classification for MDS.

† Bone marrow blast count ≥20% is classified by the WHO as AML. The investigators in the Survival Study (AZA-001) classified RAEB-T as blasts 21%-29%.[1]

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

Please see Important Safety Information and Brief Summary of full Prescribing Information on following pages.

For proven survival in higher-risk MDS

There's only VIDAZA®

VIDAZA significantly extended median overall survival vs CCR

- 24.5 months for patients on VIDAZA vs 15 months for patients on CCR (*P*=.0001; HR=0.58 [95% CI, 0.43-0.77])

VIDAZA nearly doubled the 2-year overall survival rate vs CCR

- 51% survival for VIDAZA vs 26% survival for CCR [24.6% difference, 95% CI, 13.1-36.1][1]

Patients continued treatment until disease progression, relapse after response, or unacceptable toxicity

- To optimize patient benefit, investigators aimed to treat patients with VIDAZA for at least 6 cycles[1]
- Patients receiving VIDAZA were treated for a median of 9 cycles (range 1-39)
- Patients should be monitored for hematologic response and renal toxicities, with dosage delay or reduction as appropriate

Important Safety Information

- VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol and in patients with advanced malignant hepatic tumors
- In Studies 1 and 2, the most commonly occurring adverse reactions by SC route were nausea (70.5%), anemia (69.5%), thrombocytopenia (65.5%), vomiting (54.1%), pyrexia (51.8%), leukopenia (48.2%), diarrhea (36.4%), injection site erythema (35.0%), constipation (33.6%), neutropenia (32.3%), and ecchymosis (30.5%). Other adverse reactions included dizziness (18.6%), chest pain (16.4%), febrile neutropenia (16.4%), myalgia (15.9%), injection site reaction (13.6%), and malaise (10.9%). In Study 3, the most common adverse reactions by IV route also included petechiae (45.8%), weakness (35.4%), rigors (35.4%), and hypokalemia (31.3%)
- In Study 4, the most commonly occurring adverse reactions were thrombocytopenia (69.7%), neutropenia (65.7%), anemia (51.4%), constipation (50.3%), nausea (48.0%), injection site erythema (42.9%), and pyrexia (30.3%). The most commonly occurring Grade 3/4 adverse reactions were neutropenia (61.1%), thrombocytopenia (58.3%), leukopenia (14.9%), anemia (13.7%), and febrile neutropenia (12.6%)
- Because treatment with VIDAZA is associated with anemia, neutropenia, and thrombocytopenia, complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle
- Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. In addition, azacitidine and its metabolites are substantially excreted by the kidneys and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function
- VIDAZA may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be apprised of the potential hazard to the fetus. Men should be advised not to father a child while receiving VIDAZA
- Nursing mothers should be advised to discontinue nursing or the drug, taking into consideration the importance of the drug to the mother

Please see Brief Summary of full Prescribing Information on following pages.

Reference: 1. Data on file, Celgene Corporation.

Celgene

Vidaza®

azacitidine for injection

Proven Results. Extended Survival.

VIDAZA® (azacitidine for injection)
The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

1.1 Myelodysplastic Syndromes (MDS)

VIDAZA® is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

4 CONTRAINDICATIONS

4.1 Advanced Malignant Hepatic Tumors

VIDAZA is contraindicated in patients with advanced malignant hepatic tumors *[see Warnings and Precautions (5.2)]*.

4.2 Hypersensitivity to Azacitidine or Mannitol

VIDAZA is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia, Neutropenia and Thrombocytopenia

Treatment with VIDAZA is associated with anemia, neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and hematologic response *[see Dosage and Administration (2.3) in full prescribing information]*.

5.2 Severe Preexisting Hepatic Impairment

Because azacitidine is potentially hepatotoxic in patients with severe preexisting hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors *[see Contraindications (4.1)]*. Safety and effectiveness of VIDAZA in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.

5.3 Renal Abnormalities

Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported rarely in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for nonMDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held *[see Dosage and Administration (2.4) in full prescribing information]*. Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys *[see Dosage and Administration (2.4, 2.5) in full prescribing information]*. Safety and effectiveness of VIDAZA in patients with MDS and renal impairment have not been studied as these patients were excluded from the clinical trials.

5.4 Monitoring Laboratory Tests

Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of therapy.

5.5 Pregnancy

Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine caused congenital malformations in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. There are no adequate and well-controlled studies in pregnant women using VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5.6 Use in Males

Men should be advised to not father a child while receiving treatment with VIDAZA. In animal studies, pre-conception treatment of male mice and rats resulted in increased embryofetal loss in mated females *[see Nonclinical Toxicology (13)]*.

6 ADVERSE REACTIONS

6.1 Overview

Adverse Reactions Described in Other Labeling Sections: anemia, neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC or IV Route):
Discontinuation: leukopenia, thrombocytopenia, neutropenia.
Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

6.2 Adverse Reactions in Clinical Trials

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. The data described below reflect exposure to VIDAZA in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (SC administration), Studies 2 and 3 were single arm studies (one with SC administration and one with IV administration), and Study 4 was an international randomized trial (SC administration) *[see Clinical Studies (14)]*. In Studies 1, 2 and 3, a total of 268 patients were exposed to VIDAZA, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). VIDAZA was studied primarily in supportive-care controlled and uncontrolled trials (n=150 and n=118, respectively). The population in the subcutaneous studies (n=220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the IV study (n=48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 mg/m^2. In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to VIDAZA. Of these patients, 119 were exposed for 6 or more cycles, and 63 for at least 12 cycles. The mean age of this population was 68.1 years (ranging from 42 to 83 years), 74% were male, and 99% were white. Most patients received daily VIDAZA doses of 75 mg/m^2.

Table 1 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA (SC) in Studies 1 and 2. It is important to note that duration of exposure was longer for the VIDAZA-treated group than for the observation group: patients received VIDAZA for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 1: Most Frequently Observed Adverse Reactions (≥5.0% in All SC VIDAZA Treated Patients; Studies 1 and 2)

	Number (%) of Patients			
System Organ Class Preferred Term[a]	**All VIDAZA[b] (N=220)**		**Observation[c] (N=92)**	
Blood and lymphatic system disorders				
Anemia	153	(69.5)	59	(64.1)
Anemia aggravated	12	(5.5)	5	(5.4)
Febrile neutropenia	36	(16.4)	4	(4.3)
Leukopenia	106	(48.2)	27	(29.3)
Neutropenia	71	(32.3)	10	(10.9)
Thrombocytopenia	144	(65.5)	42	(45.7)
Gastrointestinal disorders				
Abdominal tenderness	26	(11.8)	1	(1.1)
Constipation	74	(33.6)	6	(6.5)
Diarrhea	80	(36.4)	13	(14.1)
Gingival bleeding	21	(9.5)	4	(4.3)
Loose stools	12	(5.5)	0	
Mouth hemorrhage	11	(5.0)	1	(1.1)
Nausea	155	(70.5)	16	(17.4)
Stomatitis	17	(7.7)	0	
Vomiting	119	(54.1)	5	(5.4)
General disorders and administration site conditions				
Chest pain	36	(16.4)	5	(5.4)
Injection site bruising	31	(14.1)	0	
Injection site erythema	77	(35.0)	0	
Injection site granuloma	11	(5.0)	0	
Injection site pain	50	(22.7)	0	
Injection site pigmentation changes	11	(5.0)	0	
Injection site pruritus	15	(6.8)	0	
Injection site reaction	30	(13.6)	0	
Injection site swelling	11	(5.0)	0	
Lethargy	17	(7.7)	2	(2.2)
Malaise	24	(10.9)	1	(1.1)
Pyrexia	114	(51.8)	28	(30.4)
Infections and infestations				
Nasopharyngitis	32	(14.5)	3	(3.3)
Pneumonia	24	(10.9)	5	(5.4)
Upper respiratory tract infection	28	(12.7)	4	(4.3)
Injury, poisoning, and procedural complications				
Post procedural hemorrhage	13	(5.9)	1	(1.1)
Metabolism and nutrition disorders				
Anorexia	45	(20.5)	6	(6.5)
Musculoskeletal and connective tissue disorders				
Arthralgia	49	(22.3)	3	(3.3)
Chest wall pain	11	(5.0)	0	
Myalgia	35	(15.9)	2	(2.2)
Nervous system disorders				
Dizziness	41	(18.6)	5	(5.4)
Headache	48	(21.8)	10	(10.9)
Psychiatric disorders				
Anxiety	29	(13.2)	3	(3.3)
Insomnia	24	(10.9)	4	(4.3)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	64	(29.1)	11	(12.0)
Skin and subcutaneous tissue disorders				
Dry skin	11	(5.0)	1	(1.1)
Ecchymosis	67	(30.5)	14	(15.2)
Erythema	37	(16.8)	4	(4.3)
Rash	31	(14.1)	9	(9.8)
Skin nodule	11	(5.0)	1	(1.1)
Urticaria	13	(5.9)	1	(1.1)
Vascular disorders				
Hematoma	19	(8.6)	0	
Hypotension	15	(6.8)	2	(2.2)
Petechiae	52	(23.6)	8	(8.7)

[a] Multiple terms of the same preferred terms for a patient are only counted once within each treatment group.
[b] Includes adverse reactions from all patients exposed to VIDAZA, including patients after crossing over from observations.
[c] Includes adverse reactions from observation period only; excludes any adverse events after crossover to VIDAZA.

Table 2 presents adverse reactions occurring in at least 5% of patients treated with VIDAZA in Study 4. Similar to Studies 1 and 2 described above, duration of exposure to treatment with VIDAZA was longer (mean 12.2 months) compared with best supportive care (mean 7.5 months).

Table 2: Most Frequently Observed Adverse Reactions (≥5.0% in the VIDAZA Treated Patients and the Percentage with NCI CTC Grade 3/4 Reactions; Study 4)

	Number (%) of Patients			
	Any Grade		Grade 3/4	
System Organ Class Preferred Term[a]	VIDAZA (N=175)	Best Supportive Care Only (N=102)	VIDAZA (N=175)	Best Supportive Care Only (N=102)
Blood and lymphatic system disorders				
Anemia	90 (51.4)	45 (44.1)	24 (13.7)	9 (8.8)
Febrile neutropenia	24 (13.7)	10 (9.8)	22 (12.6)	7 (6.9)
Leukopenia	32 (18.3)	2 (2.0)	26 (14.9)	1 (1.0)
Neutropenia	115 (65.7)	29 (28.4)	107 (61.1)	22 (21.6)
Thrombocytopenia	122 (69.7)	35 (34.3)	102 (58.3)	29 (28.4)
Gastrointestinal disorders				
Abdominal pain	22 (12.6)	7 (6.9)	7 (4.0)	0
Constipation	88 (50.3)	8 (7.8)	2 (1.1)	0
Dyspepsia	10 (5.7)	2 (2.0)	0	0
Nausea	84 (48.0)	12 (11.8)	3 (1.7)	0
Vomiting	47 (26.9)	7 (6.9)	0	0
General disorders and administration site conditions				
Fatigue	42 (24.0)	12 (11.8)	6 (3.4)	2 (2.0)
Injection site bruising	9 (5.1)	0	0	0
Injection site erythema	75 (42.9)	0	0	0
Injection site hematoma	11 (6.3)	0	0	0
Injection site induration	9 (5.1)	0	0	0
Injection site pain	33 (18.9)	0	0	0
Injection site rash	10 (5.7)	0	0	0
Injection site reaction	51 (29.1)	0	1 (0.6)	0
Pyrexia	53 (30.3)	18 (17.6)	8 (4.6)	1 (1.0)
Infections and infestations				
Rhinitis	10 (5.7)	1 (1.0)	0	0
Upper respiratory tract infection	16 (9.1)	4 (3.9)	3 (1.7)	0
Urinary tract infection	15 (8.6)	3 (2.9)	3 (1.7)	0
Investigations				
Weight decreased	14 (8.0)	0	1 (0.6)	0
Metabolism and nutrition disorders				
Hypokalemia	11 (6.3)	3 (2.9)	3 (1.7)	3 (2.9)
Nervous system disorders				
Lethargy	13 (7.4)	2 (2.0)	0	1 (1.0)
Psychiatric disorders				
Anxiety	9 (5.1)	1 (1.0)	0	0
Insomnia	15 (8.6)	3 (2.9)	0	0
Renal and urinary disorders				
Hematuria	11 (6.3)	2 (2.0)	4 (2.3)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	26 (14.9)	5 (4.9)	6 (3.4)	2 (2.0)
Dyspnea exertional	9 (5.1)	1 (1.0)	0	0
Pharyngolaryngeal pain	11 (6.3)	3 (2.9)	0	0
Skin and subcutaneous tissue disorders				
Erythema	13 (7.4)	3 (2.9)	0	0
Petechiae	20 (11.4)	4 (3.9)	2 (1.1)	0
Pruritus	21 (12.0)	2 (2.0)	0	0
Rash	18 (10.3)	1 (1.0)	0	0
Vascular disorders				
Hypertension	15 (8.6)	4 (3.9)	2 (1.1)	2 (2.0)

[a] Multiple reports of the same preferred term from a patient were only counted once within each treatment.

In Studies 1, 2 and 4 with SC administration of VIDAZA, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of VIDAZA. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Overall, adverse reactions were qualitatively similar between the IV and SC studies. Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (e.g., erythema or pain) and catheter site reactions (e.g., infection, erythema, or hemorrhage).

In clinical studies of either SC or IV VIDAZA, the following serious adverse reactions occurring at a rate of < 5% (and not described in Tables 1 or 2) were reported:

Blood and lymphatic system disorders: agranulocytosis, bone marrow failure, pancytopenia, splenomegaly. **Cardiac disorders:** atrial fibrillation, cardiac failure, cardiac failure congestive, cardiorespiratory arrest, congestive cardiomyopathy. **Eye disorders:** eye hemorrhage. **Gastrointestinal disorders:** diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess. **General disorders and administration site conditions:** catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome. **Hepatobiliary disorders:** cholecystitis. **Immune system disorders:** anaphylactic shock, hypersensitivity. **Infections and infestations:** abscess limb, bacterial infection, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis. **Metabolism and nutrition disorders:** dehydration. **Musculoskeletal and connective tissue disorders:** bone pain aggravated, muscle weakness, neck pain. **Neoplasms benign, malignant and unspecified:** leukemia cutis. **Nervous system disorders:** cerebral hemorrhage, convulsions, intracranial hemorrhage. **Renal and urinary disorders:** loin pain, renal failure. **Respiratory, thoracic and mediastinal disorders:** hemoptysis, lung infiltration, pneumonitis, respiratory distress. **Skin and subcutaneous tissue disorders:** pyoderma gangrenosum, rash pruritic, skin induration. **Surgical and medical procedures:** cholecystectomy. **Vascular disorders:** orthostatic hypotension.

6.3 Postmarketing Experience

Adverse reactions identified from spontaneous reports have been similar to those reported during clinical trials with VIDAZA.

7 DRUG INTERACTIONS

No formal assessments of drug-drug interactions between VIDAZA and other agents have been conducted *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

VIDAZA may cause fetal harm when administered to a pregnant woman. Azacitidine was teratogenic in animals. Women of childbearing potential should be advised to avoid pregnancy during treatment with VIDAZA. If this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Female partners of male patients receiving VIDAZA should not become pregnant *[see Nonclinical Toxicology (13)]*.

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m^2 (approximately 8% of the recommended human daily dose on a mg/m^2 basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3-12 mg/m^2 (approximately 4%-16% the recommended human daily dose on a mg/m^2 basis). In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 (postimplantation) at a dose of 6 mg/m^2 (approximately 8% of the recommended human daily dose on a mg/m^2 basis), although treatment in the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m^2 (approximately 8% the recommended human daily dose on a mg/m^2 basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3-12 mg/m^2 on gestation days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

8.3 Nursing Mothers

It is not known whether azacitidine or its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients. Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients < 65 years of age and patients 65 years of age and older. Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function *[see Dosage and Administration (2.5) in full prescribing information* and *Warnings and Precautions (5.3)]*.

8.6 Gender Differences

There were no clinically relevant differences in safety and efficacy based on gender.

8.7 Race

Greater than 90% of all patients in all trials were Caucasian. Therefore, no comparisons between Caucasians and non-Caucasians were possible.

13 NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m^2, approximately 8% of the recommended human daily dose on a mg/m^2 basis) administered IP three times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/m^2, approximately 8% the recommended human daily dose on a mg/m^2 basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m^2 (approximately 20-80% the recommended human daily dose on a mg/m^2 basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in in vitro bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, Escherichia coli strains WP14 Pro, WP3103P, WP3104P, and CC103; in in vitro forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an in vitro micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/m^2 (approximately 9% the recommended human daily dose on a mg/m^2 basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15-30 mg/m^2 (approximately 20-40%, the recommended human daily dose on a mg/m^2 basis) resulted in decreased weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m^2 resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their physician about any underlying liver or renal disease.

Advise women of childbearing potential to avoid becoming pregnant while receiving treatment with VIDAZA. For nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into consideration the importance of the drug to the mother. Advise men not to father a child while receiving treatment with VIDAZA.

Manufactured for: Celgene Corporation
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International Oncology News

Reports from International Meetings and Researchers

Possible Link Between Skin Cancer and Posttransplant Voriconazole Use

PARIS—New data suggest that voriconazole, which has been used as standard antifungal prophylaxis in lung transplant recipients, may increase the risk of skin cancer in lung transplant recipients.

The findings were reported at the 29th Annual Meeting of the International Society for Heart and Lung Transplantation (ISHLT).

A. A. Feist, MD, of the University of California Medical Center, San Diego, and colleagues compared the incidence of skin cancer in a group of lung transplant recipients who received voriconazole for the prevention or treatment of aspergillus versus those who received other antifungal therapy or no antifungal therapy. The cohort included 149 patients who underwent a lung transplant procedure at their institution over a recent 6-year period.

Overall, 12 of 28 patients, or 42.9%, who received voriconazole developed squamous and/or basal cell carcinoma versus 12 of 21 patients, or 9.9%, who did not receive prophylaxis.


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The data also showed that skin cancer was more "clinically aggressive" in lung transplant patients treated with voriconazole. That is, skin cancers developed at a mean of 910 days in voriconazole-treated patients versus 372 days in patients not receiving the drug. In addition, nine of 12 patients who developed skin cancers at multiple sites or with local recurrence had received voriconazole.


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Skin cancer is the most common malignancy following a lung transplant.

Omega-3 Helps Patient Recovery After Surgery

DUBLIN—Omega-3 fatty acids given as part of an oral nutritional supplement help preserve muscle mass in patients undergoing surgery for esophageal cancer, researchers reported in the March 2009 issue of *The Annals of Surgery*.

A group from Trinity College Dublin and St. James Hospital randomized a group of patients undergoing esophagectomy to receive a nutritional supplement enriched with omega-3 starting 5 days before surgery and continuing for 5 weeks after surgery or to standard enteral nutrition.

Results in 53 patients showed that individuals who received omega-3 maintained all aspects of their body composition postoperatively, whereas the control group lost a mean of 4 lb of muscle mass after surgery. The amount of weight loss in the control group was "clinically severe," the authors wrote in their article.

"Weight loss is extremely common before and particularly after surgery for esophageal cancer," principal investigator John V. Reynolds, MD, said in a news release. "Any approach that can preserve weight, in particular muscle weight and strength, may represent a real advance."

Omega-3 fats are essential fats that are found naturally in oily fish, with the highest concentrations in salmon, herring, mackerel, and sardines.

Denosumab Strengthens Bones in Prostate Cancer Patients

STOCKHOLM—Denosumab, a genetically engineered antibody, significantly increases bone mineral density (BMD) in men with nonmetastatic prostate cancer who are being treated with androgen deprivation therapy, according to data presented at the 24th Annual European Association of Urology (EAU) Congress.

Androgen deprivation therapy is associated with accelerated bone loss and increased risk of bone fractures.


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Matthew Smith, MD, with Massachusetts General Hospital in Boston, and colleagues, reported findings in 1468 men who had been randomized to 3 years' treatment with denosumab, 60 mg per day, or placebo. All men took calcium and vitamin D supplements throughout the trial.

The primary end point was the change from baseline for lumbar spine BMD on dual x-ray absorptiometry obtained at 24 months.

Results showed that the change in lumbar spine BMD from baseline was 6.7% more in denosumab-treated patients than placebo. The difference between the two groups was significant.

Denosumab was also superior to placebo on several secondary end points including the incidence of new vertebral fractures and changes from baseline for total hip, femoral neck, and lumbar spine BMD at 36 months.

—Jill Stein

SKIN CANCERS

Phone Consultation Cuts Delay to Skin Cancer Surgery

SAN FRANCISCO—Researchers are reporting that skin cancer patients can decrease the time they have to wait between a biopsy and Mohs micrographic surgery by having a preoperative consultation by telephone instead of an office visit.

Mohs surgery is used mainly to treat basal cell and squamous cell carcinomas but may be used to treat less common tumors, including early-stage melanoma.

The new findings, released at the 67th Annual Meeting of the American Academy of Dermatology (AAD), show that the waiting time can be lowered by roughly 25% if the patient opts for a preoperative phone discussion with a Mohs surgical nurse in place of the standard preoperative visit to a surgeon.

Researchers from St. Louis University School of Medicine compared waiting times and satisfaction levels in patients who had an office consultation per standard practice and patients who had a phone consultation before Mohs surgery for nonmelanoma skin cancer. For the study, 152 patients who had undergone Mohs surgery over a recent 6-month period were asked to participate in a 5-minute telephone survey.


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"While the increase in nonmelanoma skin cancer has fueled a demand for Mohs surgery, a shortage of Mohs surgeons has produced long delays for Mohs consultation and treatment," Sharone Askari, MD, one of the researchers, said.

Typically, patients have an office consultation with their surgeon before their day of surgery. Phone consultations were recently introduced at St. Louis University Hospitals to reduce lengthy delays between the biopsy and surgery. The phone consultation involves a discussion between the patient and a Mohs surgical nurse, who provides the same information as the surgeon provides with a standard office visit.

Results from 136 patients who completed the survey revealed that the waiting time from biopsy to surgery was 75 days for patients who had a phone consult compared with 104 days for those who had an office consult.

Overall, 98% of phone consult patients said they were "very satisfied" with their overall surgical experience versus 87% of office consult patients. Ninety percent of phone consult patients said they preferred a phone consult, whereas 70% of office consultation patients reported a preference for an office consultation. Of a subset of patients who had both a recent phone consultation and a prior office consultation, 69% said they favored the phone consult.

Askari said additional research is needed to confirm the findings and also to identify additional ways to better prepare patients for Mohs surgery.

—Jill Stein

Cancer Clinical Trials

Coalition Works to Increase Awareness, Participation in Cancer Clinical Trials

An interview with Karen Creamer, RN

Although participation in a clinical trial has many advantages to patients, including access to the latest treatments, enrollment in cancer trials among adults in the United States remains low. The Coalition of Cancer Cooperative Groups was established in 1997 to increase patient awareness of clinical trials, facilitate access, and promote participation. In this interview with *The Oncology Nurse*, Karen Creamer, RN, discusses obstacles to patient enrollment, the coalition's goals and services, and the nurse's role in promoting trial participation. Ms Creamer serves as director of patient advocacy and education for the coalition.

Currently, what percentage of cancer patients in the United States participate in cancer clinical trials?

Overall, about 3% to 5% of adults with cancer in the United States enroll in clinical trials. The coalition teamed up with Northwestern University in 2005 to conduct a clinical trial awareness survey to determine why the number is so alarming low. The researchers contacted more than 2000 US cancer survivors, and they determined that the primary issue related to clinical trial enrollment was access to information. The survey, which was reported at the 2007 annual meeting of the American Society for Clinical Oncology (Comis RL, et al. *J Oncol Pract*. 2009;5:50-56), found that only 10% of the survivors surveyed knew that participation in a trial was an option at the time of their diagnosis. The majority of the survivors said they would have considered participating if their healthcare provider had made them aware it was a treatment option. So, we think awareness plays a key role in why participation in clinical trials is so low and that nurses have a special interaction with patients that can be helpful in raising awareness.

Were the researchers able to determine what accounted for this lack of awareness?

The survey showed that 73% of survivors who participated in a clinical trial or knew that it was an option at the time of their diagnosis reported that the physician was the source of the information. Awareness of clinical trials varied significantly based on the cancer type (Figure), as well as the type of treatment that the patient received. Patients with leukemia were the most likely to be informed about clinical trials; breast cancer, lymphoma, lung cancer, and prostate cancer followed.


Karen Creamer, RN

That leads us to believe that some physicians may be more likely to provide clinical trial information for certain types of cancer, whereas for other types of cancers, they may not even discuss clinical trials as an option or the types of treatments available. When a drug or chemotherapy was involved in their therapy, survivors were the most informed that a clinical trial was available for them (18%) and the most frequently enrolled (8%). Survivors who received surgery alone were the least informed (5%) and least frequently enrolled (1%).

Is concern about the possible adverse effects of experimental drugs a factor in the decision to participate in a clinical trial? And what about the cost of medical care and concern about reimbursement by insurance companies?

As part of the decision-making process, a patient may choose not to participate in a trial of a new drug because they have been informed of possible adverse effects. The cost of medical care and concern about reimbursement may occasionally be factors as well, but in some cases, the patient goes on a trial because sometimes the cost is covered as a part of the trial.

According to the survey, failure to enroll was noted to be mainly because of lack of awareness of the availability of a trial. In fact, 65% of the survivors surveyed said they would have been somewhat or very receptive to enrolling in a trial if they had been made aware of it at the time of initial diagnosis, and 87% would have considered participating if their initial treatment had failed.

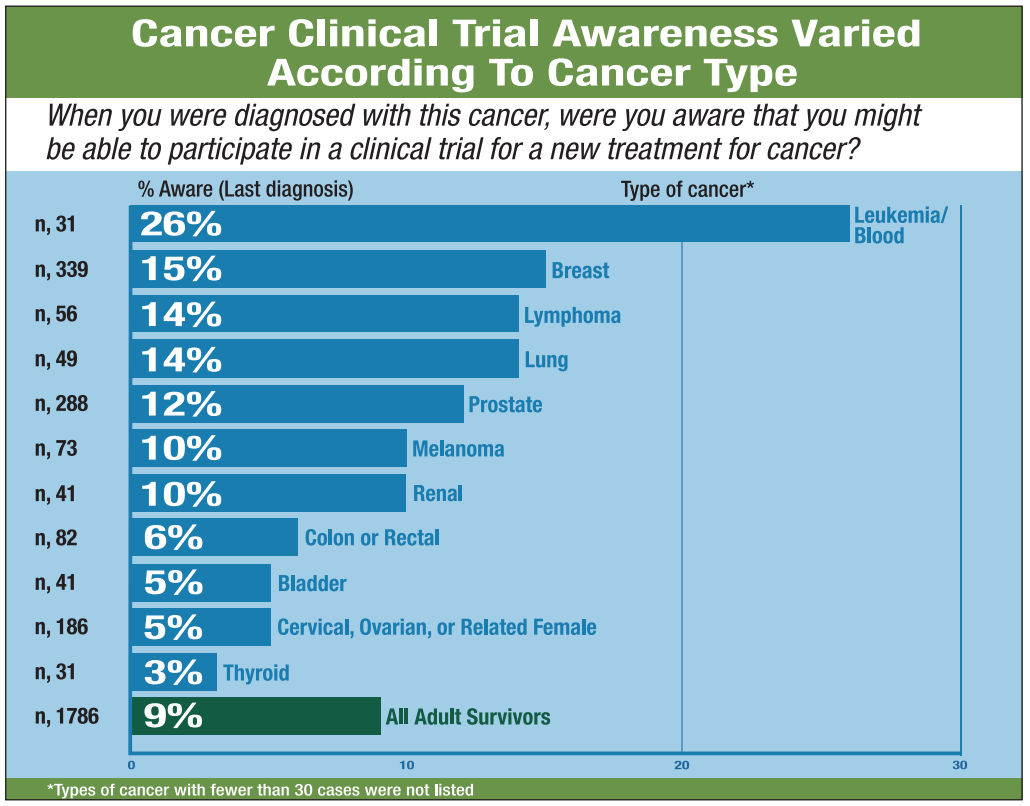

Figure. Cancer clinical trial awareness by cancer type.

What can be done to increase patient awareness of and enrollment in clinical trials?

The coalition provides an Internet-based clinical trial navigation and matching service called TrialCheck (www.CancerTrialsHelp.org). It is a user-friendly database of all cancer clinical trials and is available free of charge to anyone who wants to search by type of cancer and zip code for clinical trials nearby. (Call 877-227-8451 to search TrialCheck with the help of a trained professional from the American Cancer Society.) Nurses can benefit from this service by becoming more aware of what trials are available for their patients.

Also, researchers are working to create more patient-friendly trials. For instance, they can make sure that the criteria for enrollment are absolutely necessary and that they are not requiring any undue tests that would prevent a patient from participating. It is important too for nurses to be familiar with the trial protocol so that they can explain it to their patients. The more the nurse knows about the trial, the better he or she can explain it to the patient and the more comfortable the patient might feel with the topic in general and with making the decision as to whether to participate. If the patient does decide to enroll, the nurse can assist the patient adhere to the protocol, for example, by creating patient-friendly calendars to follow when on a protocol.

What other services does the coalition provide?

The coalition is a nonprofit service organization that works to improve physician and patient access to clinical trials through increased awareness, education, advocacy, and outreach.

We look at issues that are impeding cancer clinical research and participation in clinical trials. A lot of the services we offer are focused around increasing awareness of clinical research which can result in an increase of enrollment to trials.

The coalition convenes scientific leadership councils designed to bring together the thought leaders in specific disease areas to focus on prioritizing clinical trials in that particular disease, identifying recommendations for clinical research, and communicating those priorities and recommendations to the cancer community at large.

The coalition also conducts national clinical trial awareness campaigns in the media and in partnership with patient advocate organizations to get the right type of information out to cancer patients so that when they receive a diagnosis they can make an educated decision about participating in a clinical trial. We have a patient advocacy program through which we work with patient advocate organizations as well as advocate committees within the cancer cooperative groups to ensure that researchers are designing more patient-friendly protocols, and we train advocates to ensure that they can assist patients and bring the patient perspective more prominently into the clinical research design process.

Awareness is a key factor in increasing clinical trial participation, and nurses need to be familiar with the trials in their particular field so they can inform their patients about them.

—Karen Rosenberg

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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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AUA Recommendations

Continued from cover

Peter Carroll, MD

well-informed men aged 40 years or older who have a life expectancy of at least 10 years.

The PSA test, as well as how it is used to guide patient care (ie, at what age men should begin regular testing, intervals at which the test should be repeated, and at what point a biopsy is necessary), are highly controversial. The AUA believes, however, that when offered and interpreted appropriately, the PSA test may provide essential information for the diagnosis, pretreatment staging or risk assessment, and posttreatment monitoring of prostate cancer.

The new Best Practice Statement updates the AUA's previous guidance, which was issued 9 years ago. Major changes to the AUA statement include new recommendations about who should be considered for PSA testing, as well as when a biopsy is indicated following an abnormal PSA reading. According to the AUA, early detection and risk assessment of prostate cancer should be offered to well-informed men 40 years of age or older who have a life expectancy of at least 10 years. A baseline PSA level above the median for age 40 is a strong predictor of prostate cancer. Such testing may not only allow for earlier detection of more curable cancers, but may also allow for more efficient, less frequent testing, according to the AUA.

Men who wish to be screened for prostate cancer should have both a PSA test and a digital rectal examination. The statement by the AUA also notes that other factors, such as family history, age, overall health, and ethnicity, should be combined with the results of PSA testing and physical examination to better determine the risk of prostate cancer. The statement recommends that the benefits and risks of screening for prostate cancer should be discussed, including the risk of overdetection (detecting some cancers which may not need immediate treatment).

"The single most important message of this statement is that prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists. There is no single standard that applies to all men, nor should there be at this time," said Peter Carroll, MD, chair of the panel that developed the statement. "[The] panel carefully reviewed the most recently reported trials of PSA testing in both the United States and Europe before finalizing its guidelines. The strengths and limitation of these trials are reviewed in the guidelines."

Prostate cancer testing is an individual decision that patients of any age should make in conjunction with their physicians and urologists.

In regard to biopsy, a continuum of risk exists at all values, and major studies have demonstrated that there is no safe PSA value below which a man may be reassured that he does not have biopsy-detectable prostate cancer. Therefore, the AUA does not recommend a single PSA threshold at which a biopsy should be obtained. Rather, the decision to perform a biopsy should take into account additional factors, including free and total PSA levels, PSA velocity and density, patient age, family history, race/ethnicity, previous biopsy history, and comorbidities. In addition, the AUA statement emphasizes that not all prostate cancers require active treatment and that not all prostate cancers are life-threatening. The decision to proceed to active treatment is one that men should dis-

Continued on page 41

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Oral Biologic Therapy versus Chemotherapy for Pretreated Non–small-cell Lung Cancer

BY **EDWARD S. KIM, MD**
The University of Texas M.D. Anderson Cancer Center, Houston

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LEARNING OBJECTIVES

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

- Describe findings of phase 2 and phase 3 trials of gefitinib in non–small-cell lung cancer (NSCLC).
- Discuss the potential clinical implications of the INTEREST trial.
- Explain how patient characteristics such as race, sex, smoking history, and biomarkers such as epidermal growth factor receptor-gene-copy number may affect response to NSCLC therapy.
- Discuss management of skin toxicities associated with epidermal growth factor receptor inhibitor therapy.

TARGET AUDIENCE

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

COST

This program is complimentary for all learners.

Lung cancer remains a leading cause of cancer-related deaths worldwide and in the United States accounts for more cancer deaths than breast, colorectal, and prostate cancer combined. The rate of lung cancer deaths is alarmingly high because patients usually present with advanced metastatic disease, which has limited treatment options. Standard treatment involves chemotherapy and supportive care, albeit with modest response rates and a high recurrence rate after standard first-line platinum-based doublet therapy.

Background

The taxane docetaxel, at a dose of 75 mg/m^2, is approved by the US Food and Drug Administration (FDA) for second-line treatment of advanced non–small-cell lung cancer (NSCLC). The pivotal trials that led to docetaxel's approval for this indication demonstrated an improved survival and quality of life with docetaxel compared with best supportive care and compared with vinorelbine or ifosfamide chemotherapy. Side effects may include diarrhea, neuropathy, and severe neutropenia. Other agents such as pemetrexed and erlotinib are also indicated for second-line treatment of NSCLC.

Two randomized phase 2 trials (known as Iressa Dose Evaluation in Advanced Lung Cancer, or IDEAL 1 and 2) in patients with previously treated advanced NSCLC suggested that gefitinib—an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor that is taken orally—was efficacious and less toxic than chemotherapy in patients who had undergone prior treatment for NSCLC.[1,2]

Based on the data from these trials, gefitinib received accelerated approval by the FDA in 2003 as a single agent for patients with advanced lung cancer that progressed despite treatment with platinum-based and docetaxel chemotherapy. In 2005, however, a phase 3 trial (Iressa Survival Evaluation in Lung Cancer [ISEL]) showed that gefitinib compared with placebo did not improve survival in patients with NSCLC.[3] The FDA subsequently altered gefitinib's labeling, limiting its use to patients who were already receiving the drug and appeared to be benefitting from it.

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INTEREST study findings

The Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) was an open-label, phase 3 study that compared gefitinib with docetaxel in patients with locally advanced or metastatic NSCLC who had received at least one prior platinum-based chemotherapy regimen.[4] Overall, 1466 patients were recruited from 149 centers in 24 countries and then randomized to gefitinib, 250 mg/day orally, or docetaxel, 75 mg/m^2, administered as a 1-hour intravenous infusion every 3 weeks.

The two treatment groups were well matched in terms of demographic and clinical characteristics and were generally representative of a pretreated population with advanced NSCLC.

There were two primary survival end points: survival in all treated patients and in those whose tumors had high EGFR-gene-copy number.

In the 1433 patients whose results were analyzed, efficacy rates were similar for gefitinib and docetaxel. That is, gefitinib-treated patients had a median overall survival of 7.6 months versus 8.0 months in docetaxel-treated patients, while 32% of gefitinib and 34% of docetaxel patients were alive at 1 year, confirming noninferiority of gefitinib. The median progression-free survival (2.2 vs 2.7 months) and objective response rates (9.1% vs 7.6%) were also similar for the two groups.

The similar rates of overall survival were seen across multiple preplanned subgroups except in patients who received third-line treatment. In fact, patients who received third-line treatment had significantly longer survival with docetaxel than with gefitinib.

Gefitinib was better tolerated than docetaxel. Overall, gefitinib-treated patients experienced fewer treatment-related adverse events than docetaxel-treated patients (72% vs 82%), overall events (72% vs 82%), serious adverse events (4% vs 18%), adverse events prompting withdrawal from therapy (4% vs 11%), grade 3 to 4 adverse events (9% vs 41%), and adverse events resulting in death (1% vs 2%). The type of adverse event also differed between the two treatment groups.

Rash, acne, and diarrhea were more common with gefitinib, while hematologic toxic effects, asthenic disorders, and alopecia were more common with docetaxel.

Researchers also found that more gefitinib-treated patients had sustained and clinically relevant improvement in quality of life as assessed by Functional Assessment of Cancer Therapy-Lung (FACT-L) total score. The FACT-L is a widely validated tool that measures quality of life in patients being treated for lung cancer using a patient-completed questionnaire. The two treatment groups had similar improvements in lung cancer symptoms.

More gefitinib-treated patients had sustained and clinically relevant improvement in quality of life as assessed by FACT-L total score.

The study additionally showed that individuals who had never smoked, women, persons of Asian ethnic origin, and those with adenocarcinoma lived longer than smokers, men, people of non-Asian ethnic origin, and

COMMENTARY

Oral Biologic Therapy versus Chemotherapy for Pretreated Non–small-cell Lung Cancer: A Pharmacist's Perspective

BY **KATIE TIPTON, PHARMD, BCOP**
The University of Texas M.D. Anderson Cancer Center, Houston

Recurrent disease after primary therapy of non–small-cell lung cancer (NSCLC) has few effective treatment options. In patients with poor performance status or multiple comorbidities, practitioners must often choose between best supportive care and potential harm to the patient associated with treatment that offers poor response rates. Docetaxel, pemetrexed, and erlotinib are the only drugs currently approved for second-line treatment of recurrent or metastatic lung cancer with response rates rarely reported to be greater than 10%. An optimal second-line treatment would have a mild side effect profile, increase quality of life, and provide improved response compared with traditional agents. Treatments such as the oral tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib are generally well tolerated, but provide similar rates of response as chemotherapy.

Despite promising data from the phase 2 studies Iressa Dose Evaluation in Advanced Lung Cancer 1 and 2 (IDEAL 1; IDEAL 2),[1,2] gefitinib was removed from the US drug market in June 2005 because of a lack in evidence of improved survival versus placebo as second-line therapy for NSCLC. The Iressa Survival Evaluation in Lung Cancer (ISEL) trial showed median survival of 5.6 and 5.1 months, respectively, for gefitinib and placebo.[3] The study did show significant improvement in never-smokers and Asian patients for gefitinib, but no advantage for patients with adenocarcinoma or women. There has been much discussion of the issues that may have affected the trial's outcomes. Specifically, 90% of the patient population was chemotherapy-refractory, and possible underdosing of gefitinib may have altered the outcomes of the trial.

Currently, the availability of gefitinib in the United States is limited. The drug is available through clinical trials and to patients who have and continue to benefit from gefitinib therapy. Recently, US trials have reexamined the use of gefitinib in NSCLC. The Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) investigated the effectiveness of gefitinib in recurrent or metastatic NSCLC versus docetaxel, a standard treatment in the setting.[4]

The INTEREST study compared gefitinib with docetaxel in previously treated NSCLC patients. Primary outcomes were noninferiority of gefitinib on overall survival (OS) for the entire population and superiority of gefitinib in patients with high epidermal growth factor receptor (EGFR)-gene-copy number by fluorescence in situ hybridization. Secondary outcomes included objective response rates and progression-free survival (PFS). All patients were previously treated with platinum-based regimens, with approximately 16% of patients in each arm having had received more than one treatment for metastatic or recurrent disease. At baseline, 53.8% and 56.3% of patients were chemotherapy-refractory to platinum-based chemotherapy, and 9.3% and 7.8% were refractory to paclitaxel-based regimens in the gefitinib and docetaxel arms, respectively.[2] Fifty-seven percent of patients in the gefitinib arm and 59.6% of those in the docetaxel arm were refractory to their most recent chemotherapy. Nearly 55% of all patients had adenocarcinoma, and approximately 60% had a performance status of 1.

Median OS was similar in the two arms (8 months for gefitinib and 7.8 months for docetaxel), and the noninferiority hazard ratio for OS was 1.020 (96% confidence interval [CI]: 0.905-1.150). PFS and response rates were also similar.[2] Superiority in OS was not observed for gefitinib in patients with a high EGFR-gene-copy number or any other subgroup. Patients previously reported to have favorable response rates to EGFR inhibitors, such as those with adenocarcinoma, those of Asian ethnic origin, women, and never-smokers, had comparable outcomes regardless of treatment group. Such patients in both groups also experienced higher survival rates than those with other NSCLC histologies, those of non-Asian ethnic origin, men, and smokers. Patients

those without adenocarcinoma. However, contrary to expectation, patients with these factors had a similarly long survival whether they were treated with gefitinib or docetaxel. Earlier research had suggested that docetaxel chemotherapy provided similar survival benefit in all patients.

Several biomarkers had been reported to help predict which patients are more likely to respond to EGFR inhibitor treatment. The INTEREST study found, for the most part, no link between treatment outcome and biomarkers.

It is important to note that the study differed in several respects from the ISEL study, which found no significant improvement in overall survival in gefitinib-treated patients with advanced NSCLC compared with placebo-treated patients. The ISEL trial enrolled a large number of patients who were refractory to chemotherapy. This population is notoriously difficult to treat and has a poor prognosis, which may account for the lack of significant improvement in the gefitinib group.

Clinical implications

The management of advanced NSCLC remains a clinical challenge. However, an oral agent that rivals intravenous chemotherapy in terms of efficacy but has better tolerability and improves quality of life represents an important shift in the treatment paradigm for this disease and also offers patients an attractive treatment alternative.

What we now know:

- Lung cancer is a key cause of cancer deaths worldwide. Standard therapy involves chemotherapy and supportive care, but response rates are suboptimal and disease recurrence is common.
- Docetaxel is widely used for second-line treatment of advanced NSCLC.
- The molecularly-targeted oral agent gefitinib and cytotoxic intravenous chemotherapy with docetaxel are equally effective in advanced NSCLC. The two treatments provide similar overall survival, tumor response, and progression-free survival.
- Gefitinib decreases toxicity compared with docetaxel.
- Gefitinib improves quality of life more than docetaxel. In fact, it is the first agent that has been shown to improve quality of life more than a chemotherapy agent.

Jill Stein contributed to the preparation of this manuscript.

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with other NSCLC histologies, those of non-Asian ethnic origin, men, and smokers had similar survival rates with gefitinib and docetaxel treatment.[2] These findings indicate that gefitinib is not inferior to US Food and Drug Adminstration–approved second-line treatments for NSCLC docetaxel in response rate, OS, or PFS.

Although the findings from the INTEREST study raise questions about the ability to predict response to EGFR inhibitors, they offer evidence that gefitinib is a viable option for second-line treatment of metastatic/recurrent NSCLC. If reapproved, gefitinib will join the approved second-line options of docetaxel, pemetrexed, and erlotinib as well as unapproved alternatives of gemcitabine and vinorelbine. Choice of available second-line therapies is primarily dictated by a patient's previous exposure to chemotherapy, comorbidities, hepatic and renal function, and performance status. Dosing convenience, potential drug interactions, and toxicities should also be considered. Gefitinib may be offered to patients with poor performance status, renal dysfunction, and mild hepatic dysfunction or moderate-to-severe hepatic dysfunction due to liver metastases. Concomitant medications should be reviewed, however, to avoid drug interactions resulting in toxicities.

Oral TKIs such as gefitinib and erlotinib also present new challenges in toxicity management. Early intervention and management are instrumental to improving tolerability of the EGFR inhibitors gefitinib, erlotinib, and cetuximab. Most notably, dermatologic toxicity may affect a patient's tolerance of therapy. Forty-three percent to 86% of patients experience dermatologic toxicities with EGFR inhibitors, and up to 16% may have grade 3 rash. In addition to appropriate dosing reductions, familiarity with treatment algorithms for management of dry skin and acnelike and maculopapular rash are necessary to assist oncologists in managing these toxicities.[5,6]

Early intervention and management are instrumental to improving tolerability of the EGFR inhibitors gefitinib, erlotinib, and cetuximab.

Little experimental evidence exists to support dermatologic toxicity management. A study by Scope and colleagues aimed to determine whether minocycline or tazarotene could reduce and prevent cetuximab-induced acnelike rash in patients with metastatic colorectal cancer.[7] Forty-eight patients were randomized to receive either placebo or minocycline in addition to either topical tazarotene or placebo applied to one side of the face for a total of 8 weeks starting on day 1 of cetuximab therapy. Fewer patients receiving minocyclines reported moderate-to-severe itching or rash. A significant difference in the number of facial lesions was observed, with a maximal effect near week 4 and a decline in effect by week 8. Although four patients receiving placebo required dose interruptions in cetuximab due to grade 3 rash, no patients receiving minocycline required interruptions. Tazarotene treatment had no benefit and caused significant skin irritation. Nearly 33% of patients discontinued tazarotene therapy because of irritation. These data suggest benefit with approximately 1 month of prophylactic minocycline treatment and no advantage to use of tazarotene in management of EGFR-related rash.

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COMMENTARY

Oral Biologic Therapy versus Chemotherapy for Pretreated Non–small-cell Lung Cancer: A Nurse's Perspective

BY KAREN OISHI, RN, MSN, GNP, ANP, OCN
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Lung cancer is the cause of approximately one third of all cancer-related deaths and is the number one cause of cancer deaths in the United States and worldwide.[1,2] Traditionally, it has been a difficult disease to manage and treat, because lung cancer is usually diagnosed at an advanced stage and because we have a limited number of effective drugs. The oncology community constantly strives to better understand the biology of the disease and to develop better drugs. Several phase 3 trials indicate that current doublet chemotherapy regimens yield equivalent efficacies and similar toxicity profiles,[3] and new-generation molecularly targeted therapies are emerging.

Gefitinib, the first epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor to reach the market, targets the specific physiologic pathway of tumor survival and proliferation. Later-introduced EGFR inhibitors approved for treatment of non–small-cell lung cancer (NSCLC) after at least one prior chemotherapy regimen include erlotinib, docetaxel, and pemetrexed. Since the negative results of the Iressa Survival Evaluation in Lung Cancer (ISEL) trial were reported in 2005,[4] gefitinib has been slowly fading away from the domain of NSCLC treatment options.

The surprising results of the Iressa in NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) reported late last year has caused the oncology community to rethink the options for lung cancer therapy. This trial showed the statistical noninferiority of gefitinib compared with the previously approved second-line agent docetaxel.[5] In light of these findings, the role of gefitinib is now being reassessed, and we are all asking what the study outcomes will mean in clinical management of patients with NSCLC.

The INTEREST study examined quality-of-life (QOL) measures, as well as the safety and tolerability of gefitinib and docetaxel.[5] QOL is often overlooked in clinical trials, because the primary end point tends to evaluate the survival advantages exclusively. In NSCLC, achieving QOL is a very important goal, because most lung cancer patients experience many symptoms related to their disease. Trial participants who received gefitinib and docetaxel showed improvements in their lung cancer symptoms, but significantly more patients had sustained and clinically relevant improvement in QOL with gefitinib.[5]

The results of the INTEREST study have raised more questions than answers for the lung cancer community. Will gefitinib be US Food and Drug Administration–approved and available as a second-line therapy? Will the positive INTEREST data have any influence on our selection of specific agents for treatment? Do second-line chemotherapy agents, such as docetaxel or pemetrexed, show efficacy equivalent to that of molecularly targeted agents, such as erlotinib and gefitinib? Is there a need for a head-to-head trial comparing erlotinib with gefitinib? How do we sequence second-line therapies to best benefit patients? Is there a need for molecular marker testing in patients receiving chemotherapy agents as well as targeted agents? Answers to these and other questions, will, I believe, lead in the next 5 or 10 years to more sophisticated and less controversial treatment algorithms for the NSCLC community.

As oncology nurses, we have the responsibility to inform and educate the public as well as patients and their families about significant new findings that may potentially provide new options for lung cancer treatment. This enables patients to choose more suitable options from those that are available to them. If it gets the necessary approval, gefitinib will be among the options available to treat lung cancer, and we must be prepared for the possibility of a need to educate the oncology community about its use and potential side effects. Oncology nurses not only educate patients about available therapy options, but also help them decide which side effects they are willing to tolerate, for example, dermatologic (rash with EGFR inhibitors) versus gastrointestinal (nausea/vomiting with chemotherapies) toxicities. The INTEREST study shows the need for further study of QOL measures. Oncology nurses should be encouraged to pursue research on these measures, as we are advocates for our patients.

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Statement of Need
The purpose of this activity is to enhance knowledge concerning the treatment of patients with multiple myeloma (MM).

Target Audience
This activity was developed for physicians, nurses, and pharmacists.

Learning Objectives
At the completion of this educational activity, participants should be able to:
- Define the role of posttransplant maintenance therapy in the treatment of patients with multiple myeloma (MM)
- Describe how novel agents for MM can be used to sustain response and possibly delay relapse in patients with MM
- Interpret new data from clinical trials of maintenance regimens for MM as reported at the 2008 ASH annual meeting
- Identify the risks and benefits associated with novel agents used in the maintenance setting, including increased toxicity and acquired drug resistance

Physician Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Global Education Group (Global) and Medical Learning Institute, Inc. (MLI). Global is accredited by the ACCME to provide continuing medical education for physicians.

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Date of original release: May 11, 2009
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Practice Guidelines

Colon and Rectal Cancers Guidelines

HOLLYWOOD, FL—New Kirsten rat sarcoma (*KRAS*) testing recommendations, survivorship protocols, and resectability criteria are the main highlights from the latest colon and rectal cancers guideline updates from the National Comprehensive Cancer Network (NCCN), as reported at the 14th Annual NCCN Conference: Clinical Practice Guidelines & Quality Cancer Care.

The guidelines were presented by Paul F. Engstrom, MD, Fox Chase Cancer Center, Philadelphia, Pennsylvania, and head of the NCCN committee for colon, rectal, and anal cancer guidelines.

"I think the *KRAS* story is probably the number one story of the guidelines," Engstrom said during an interview. "I think the second one is the addition of the survivorship guidelines to our panel. I think other than lung cancer, really we're the only cancer right now to have a full inclusion in the guidelines of survivorship. And then I think third is judging who's resectable for liver metastasis."

Several studies published in 2008 demonstrated that the status of the tumor *KRAS* gene is highly predictive of outcome with anti–epidermal growth factor receptor agents, such as cetuximab and panitumumab. However, these agents have been found to be effective only in colorectal cancer patients with tumors that express the normal (or wild-type) *KRAS* gene and not with tumors that express *KRAS* gene mutations.

So the colon and rectal cancers guideline updates include the recommendation that *KRAS* testing should be done for all patients diagnosed with metastatic colorectal cancer before finalizing their treatment plan, with these agents used only for those who have tumors with wild-type *KRAS* genes.

Said Engstrom, "I think the finding [from those studies] was an eye-opener to oncologists because we didn't know why some patients didn't respond before. Just like we have a lot of other agents that we don't know why patients don't respond to, such as irinotecan. Some of our patients do [respond] and some don't. And now we're starting to tease this apart with these molecular tests. I think this is an important new direction in the management of colorectal cancer."

The guidelines' new section on survivorship outlines principles for long-term follow-up care for patients in remission. In addition to monitoring these patients for disease-specific recurrence, the new guidelines stress the need for screening and monitoring for other cancers. Specifically, the guidelines state that special attention should be paid to prevention of breast and cervical cancers among women survivors, while surveillance for prostate cancer should be stressed to male cancer survivors.

In addition, the survivorship section describes healthy lifestyle recommendations (especially exercise), the management of long-term treatment side effects, wellness counseling, and transferring care to a primary care physician.

"There are many survivors in the group of colorectal patients, and they're a little bit neglected," said Engstrom. "Some of them have had colonoscopies. Many of them have had radiotherapy along with chemotherapy. I have patients that are out 20, 25, 30 years from their treatment of [colorectal] cancer and they still have some sequelae that they are living with. And nobody's ever really talked to them about that. So I think these survivorship guidelines are important. The breast cancer patients are usually the model that we go by, but I think there are as many survivors in colorectal cancer as there are in breast cancer."

The guideline updates also include a recommendation for the reevaluation of patients with initially unresectable metastatic colorectal disease to determine whether they would be suitable for resection following chemotherapy. Specifically, the guidelines now include the words "potentially convertible" or "unconvertible," which have been added to the definition of unresectable disease.

An up-front multidisciplinary team evaluation is now recommended, including a surgeon with resection expertise. "Before, we defined 'resectable' by what comes out, asking how many metastases are there and how large?" said Engstrom during his presentation. "Now we're defining it by what stays in, such as preserving liver segments."

In addition, the guideline updates provide new data on using cetuximab in treatment of patients with metastatic colorectal cancer, including in combination with specific chemotherapy drugs as an initial therapy option.

—Deborah Brauser

Breast Cancer Guidelines

In the annual update of its breast cancer guidelines, the National Comprehensive Cancer Network (NCCN) encourages oncologists and their staff to offer genetic counseling for patients with ductal carcinoma in situ (DCIS) and a strong family history to consider eliminating the "boost" after radiotherapy in older patients with early invasive breast cancer. The breast cancer panel lists surgical excision as an option for locally advanced or recurrent stage IV disease, and advocates skin-sparing mastectomy, when possible, for breast reconstruction.

The updates were presented at the NCCN Annual Conference by Beryl McCormick, MD, of Memorial Sloan-Kettering Cancer Center, New York, and Stephen B. Edge, MD, of Roswell Park Cancer Institute, Buffalo, New York.

DCIS and early breast cancer

Family history suggestive of hereditary breast cancer is a reason to offer genetic counseling to patients with DCIS or early invasive breast cancer, the NCCN panel decided. Data suggest that women at high risk are increasingly opting for prophylactic mastectomy. A Surveillance, Epidemiology and End Results (SEER) analysis of DCIS patients found the rate of bilateral mastectomy to be 6% in 1998 but 18% in 2005 (Tuttle TM, et al. *J Clin Oncol.* 2009; 1362-1367).

Patients with DCIS should also undergo mammography after excision, when there is uncertainty about the adequacy of excision, the panel said.

Radiotherapy recommendations

Reflecting trends in whole breast irradiation, the panel included a recommendation for computed tomography (CT)-based treatment planning, and gave the option for radiotherapy doses of 45 Gy to 50 Gy in 1.8 Gy to 2 Gy per fraction or a hypofractionated dose of 42.5 Gy at 2.66 Gy per fraction (ie, lower dose over a shorter period).

Trials have suggested that faster courses of radiotherapy will decrease the time to treatment initiation, reduce the cost of healthcare, and increase the proportion of women who complete radiotherapy after breast-conserving surgery. "We offer hypofractionation to our patients, and 60% opt for it," McCormick said.

Radiotherapy should be considered after mastectomy in patients with one to three positive nodes, as this has been shown to reduce local recurrence and increase survival, the panel added.

The updated guidelines also contain an option for radiotherapy without additional radiation (boost) in early invasive breast cancer (stage I, IIA, or IIB or T3N1M0). The previous recommendation was for radiotherapy to the whole breast with boost. A European Organisation for Research and Treatment of Cancer (EORTC) study of 5318 stage I and II patients found significant advantages to the boost except in patients aged 60 years and older (Bartelink H, et al. *N Engl J Med.* 2001; 345:1378-1387).

"Based on this study, the panel believed the boost had little biological value in older patients and should be optional for older patients with negative margins," she said, adding that she often does include the boost for patients over 60 who have positive margins.

Local therapy for stage IV disease

Another addition to the guidelines is the option for surgical resection and radiation therapy to the chest wall and internal mammary nodes for patients with stage IV or recurrent disease who were initially treated with mastectomy without radiation therapy.

This is supported by a database from EORTC 10801 and Danish Breast Cancer Cooperative Group 82TM of salvage treatment for local recurrence, which compared breast-conserving therapy (n = 66) to mastectomy (n = 67) in stage I and II patients (with the majority also receiving radiotherapy). Out to 10 years, no difference in survival has emerged, with approximately 50% of both groups still alive, McCormick noted.

The panel also concluded that women who are diagnosed initially with metastatic disease may benefit from local breast surgery with or without radiation therapy. Generally, this palliative local therapy should be considered only after a response to initial systemic therapy, Edge said.

Studies have suggested that excision of a primary tumor (with negative margins) can impact survival in stage IV patients. For example, in a recent study, surgery reduced the risk of death by 51% (Bafford AC, et al. *Breast Cancer Res Treat.* 2009;115:7-12).

"Some 3% to 5% of women present with metastases at diagnosis, and their 5-year survival is 5% to 15%," he noted. "Local therapy has historically been reserved for palliation in those with local progression of tumor, but for many patients, metastases are discovered only after surgery, on postoperative imaging."

Increased survival after radiation as local therapy in stage IV disease was also recently documented in a series in which overall survival at 3 years was 43% with treatment, versus 27% in the untreated arm (Le Scodan R, et al. *J Clin Oncol.* 2009;27:1375-1381).

Imaging issues addressed

The panelists did not advocate the use of positron-emission tomography/

Continued on page 40

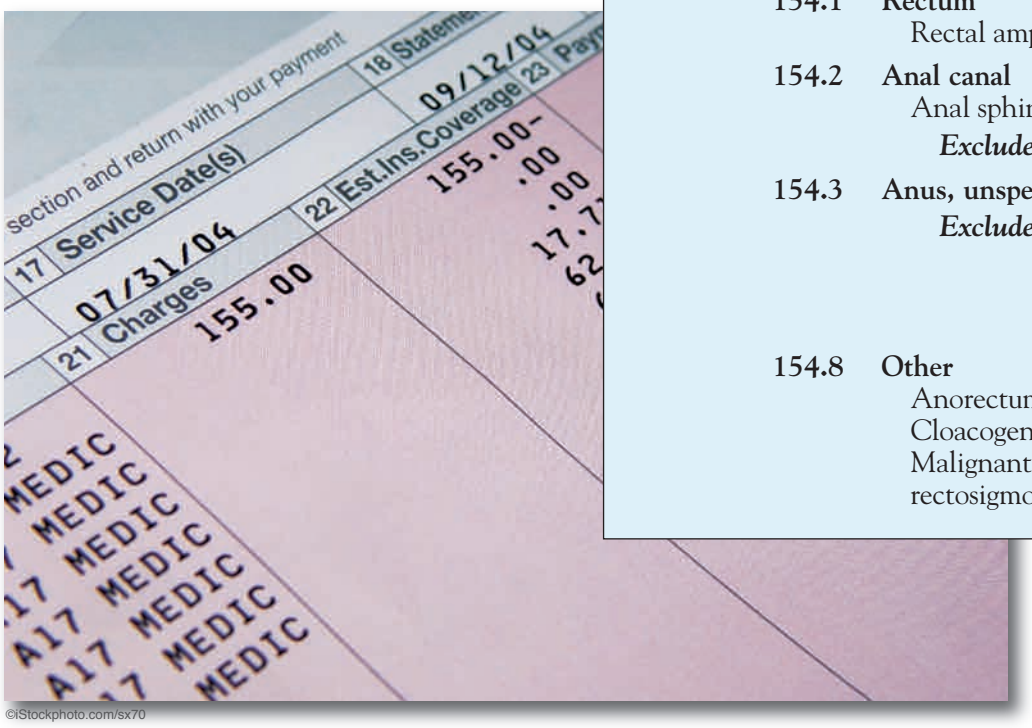
Oncology Drug Codes

Medications Used for the Treatment of Colorectal Cancer

Colorectal cancer is a term used to refer to cancer that starts in either the colon or the rectum. Colon cancer and rectal cancer have many features in common. The following sections will assist healthcare professionals and payers by providing appropriate coding, billing, and reimbursement information associated with the management of colorectal cancer.

The following sections include:

- Associated *ICD-9-CM* codes used for the classification of colorectal cancer
- Drugs that have been FDA-approved in the treatment of colorectal 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 colorectal cancer. 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.



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Associated *ICD-9-CM* Codes Used for Colorectal Cancer

153 Malignant neoplasm of colon
Excludes: *benign carcinoid tumor of colon (209.50-209.56)*
malignant carcinoid tumor of colon (209.10-209.16)

153.0 Hepatic flexure

153.1 Transverse colon

153.2 Descending colon
Left colon

153.3 Sigmoid colon
Sigmoid (flexure)
Excludes: *rectosigmoid junction (154.0)*

153.4 Cecum
Ileocecal valve

153.5 Appendix

153.6 Ascending colon
Right colon

153.7 Splenic flexure

153.8 Other specified sites of large intestine
Malignant neoplasm of contiguous or overlapping sites of colon whose point of origin cannot be determined
Excludes: *ileocecal valve (153.4)*
rectosigmoid junction (154.0)

153.9 Colon, unspecified
Large intestine NOS

154 Malignant neoplasm of rectum, rectosigmoid junction, and anus
Excludes: *benign carcinoid tumor of rectum (209.57)*
malignant carcinoid tumor of rectum (209.17)

154.0 Rectosigmoid junction
Colon with rectum
Rectosigmoid (colon)

154.1 Rectum
Rectal ampulla

154.2 Anal canal
Anal sphincter
Excludes: *skin of anus (172.5, 173.5)*

154.3 Anus, unspecified
Excludes: *anus:*
margin (172.5, 173.5)
skin (172.5, 173.5)
perianal skin (172.5, 173.5)

154.8 Other
Anorectum
Cloacogenic zone
Malignant neoplasm of contiguous or overlapping sites of rectum, rectosigmoid junction, and anus whose point of origin cannot be determined

Generic (brand) name	HCPCS code: code description	FDA-approved for colorectal cancer	*NCCN Drugs & Biologics Compendium* off-label use for colorectal cancer	Current code price (AWP-based pricing)	Medicare allowable (ASP + 6%), effective 4/1/09-6/30/09	CPT administration codes
bevacizumab (Avastin)	J9035: injection bevacizumab, 10 mg	✓		$68.75	$57.40	96413, 96415
capecitabine (Xeloda)	J8520: capecitabine, oral, 150 mg	✓		$7.35	$5.28	N/A
capecitabine (Xeloda)	J8521: capecitabine, oral, 500 mg	✓		$24.50	$17.51	N/A
cetuximab (Erbitux)	J9055: injection, cetuximab, 10 mg	✓		$60.00	$49.73	96413, 96415
floxuridine (FUDR)	J9200: injection, floxuridine, 500 mg		✓	$121.50	$58.08	96422, 96423, 96425
fluorouracil (Adrucil)	J9190: injection, fluorouracil, 500 mg	✓		$3.44	$1.55	96409
irinotecan (Camptosar)	J9206: injection, irinotecan, 20 mg	✓		$32.82	$18.30	96413, 96415
leucovorin calcium	J0640: injection, leucovorin calcium, per 50 mg	✓		$3.75	$0.87	96372, 96374, 96409
oxaliplatin (Eloxatin)	J9263: injection, oxaliplatin, 0.5 mg	✓		$12.26	$9.54	96413, 96415
panitumumab (Vectibix)	J9303: injection, panitumumab, 10 mg	✓		$106.09	$84.29	96413, 96415

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 2; RJ Health Systems International LLC; 2nd Quarter 2009 • FDA-approved indication (from products' prescribing information) • NCCN • American Cancer Society • www.ReimbursementCodes.com powered by RJ Health Systems International, LLC., Wethersfield, Connecticut • CMS-Medicare allowable 2nd Quarter 2009 (effective dates 4/1/09-6/30/09).

Prices listed herein are effective as of May 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.

Safe Handling

National Safe Handling Month Calls Attention to Need for Increased Awareness, Education about Occupational Drug Exposure

April 2009 was designated the first-ever National Safe Handling Awareness Month in an effort to increase awareness of the risks of occupational exposure to chemotherapeutic agents and other hazardous drugs and educate healthcare providers on guidelines and safety measures that can minimize the risks. The initiative, supported by an unrestricted educational grant provided by Carmel Pharma, Inc., the maker of PhaSeal, included regional and national continuing education activities. *The Oncology Pharmacist* recently spoke with Byron Peters, RPh, and MiKaela Olsen, RN, MS, OCN, about ways to ensure safe handling of hazardous drugs in the clinical setting. Mr Peters is director of pharmacy, Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri. Ms Olsen is an oncology and hematology clinical nurse specialist at Johns Hopkins Hospital, Baltimore, Maryland.

The National Institute for Occupational Safety and Health, the Oncology Nursing Society, the American Society of Health-System Pharmacists, and other organizations have issued guidelines on safe handling. Why is this campaign to increase awareness needed?

Byron Peters (BP): Many people think that measures such as use of biological safety cabinets and personal protective equipment are enough. But when we conducted an environmental wipe sample study some years ago, it was striking to see that despite doing everything we thought we were supposed to be doing, there was still surface contamination in a relatively new work environment (Harrison BR, et al. *Am J Health-Syst Pharm*. 2006;63:1763-1744). More and more studies are showing contamination in all areas of the workplace.


Byron Peters, RPh

MiKaela Olsen (MO): Workplace health is becoming more of a concern in general across the country, and hazardous drugs are a part of that. Hazardous drugs are being increasingly used for nonmalignant diseases, and nononcology providers may not be aware of the hazards of these drugs. Another concern is the increasing use of potentially hazardous oral drugs that may carry risks similar to intravenously administered agents.


MiKaela Olsen, RN, MS,OCN

We need to recognize and take hold of this problem and ensure safe handling. Unfortunately, not everyone uses the recommended personal protective equipment when handling these agents. There's a huge knowledge deficit, and maybe peer pressure issues too. If more experienced staff in the department choose not to use protective equipment, their less experienced colleagues may not realize how important it is to do so or may feel it is not a priority.

How can institutions be sure that employees are following safe handling procedures?

MO: Monitoring of employees to determine whether they are experiencing any symptoms that may be related to hazardous drug exposure is important. Employees may be experiencing nonspecific symptoms, such as headache, nausea, and eye or skin irritation, and may not necessarily associate them with exposure to a particular substance.

BP: We do need heightened awareness because people have been exposed, either knowingly or unknowingly. Fifteen years ago, we did not have some of the environmental controls or engineering devices that we now have to protect us. We are making great strides. We have containment isolators, better biological safety cabinets, and we know how frequently we have to inspect them. We also use a closed-system transfer device (CSTD) that has been clinically proven to reduce the risk of drug exposure (the PhaSeal System). Studies have shown that when two levels of protection were implemented, subjects' urine became negative for drug traces (Wick C, et al. *Am J Health-Syst Pharm*. 2003;60:2314-2320). We don't know if we have the perfect solution, but at least based on what we know now, there are some additional steps that people can take to ensure safety. The problem is that not everyone is using all the levels of protection we now have; some are not even at the minimum level.

What are some of the barriers to more widespread use of safe handling measures?

MO: I think that sometimes stems partly from the leadership of the facility. We have to educate our leadership about the hazards of these drugs and the potential risks to employees. They need to develop policies to protect everyone in the environment from hazardous drugs, and implement those policies. This shows that they are committed to protecting their employees.

Costs should not be a reason for not implementing safeguards. Providing a safe work environment is the cost of doing business.

BP: Unfortunately, I think part of the problem is probably financially motivated. Interventions cost money and may not be reimbursed. Costs, however, should not be a reason for not implementing safeguards. Providing a safe work environment is the cost of doing business and something that you just have to do.

What can nurses and pharmacists do to ensure proper handling of oral chemotherapy agents by patients and healthcare providers?

MO: There is less regulation safety measures for oral versus intravenous chemotherapy. In the Oncology Nursing Society Chemotherapy and Biotherapy course, we cover handling of oral chemotherapy drugs in the home and we discuss that in our teaching to nurses. Many institutions have patient education materials that they provide to the family about how to handle these drugs and to dispose of body excretions at home.

BP: When we as pharmacists dispense drugs to patients, part of the process involves counseling. We share information about safe handling, such as not breaking tablets in half, and how to dispose of the drugs. Interestingly, there are no regulations about packaging of hazardous drugs when dispensing. Oral chemotherapy agents are packaged the same way as drugs like amoxicillin.

What practical steps can hospitals and other institutions take to ensure adherence to safe handling guidelines?

MO: It is the employee's right to be informed about the risks, and they need to receive annual training about how to protect themselves. Women who are trying to conceive are pregnant or breast feeding and men who are trying to conceive need to be informed about the risks and should be offered alternate duty if requested.

BP: Frequently we talk about specially trained and experienced nurses and pharmacists, but there are also other levels of people who come in contact with hazardous drugs, such as technicians, students, housekeeping staff, and those who ship and receive drugs. These individuals need to be trained on safe handling as well. Studies have shown that vials can come from the manufacturer with hazardous drugs on the outside of the container even when they are properly sealed.

MO: When these drugs are given, we may be unknowingly exposing staff, visitors, and caregivers. We have to think about the whole continuum and protect everyone in the environment. We have to look at this problem from the time the drug is delivered all the way to its proper disposal.

BP: The work surface contamination study we conducted got management's attention. We've implemented a CSTD, the PhaSeal product. People realize that this is an added cost, but they understand that we are willing to do what is needed to do to protect our staff, our patients, and our visitors and to protect the environment. We try to take a leading role in our community showing that we understand the problem and will do whatever it takes to provide the utmost safety. The leadership has to make safe handling a priority. If you start at the top, it sends a good message to heighten awareness about the hazards of handling these drugs. You need to continue to reinforce policies with training programs, annual recertification, annual assessment of technique and competency, and in-service training.

For additional information on the safe handling of hazardous drugs and to hear more from Byron Peters and MiKaela Olsen, please view the archived Safe Handling Awareness Day CE webinar at www.carmelpharmausa.com/CE. Free CE credit for this archived webinar presentation is available for pharmacists, pharmacy technicians, nurses, and risk managers.

New ACCC President

Continued from cover

oncology team. What I think is particularly useful about ACCC is that the membership pretty much makes up the team of people most of us work with every day. None of us work with all physicians, pharmacists, or nurses. We are all part of a multidisciplinary team, and ACCC membership reflects that.

Why is it important for nurses to become involved in professional organizations other than their own?

All of us associated with ACCC also belong to our own professional organizations. That's where we get a lot of our scientific needs met and some networking needs as well. But the ACCC membership mirrors the cancer care team that we work with every day, and it is very helpful to have an organization that represents all of us.

We have a shortage of nurses, pharmacists, and physicians, and we need to think about ways to succeed in the future.

What are your goals as ACCC president?

Each president gets to choose a focus for the year. My goal is to shine a light on issues of the oncology workforce. We have a shortage of nurses, pharmacists, and physicians, and we need to think about ways to succeed in the future. I am very concerned because it is estimated that between now and 2020, we will have a 55% increase in the number of cancer patients in the United Sates but just a 14% increase in the number of medical oncologists. The estimate now is that there will be 285,000 nursing vacancies nationally by 2020.

What are your thoughts about how to ensure that we have an oncology workforce adequate to deal with the growing number of patients?

The goals of the ACCC are twofold: (1) education of ourselves and our cancer team community, and (2) advocacy. First, in terms of education, in the next two ACCC meetings, we will spend considerable time on topics related to the oncology workforce. We have to educate ourselves on the looming crisis and begin to look at models that will help us avoid this. One thing to consider is the role of the nurse practitioner and how we can go about preparing more nurse practitioners to take on roles of midlevels in oncology practice. Another step is to work with other groups that already fund education for nurses, pharmacists, and physicians and encourage them to continue and even increase that funding. In our advocacy role, there is quite a lot we can do in terms of working with state and federal legislators on new legislation that would increase funding for education of nurses, pharmacists, and physicians, particularly in oncology and particularly in midlevel roles.

One positive thing to come of the current economic situation is that it seems that more people are going into the healthcare professions. Healthcare is still a strong employer and a good business to go into. Many more men are now in nursing school. Almost all are men who have had other careers. It's wonderful to see the combination of intelligence and emotional intelligence they bring to their work.

What factors are most important in attracting new providers into the oncology field?

I think that most people who are choosing healthcare overall and nursing specifically are doing it because they see a stable work life ahead of them and because they want to do something that is meaningful. Those of us in oncology have not been articulate enough in explaining to younger and middle-aged students just how meaningful a role in oncology can be. It is one of the few specialties in which you sometimes have the same patients for years now that cancer is becoming a chronic disease. I am always pleased to see that patient satisfaction scores are generally higher in oncology areas than in other areas of the hospital, even in the maternity department. That is true for employee satisfaction scores as well. I think it is because we see our patients long enough to develop relationships with them. We feel a sense of family with our patients, and I think they feel that with us. Young healthcare practitioners who are looking for meaningful work can do no better than go into oncology.

What are some of the other challenges that community oncology practices are facing?

Certainly declining Medicare reimbursement for our services is a challenge. The economy is having an interesting impact in another way as well. The number of new patients is declining. There may be as much as a 10% decline in new patients, and this has been sustained for at least 6 months. That is concerning because we know the incidence of cancer is not going down. It seems to me that people without insurance or with big gaps in their insurance are choosing not to heed the warning signals that they are getting. The lack of insurance and the perception that cancer is a very expensive disease to treat must be having an impact. We are going to see these patients eventually, but when we do, they will be much further along in their disease.

What are your thoughts on how the healthcare system reforms proposed by the Obama administration may affect community cancer care?

Healthcare reform could increase the number of insured patients, which should result in more people with cancer symptoms being able to seek care. Second, there is a great emphasis on higher education, and nurse practitioners and others in the healthcare professions could be assisted by that. The Kennedy-Hutchinson bill, which is a comprehensive cancer bill that we hope to see introduced very soon, is reported to include provisions that would increase funding for cancer survivorship programs and patient navigator assistance, which would be very beneficial.

—Karen Rosenberg

PRACTICE GUIDELINES

Breast Cancer Guidelines

Continued from page 36

CT scanning in the evaluation of newly diagnosed patients with early-stage disease, except in those clinical situations where other staging studies are equivocal or suspicious. Even then, biopsy is recommended, as always for accurate staging.

They further maintained that the value of magnetic resonance imaging (MRI) remains unclear, but they revised the guidelines to address the utility of dedicated breast MRI. The panel noted that MRI has a role in screening women at high risk, detecting disease in dense breasts, evaluating extent of disease, defining response to neoadjuvant therapy, and evaluating cases of axillary nodal adenocarcinoma but normal mammography.

Edge advised physicians, however, not to make surgical decisions on the basis of MRI findings, due to the high rate of false positives. Instead, biopsy and tissue sampling should help guide treatment decisions. He noted that MRI outperforms mammography in detecting second cancers. In one study, MRI found contralateral tumors in 3% of breast cancer patients (Lehman CD, et al. *N Engl J Med.* 2007;356:1295-1303). MRI also helps select patients for breast-conserving therapy after neoadjuvant therapy by evaluating response to treatment and defining the extent of cancer; however, it also underestimates the amount of residual disease.

The use of MRI does lead to a change in therapy for some patients, Edge noted. In a meta-analysis of all retrospective literature on the topic, Houssami and colleagues showed that 11% of patients underwent more extensive surgery than originally planned, and 8% converted from lumpectomy to mastectomy (*J Clin Oncol.* 2008;26:3248-3258). It is still unclear whether the rate of mastectomies is increasing in parallel with increased use of MRI, however. In an NCCN database, rates have been stable despite rising MRI use, according to Edge.

Evidence is also lacking to show that MRI actually affects outcomes, he noted. Although MRI does pick up lesions not seen on mammography, 80% are determined to be benign. "We may identify more lesions on MRI, but they may not be clinically significant or they may be controlled by the radiation we give," he commented.

The NCCN's bottom line on MRI is that its value remains uncertain, the practice of obtaining MRI varies (and should meet standards for performance), and the downsides are real.

New reconstruction guidelines

New guidelines have been added for postsurgical reconstruction using breast implants, autologous tissue (flaps), or a combination of the two (eg, latissimus/implant composite reconstruction). The options are to perform reconstruction in conjunction with mastectomy (immediate) or after the completion of cancer treatment (delayed). The preference for one over the other is based on factors such as the need for radiotherapy (delayed) and use of implants (immediate), McCormick noted. "Women who need radiotherapy should be identified at diagnosis, and reconstruction in those cases should be delayed," she said.

AUA Recommendations

Continued from page 30

cuss in detail with their physician to determine whether active treatment is necessary, or whether surveillance may be an option for their prostate cancer.

"Prostate cancer comes in many forms, some aggressive and some not," said Carroll, who is professor and chair of urology at the University of California, San Francisco. "The AUA is committed to timely, expert, and appropriate care for men either with or at risk of getting prostate cancer and is prepared to revise these guidelines continuously as new information becomes available."

Key points

The Best Practice Statement by the AUA also clarifies a number of key points about the use of PSA in treatment selection and posttreatment follow-up of prostate cancer patients:

- Serum PSA predicts the response of prostate cancer to local therapy.
- Routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA level is ≤20.0 ng/mL.
- Computed tomography or magnetic resonance imaging scans may be considered for the staging of men with high-risk clinically localized prostate cancer when the PSA is >20.0 ng/mL or when locally advanced or when the Gleason score is ≥8.
- Pelvic lymph node dissection for clinically localized prostate cancer may not be necessary if the PSA level is <10.0 ng/mL and the Gleason score is ≤6.
- Periodic PSA determinations should be offered to detect disease recurrence.
- Serum PSA should decrease and remain at undetectable levels after radical prostatectomy.
- Serum PSA should fall to a low level following radiation therapy, high-intensity focused ultrasound, and cryotherapy and should not rise on successive occasions.
- PSA nadir after androgen-suppression therapy predicts mortality.
- Bone scans are indicated for the detection of metastases following initial treatment for localized disease, but the PSA level that should prompt a bone scan is uncertain. Additional important prognostic information can be obtained by evaluation of PSA kinetics (velocity).
- The kinetics of PSA rise after local therapy for prostate cancer can help distinguish between local and distant recurrence.

"What is also important in this document is that we clearly acknowledge the risks of overdetection and overtreatment. I think that brings us in line with other groups," Carroll said in an interview with *The Oncology Nurse*. "We are no longer recommending a single PSA cut point but to use PSA in conjunction with age, digital rectal examination, ethnicity, family history, and other PSA parameters. This is a more sensitive and specific way of diagnosing prostate cancer."

William Catalona, MD, who is a professor of urology at Northwestern University, Chicago, said dropping the age for a baseline PSA to age 40 may be an important new approach because it can better guide clinicians by potentially providing significantly more information.

"I think it is important. Not so much for diagnosing prostate cancer at age 40, but for establishing a baseline so that you can get data for PSA velocity. So, if you start at age 40, the PSA should be less than 1.0 ng/mL. After that, you can track it," said Catalona in an interview with *The Oncology Nurse*. "I think early PSA velocity is a promising new marker for identifying men destined to die of prostate cancer. It can help detect cancer earlier than we can now detect it using any other method. Perhaps we can now treat them and save their lives. This adds to our ability to identify the worse cancers early."

—*John Schieszer*

PSA velocity is a promising new marker for identifying men destined to die of prostate cancer.

Conference News

Grapefruit Juice May Significantly Increase Bioavailability of Rapamycin

DENVER—Adding a daily 8-ounce glass of grapefruit juice to the weekly oral delivery of rapamycin may greatly improve the drug's bioavailability, allowing for lower doses of the agent. In addition, this combination therapy may be beneficial for patients with advanced solid tumors, providing clinical benefits with fewer drug toxicities, according to new data presented at the 2009 American Association for Cancer Research (AACR) 100th Annual Meeting.

For two decades, pharmacists have pasted "Do Not Take with Grapefruit Juice" stickers on various pills' bottles, because grapefruit juice can interfere with the enzymes that break down and eliminate certain medications. This interference makes the drugs more potent. Now, researchers have discovered a way to exploit this fruit's medication-altering properties to combat cancer.

"Grapefruit juice can increase blood levels of certain drugs three to five times," said lead study investigator Ezra Cohen, MD, a cancer specialist at the University of Chicago Medical Center, Chicago, Illinois. "This has always been considered a hazard. We wanted to see if, and how much, it could amplify the availability, and perhaps the efficacy of rapamycin, a drug with promise for cancer treatment."

Previous studies have shown that mammalian target of rapamycin (mTOR) inhibitors have activity in several cancers. However, rapamycin has low oral bioavailability. In previous studies, it was found that grapefruit and grapefruit juice contain furanocoumarins, which can increase bioavailability of many drugs that undergo P450 metabolism.

Cohen and colleagues conducted a study of 28 patients (15 men and 13 women). The patients all had advanced solid tumors (14 colorectal, three pancreatic, three sarcoma, eight others) and were between the ages of 27 and 77 years. The dose of rapamycin was increased with each group of five patients, from 15 mg to 35 mg. Patients took the drug by mouth as a liquid once a week. Dose-limiting toxicity was observed in two patients at 25 mg (grade 3 hyperglycemia) and 35 mg (grade 3 mucositis).

Beginning in week 2, the subjects washed the medicine down with an 8-ounce glass of grapefruit juice (*Citius paradisi*) taken immediately after the rapamycin and then once a day for the rest of the week. Each subject drank 8 ounces of grapefruit juice 7 days a week, but took the medicine only 1 day a week.

Cohen, who presented the study findings at the meeting, said 25 of the 28 subjects remained in the study long enough to be evaluated. Among those 25 patients, seven (28%) had stable disease, with little or no tumor growth. In addition, one patient (4%) had a partial response, with the tumor shrinking by about 30%. That patient has now received rapamycin with grapefruit juice for more than 1 year and is still doing well more than a year after the beginning of the trial. This patient was diagnosed with epithelioid hemangioendothelioma with hepatic metastases and had previously been treated with sorafenib.

"There has never been a study like this," Cohen said in an interview with *The Oncology Nurse*. "We may now have a viable option for people with these types of vascular tumors that is going to be easier to take. And it is going to be less toxic and will be much cheaper."

He explained this regimen will be less expensive, because lower doses of the drug will be required thanks to the increased bioavailability of rapamycin. The researchers estimate that taking the medication with grapefruit juice could potentially cut the cost of using this drug by up to 50%.

Cohen also pointed out that "Part of the toxicity of rapamycin is diarrhea due to unabsorbed drug, but if we have grapefruit juice that absorbs significantly more of the drug, you don't see the diarrhea."

The most commonly observed toxicities in this phase 1 study were hyperglycemia (75%), diarrhea (68%), lymphopenia (57%), and hyperlipidemia (50%). The great majority of side effects were mild, including diarrhea, which was universally self-limited and not dose-limiting.

Cohen said overall the findings from this study suggest that the addition of grapefruit juice to rapamycin increases its absorbability by up to fourfold. In addition, the drug combined with grapefruit juice appears to be well tolerated without any unexpected toxicities. He and his colleagues concluded that the combination of rapamycin (35 mg) with grapefruit juice is at least comparable with what can be achieved with the mTOR inhibitor temsirolimus (25 mg IV). Dr Cohen said this approach must now be further studied in larger trials with patients who have other tumor types, such as renal cell carcinoma.

"I think it is too soon for prime time. This is a phase 1 study, and we now know the dose. But we have to be careful about the grapefruit juice product that is used. We used a standardized formula that may not be what a person gets in the grocery store. All the grocery store products will not have significant amounts of furanocoumarins. Some will, but not all of them. The active compounds in grapefruit juice can degrade over time," said Cohen.

—John Schieszer

Ginger Root May Help Lower Risk for Colon Cancer

DENVER—Patients at high risk for colorectal cancer may want to start adding more ginger to their diet. A new prospective study suggests that ginger may help combat the development of colon cancer.

So how can a person add more ginger to their diet? Think ginger tea, ginger candies, ginger snaps, and gingerbread cookies. Adding fresh ginger root to stir fry and other cooked dishes may also serve up a bit of cancer protection.

Researchers at the University of Michigan have found that ingesting 2 grams a day of ginger can decrease markers of inflammation in gut mucosa linked to colon cancer. The investigators conducted a prospective study of 33 adults (mean age, 34 years). Half the subjects (n = 17) were given placebo and half (n = 16) were given 2.0 g of ginger for 28 days. A baseline flexible sigmoidoscopy was performed on all the subjects and then again on day 28 to obtain rectal biopsies.

"We found that ginger could decrease the main inflammatory prostaglandin (PG) E_2 [in the gut]. So ginger could decrease PGE_2 in the tissue, and all the other inflammatory markers that might increase did not. You would expect them to increase but they didn't, so that is a good sign. It tends to suggest you could prevent colorectal cancer, as decreasing these inflammatory markers can lead to a decreased risk for developing colorectal cancer," said study investigator Suzanna Zick, MD, an assistant research professor in the Department of Family Medicine at the University of Michigan, Ann Arbor.

She said these findings are clinically significant because colorectal cancer is now the third most prevalent cancer in the United States and caused an estimated 50,000 deaths in 2008 alone. She said any steps that can be taken to help lower a person's risk are important and ingesting ginger appears to be safe. In this

study, ginger was found to have very low toxicity. Zick cautioned, however, that ingesting up to 6 g a day can cause gastrointestinal problems, such as gas and bloating, so it is important to not overindulge in ginger.

Zick, who presented the study findings at the 2009 American Association for Cancer Research (AACR) 100th Annual Meeting, said adding ginger to your diet on a regular basis may help lower overall cancer risk. In vivo studies have suggested ginger may help protect against leukemia, and prostate, ovarian, and lung cancers. Animal studies have also suggested it may be protective against breast, colon, and skin cancers. The current study, however, is the first to look at specific markers in the colon of human subjects following 28 days of daily ginger consumption.

Follow-up studies will now look at individuals who are at high risk for colon cancer to see whether ingestion of ginger on a regular basis may help prevent cancerous polyps.

—John Schieszer

Your Financial Future

BY **SYLVIA MAURIN**

If you have spent some time sharpening your knowledge of finance and investing, yet still feel somewhat ill-equipped to comfortably absorb the daily news regarding the performance of the many stock market indices, this article may help clear things up.

The primer that follows explains in brief a few of the more prominent US financial market indices, and is intended to provide basic insight regarding the messages they send. As with any market, the financial markets bring together willing buyers and sellers of various types of investments, and market indices provide a method of measuring a section of the stock market.

The indices also serve as benchmarks for various index mutual funds. Some examples of index mutual funds and their benchmarks are Vanguard's 500 Index Fund (uses the Standard & Poor's 500 Index [S&P 500] as its benchmark), T. Rowe Price's Total Equity Market Index (benchmarks with Dow Jones Wilshire 5000 Composite Index), and Fidelity's Small Cap Enhanced Index Fund (seeks to replicate the performance of the Russell 2000).

The Dow Jones Industrial Average

The Dow was-created by Charles Dow, nineteenth-century *Wall Street Journal* editor and Dow Jones & Company cofounder. Based on the price of 30 major stocks, it characterized the performance of the industrial sector. The specific stocks in the Dow Jones Industrial Average have been changed over the years to best reflect the changing American economy. Today, the index measures the 30 most broadly held US public companies.

S&P 500 Index

The S&P 500 is one of the most commonly used benchmarks for the overall US stock market. While the Dow was at one time the most well-regarded index of US stocks, most people today agree that the S&P 500 better represents the US market. In fact, many consider it to be the definition of the market. Made up of 500 stocks chosen for market size, liquidity, and industry grouping, it is meant to reflect the risk/return characteristics of the large cap universe. (Market capitalization or market cap is a measure of corporate or economic size equal to the share price times the number of outstanding shares of a public company.)

The Dow Jones Wilshire 5000 Composite Index

This index is market capitalization weighted and represents the market value of all stocks actively traded in the United States. The index is intended to measure the performance of all publicly traded companies based in the United States and having "readily available price data." The index, therefore, includes nearly all common stocks, real estate investment trusts, and limited partnership shares traded primarily on the New York Stock Exchange (NYSE), the National Association of Securities Dealers Automated Quotations (NASDAQ), or the American Stock Exchange.

The NASDAQ

The NASDAQ Stock Market, founded in 1971, was the world's first electronic stock market. The purpose of its founding was to popularize the over-the-counter (OTC) securities market which, up to that point, had been relatively unknown and unused by many involved in stock trading. Initially, the system displayed quotes for more than 2500 OTC stocks but, by 1975, the NASDAQ displayed only NASDAQ-listed stocks. Within 5 years of its development, the NASDAQ began displaying inside quotations, which showed the market best bid and best sell prices on the screen. This move basically kept the market makers honest and published the spreads (margin between the best bid and best sell).

NYSE Composite Index

The NYSE Composite Index tracks the price movements of all common stocks listed on the NYSE. The index is "capitalization-weighted," meaning each stock's weight in the index is proportional to the stock's market capitalization.

Russell 2000 Index

The Russell 2000 is a capitalization-weighted index designed to measure the performance of a market consisting of the 2000 smallest publicly traded US companies.

S&P Midcap 400 Index

Measuring the performance of the midsize company segment of the US market, this index is used by more than 95% of US managers and pension plan sponsors.

Examples of stock market indices used here provide a sampling of the major indices and serve to illuminate how the performance of various sections of the stock market is measured. While this column is focused on the US market, you can take the information provided and use it as a guide to better understand stock indices operating in other countries with developed stock markets.

Sylvia Maurin lives and works in Pittsburgh, Pennsylvania, where she is president of Source One, LLC, a consulting services firm. *Information presented in this column is general in nature. It is not intended to furnish or replace the expert guidance and/or advice of a financial planning professional familiar with your particular financial situation, goals, and objectives.*

"It was a completely successful textbook surgery. Unfortunately we operated on the wrong person."

Leadership and Communications Skills

Pick Your Poison: Fear or Regret

BY **JIM BARNOSKI**

It seems to be human nature to create a thousand and one excuses to avoid doing what you're supposed to. Whether it involves completing a task, asking for help, addressing colleagues or patients when they are doing something incorrectly, or questioning authority, we have a tendency to hold back and avoid uncomfortable situations. The reason lies at the base of most avoidance…fear. Fear of failure, fear of rejection, fear of the unknown, fear of being unpleasant, and the fear of looking foolish, even when dealing with a situation would be in the best interest of all concerned.

For all its rewards, taking action to correct the status quo and make change by dealing with potential conflict can be scary. Every time you speak up, you face more than just fear. You face rejection, push back, or confrontation by others who believe it's their mission in life to avoid change. Sometimes people around you act as though it is their charge to test your mettle and your conviction.

If you give in to your fears, you simply will be trading one negative feeling—fear—for another—regret. You will not only feel bad about yourself for cowering in the face of conflict, but also always wonder what you could have accomplished if you had forced yourself to push through your fear.

When someone else gets credit for resolving a problem that you recognized but failed to take action on, the thought, "I should have said something," will be pounding in your brain. When a colleague is rewarded or promoted for going above and beyond to help a patient that you could have helped but never followed through, you'll want to scream, "Hey that's my idea, I was about to do something," but you won't because you'll know you had your chance and didn't take it.

Regret leaves a bad taste in your mouth—one that lingers for a long time. Fear, on the other hand, evaporates with every positive action. So bite the bullet and take action. Eventually, the fear will dissipate altogether and the regret will never materialize.

Sandler Training (www.PerformanceSelling.sandler.com) is an international sales and management training/consulting firm. For a free paperback edition of Why Salespeople Fail And What To Do About It, *call the Sandler Training Center in New Jersey at 732-764-0200 or e-mail JBarnoski@Sandler.com.*

Jim Barnoski is a trainer with Sandler Training Center.

Calling All Navigators

AONN™ Academy of Oncology Nurse Navigators

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AONN membership is for Oncology Nurses—AND all Oncology Caregivers, including Nurse Navigators, Practice Managers, Patient Care Coordinators, and Nursing Administrators, devoted to the complexities of the cancer care treatment continuum.

Information on patient care and treatment strategies, side effect management, patient outreach, navigation programs, and much more is thoroughly covered in AONN's vast resources.

AONN membership provides you with:

- A subscription to the journal, ***The Oncology Nurse*** **(*TON*)** (a $150 value), and the bimonthly ***Journal of Multidisciplinary Cancer Care***.
- Discounts on all AONN educational programs, including free continuing education supplements, and more than $200 off future Annual Meeting registration for Full Members.
- Discounts on all AONN educational materials.
- Free patient brochures on a range of issues impacting cancer patients (eg, Treatment Guidelines, CINV, Pain Management, DVT, Chemotherapy Toxicities, Skin Reactions, Reimbursement Information, Coding Updates) will soon be available.
- An online web portal with enhanced members-only sections with clinical resources, a special section for educators, and continuing updates on grant opportunities for researchers, in addition to AONN's searchable membership directory.
- Advocacy for initiatives to increase the number of professionals entering the field of oncology; to provide fair and adequate reimbursement for clinical services; and to increase funding for research.

To become an AONN member, visit **www.aonnonline.org**

Join a network of individuals dedicated to enhancing the lives of Cancer Patients. Join AONN.

Meetings

JULY 2009

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8-11 TORONTO, CANADA
International Academy of Oral Oncology 2nd World Congress
www.iaoo2009.com

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9-10
SAN FRANCISCO, CALIFORNIA
NCCN Academy for Excellence and Leadership in Oncology
www.nccn.org

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11-12
BOSTON, MASSACHUSETTS
Understanding New Technologies and Managing Oncology Care Needs
www.cancerlearning.com

AUGUST 2009

21-23 WASHINGTON, DC
8th International Congress on Targeted Therapies in Cancer
www.cancerlearning.com

SEPTEMBER 2009

11-12
ST. LOUIS, MISSOURI
Translational Advances in Radiation Oncology and Cancer Imaging Symposium
www.astro.org

OCTOBER 2009

1-4
CHICAGO, ILLINOIS
Lynn Sage Breast Cancer Symposium
www.lynnsagebreastcancer.org

4-7
SAN DIEGO, CALIFORNIA
29th Annual Oncology Nurses Symposium
www.scripps.org

8-9
DALLAS, TEXAS
2009 Cancer Center Business Summit
www.cancerbusinesssummit.com

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.

To learn more, ask a RITUXAN representative or visit www.rituxan.com/lymphoma

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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