NURSING CAREERS
ONS Lifetime Achievement Award winner reflects on her career

An interview with Marcia Grant, RN, DNSc, FAAN

page 16

PRACTICAL APPLICATIONS
The role of the oncology nurse in optimizing medication adherence

By Raylene Langish, BSN, RN, OCN

between pages 20 and 21

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NURSE NAVIGATORS

Nurse Navigators Play Increasingly Important Role in Oncology Care

An Interview with Lillie Shockney, RN, BS, MAS

Cancer treatment is becoming increasingly complex and patients often have to see multiple specialists in different practices for their care. Often too, patients face financial or other barriers to getting the care they need. Nurse navigation is a new specialty within oncology nursing that has evolved to meet patients' need for someone to coordinate their care from diagnosis to survivorship and to provide support and education so that they can make informed decisions about treatment. In this interview, Lillie Shockney, RN, BS, MAS, administrative director of the Johns Hopkins Avon Breast Center in Baltimore, Maryland, talks about how the concept of nurse navigation grew and what she foresees for the future of the profession.

How did you get involved in nurse navigation?

I attended a 3-year RN diploma

Continued on page 20

CANCER SURVIVORSHIP

Current Issues in Providing Survivorship Care

Marcia Grant, RN, DNSc, FAAN;
Denice Economou RN, MN, CNS, AOCN
City of Hope National Medical Center, Duarte, California

The definition of cancer survivorship includes many concepts and elements within the trajectory from diagnosis to end of life. Surviving cancer brings many changes for the patient and the family, and yet no two patients, even those with the same diagnosis, experience "surviving" in the same way. As

Continued on page 14

NURSING CAREERS

Education Capacity Limits Will Lead to Continued Nursing Shortages, Says Nursing Workforce Expert

NASHVILLE—"Until we can increase the capacity of nursing education programs so that they can take in all qualified applicants, we're destined for long-term nursing shortages that could be extremely severe," reported Peter Buerhaus, RN, PhD, professor of nursing at Vanderbilt University School of Nursing, and director of the Center for Medicine and Public Health at Vanderbilt University

Continued on page 9

RECENT FDA APPROVALS

Newly Approved Pralatrexate Evoked a Complete or Partial Response in 27% of Patients

On September 25, 2009, pralatrexate (Folotyn, Allos Therapeutics) was granted accelerated approval by the US Food and Drug Administration (FDA) for treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) and should already be available for patients.

Final results released in February from the largest-ever prospectively designed single-agent phase 2 trial in patients with relapsed or refractory PTCL demonstrated that 29 (27%) of 109 evaluable patients achieved a complete or partial response to the novel targeted antifolate agent pralatrexate, with a response duration of 287 days (9.4 months), meeting both study end

Continued on page 22

When treating patients with HER2+ breast cancer

No one touches their

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

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

Adjuvant indications

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

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

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

Metastatic indications

Herceptin is indicated:

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

Boxed WARNINGS and Additional Important Safety Information

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

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

Genentech BIOONCOLOGY

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

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

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

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

www.herceptin.com

Herceptin®
trastuzumab
Targeted on HER2, Focused on Living

9568900 01/09

HERCEPTIN® (trastuzumab)

Brief Summary For full Prescribing Information, see package insert.

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

Cardiomyopathy

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

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

Infusion Reactions; Pulmonary Toxicity

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

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

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

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

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

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

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

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

Infusion Reactions Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia. [*see Adverse Reactions*]. In postmarketing reports, serious and fatal infusion reactions have been reported. Severe reactions which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction. Interrupt Herceptin infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered, which may include: epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions. There are no data regarding the most appropriate method of identification of patients who may safely be retreated with Herceptin after experiencing a severe infusion reaction. Prior to resumption of Herceptin infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated Herceptin infusions, others had recurrent severe infusion reactions despite pre-medications. **Exacerbation of Chemotherapy-Induced Neutropenia** In randomized, controlled clinical trials in women with metastatic breast cancer, the per-patient incidences of NCI CTC Grade 3-4 neutropenia and of febrile neutropenia were higher in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was not significantly increased. [*see Adverse Reactions*]. **Pulmonary Toxicity** Herceptin use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions [*see Warnings and Precautions (5.2)*]. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity. **HER2 Testing** Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied and for whom benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results. Several FDA-approved commercial assays are available to aid in the selection of patients for Herceptin therapy. These include HercepTest™ and Pathway® HER-2/neu (IHC assays) and PathVysion® and HER2 FISH pharmDx™ (FISH assays). Users should refer to the package inserts of specific assay kits for information on the validation and performance of each assay. Limitations in assay precision (particularly for the IHC method) and in the direct linkage between assay result and overexpression of the Herceptin target (for the FISH method) make it inadvisable to rely on a single method to rule out potential Herceptin benefit. A negative FISH result does not rule out HER2 overexpression and potential benefit from Herceptin. Treatment outcomes for metastatic breast cancer (Study 5) as a function of IHC and FISH testing are provided in Table 9. Treatment outcomes for adjuvant breast cancer (Studies 2 and 3) as a function of IHC and FISH testing are provided in Table 7. *HER2 Protein Overexpression Detection Methods* HER2 protein overexpression can be established by measuring HER2 protein using an IHC method. HercepTest®, one test approved for this use, was assessed for concordance with the Clinical Trial Assay (CTA), using tumor specimens collected and stored independently from those obtained in Herceptin clinical studies in women with metastatic breast cancer. Data are provided in the package insert for HercepTest®. *HER2 Gene Amplification Detection Method* The presence of HER2 protein overexpression and gene amplification are highly correlated, therefore the use of FISH to detect gene amplification may be employed for selection of patients appropriate for Herceptin therapy. PathVysion®, one test approved for this use, was evaluated in an exploratory, retrospective assessment of available CTA 2+ or 3+ tumor specimens collected as part of patient screening for clinical studies in metastatic breast cancer (Studies 5 and 6). Data are provided in the package insert for PathVysion®. **Embryo-Fetal Toxicity (Pregnancy Category D)** Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk of oligohydramnios during the second and third trimesters. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus. [*see Use in Specific Populations*]. **ADVERSE REACTIONS** The following adverse reactions are discussed in greater detail in other sections of the label: • Cardiomyopathy [*see Warnings and Precautions*] • Infusion reactions [*see Warnings and Precautions*] • Exacerbation of chemotherapy-induced neutropenia [*see Warnings and Precautions*] • Pulmonary toxicity [*see Warnings and Precautions*] The most common adverse reactions in patients receiving Herceptin are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of Herceptin treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [*see Dosage and Administration*]. **Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. *Adjuvant Breast Cancer Studies* The data below reflect exposure to Herceptin across three randomized, open-label studies, Studies 1, 2, and 3, with (n= 3355) or without (n= 3308) trastuzumab in the adjuvant treatment of breast cancer. The data summarized in Table 3 below, from Study 3, reflect exposure to Herceptin in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in Study 3, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

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

MedDRA (v. 7.1) Adverse Event Preferred Term	1 Year Herceptin (n= 1678)	Observation (n= 1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[b]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Nasopharyngitis	135 (8%)	43 (3%)
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		
Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritis	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Aesthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	43 (3%)
UTI	39 (3%)	13 (0.8%)
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

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

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

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

	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

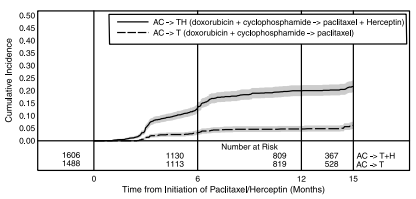
the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF <50% or ≥15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the 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)

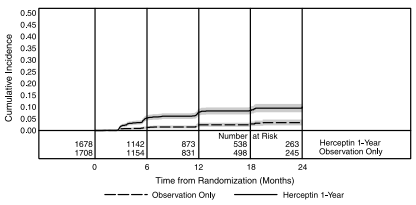
[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization. [b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[c] Study 4 regimens: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



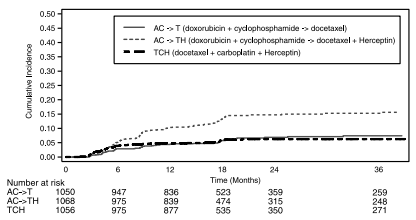
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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*].

HERCEPTIN® [trastuzumab]
Manufactured by:
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South San Francisco, CA
94080-4990

4839803
Initial US Approval: Sept. 1998
Revision Date: March 2009
LK0726 7172911
7172713

News Notes

News Updates of Relevance to Everyday Oncology Practice

■ ONS, ASCO Release Chemotherapy Safety Standards

The Oncology Nursing Society (ONS) and the American Society of Clinical Oncology (ASCO) have released the first-ever national standards for safe administration of chemotherapy drugs. The standards were developed to reduce the risk of errors and provide a framework for best practices in cancer care. The 31 standards cover a range of processes related to chemotherapy, including:

- Staff education and training
- Chemotherapy ordering, preparation, and administration
- Patient education and informed consent
- Assessment of patients' response to treatment
- Monitoring toxicity of treatment to the patient

According to the Oncology Nursing Society (ONS) and the American Society of Clinical Oncology (ASCO), to avoid chemotherapy administration errors, healthcare practitioners must follow standardized approaches for delivery of chemotherapy, develop and implement policies and procedures for system improvement, and conduct a multidiscipline review of errors when needed. They also recommend increased use of electronic medical record systems.

The standards appear in the September 28 issue of the *Journal of Clinical Oncology*; they will also be published in the November issue of the *Oncology Nursing Forum*. The standards as well as a guide ASCO has developed to help oncology practices review and develop policies and procedures needed to adhere to them are available online at www.asco.org/safety and www.ons.org/clinical/Treatment/Chemo therapy/news.shtml.

■ Azacitidine Upgraded to NCCN Category 1

The National Comprehensive Cancer Network (NCCN) has upgraded azacitidine (Vidaza, Celgene) to a Category 1 recommendation for the treatment of patients with intermediate-2 and high-risk myelodysplastic syndromes. The recommendation was based on the recently reported findings of a large international randomized phase 3 clinical trial, in which azacitidine demonstrated a near doubling of overall survival rates at 2 years compared with conventional care regimens (best supportive care, low-dose ARA-C, standard chemotherapy). In the study, median overall survival in the azacitidine group (n = 179) was 24.5 months; in the conventional care regimens arm (n = 179) it was 15 months (P = .0001) (Celgene Corporation).

■ *KRAS* Status Added to Cetuximab/Vectibix Label

The US Food and Drug Administration has approved revisions to the prescribing information for cetuximab (Eribitux, Im-

Continued on page 4

A Letter from the Editor

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

EDITOR-IN-CHIEF

Newly released statistics from the American Cancer Society show that breast cancer deaths in the United States continue to fall more than 2% per year, continuing a trend that began in 1990 (www.cancer.org/statistics). This is indeed encouraging news, but it is tempered by the fact that breast cancer remains the most common cancer among women other than skin cancer.

Despite better outcomes, a diagnosis of breast or any other type of cancer can be overwhelming for the patient, and the prospect of making decisions about treatment daunting. A new subspecialty within nursing—nurse navigation—has recently emerged to provide individualized education and support for patients, coordinate care by different providers, and improve communication between patients and their physicians. In this issue, Lillie Shockney, one of the pioneers in this field, speaks of how her own experiences as both a nurse and a patient led to her becoming a nurse navigator and how the role is evolving.

Other good news is the growing number of cancer survivors, which means an increasing need for nurses and others trained in survivorship care. The City of Hope provides an educational program for nurses and their colleagues from other disciplines who provide survivorship care, described in the article by Marcia Grant and Denice Economou.

Another article addresses an issue of concern to all of us—the continuing shortage of nurses in the United States. We would like to hear from you about what your institution is doing to meet the need for nurses and what incentives to continue working would be most important to you personally. There is lots of work ahead, so it is important for healthcare providers sand patients alike to make sure that there are enough qualified people to do it. ●

News Notes

News Updates of Relevance to Everyday Oncology Practice

Continued from page 3

Clone Systems) and panitumumab (Vectibix, Amgen) to include a modification to the indication for patients with epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer. The addition is supported by recently updated guidelines by the American Society of Clinical Oncology and the National Comprehensive Cancer Network, which recommend that all patients with metastatic colorectal cancer be tested for *KRAS* gene mutations before treatment with an anti-EGFR monoclonal antibody therapy. "Retrospective subset analyses of metastatic or advanced colorectal cancer trials have not shown a treatment benefit for Erbitux/ Vectibix in patients whose tumors had *KRAS* mutations in codon 12 or 13. Use of Erbitux/Vectibix is not recommended for the treatment of colorectal cancer with these mutations." Revisions regarding *KRAS* status were also added to the clinical studies and clinical pharmacology section of the label (ImClone Systems; Amgen).

■ IOM Recommends 100 Initial Priorities for Comparative Effectiveness Research

At the request of Congress, the Institute of Medicine (IOM) has chosen 100 health topics that should get priority attention and funding from the comparative effectiveness research effort in the American Recovery and Reinvestment Act of 2009. IOM has also detailed actions and resources needed to ensure that this initiative will be sustained with a continuous process for updating priorities and that the results will be implemented in clinical practice.

Health professionals, consumer advocates, policy analysts, and others submitted nominations. IOM received 1268 unique topic suggestions, which it narrowed to 100 based on a set of criteria that included its charge to develop a balanced portfolio. The list reflects a range of clinical categories, populations to be studied, categories of interventions, and research methodologies. The list can be viewed at www.iom.edu/Object.File/Master/71/032/Stand%20Aloe%20List%20of%20100%20CER%20Prioritie%20%20for%20web.pdf.

The IOM also pointed out that effective coordination and governance among the agencies and disciplines involved will be crucial for ensuring sustainability of comparative effectiveness research. Ultimately, comparative effectiveness research will fall short of its potential without vigorous efforts by the government to promote adoption of the findings by healthcare providers and organizations (The National Academies).

■ FDA Issues Final Rules for Expanded Access to Investigational Drugs

The US Food and Drug Administration (FDA) has amended two regulations regarding investigational new drugs. One final rule expands access to these agents for treating patients. It clarifies the existing regulations and adds new types of expanded access:

- Individual patients, including in emergencies
- Intermediate-size patient populations
- Larger populations under treatment protocol or treatment investigational new drug application.

Another rule amends the regulation on charging patients for investigational drugs by:

- Clarifying the circumstances under which charging for an investigational drug in a clinical trial is appropriate
- Setting forth criteria for charging for an investigational drug for the different types of expanded access for treatment described above
- Clarifying what costs can be recovered.

In a press release, American Society of Clinical Oncology President Douglas W. Blayney, MD, stated that the new rules "strike a balance between meeting the immediate needs of seriously ill cancer patients, while safeguarding the clinical trials system so it can develop to treat cancer patients in the future." ●

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MICHELSON TECHNOLOGY AT WORK

CONTENTS

Vol. 2, No. 6 September/October 2009

Feature Articles

Departments

Practical Applications
The role of the oncology nurse in optimizing medication adherence
Between pages 20 and 21

The Oncology Nurse

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Letter to the Editor

Healthcare Reform and How We Treat the Elderly

To the Editor:

It wasn't supposed to happen this way. The 1000-page House of Representatives healthcare reform bill, America's Affordable Health choices Act, was supposed to follow the new congressional passage sequence: distribute it to all the usual suspects, read it on the cab ride to the hotel, and immediately sign it into law. So when congressional members on both sides of the aisle started boring into the draft of the bill and came back with concern over language that only suggested a troubling threat to seniors, political veterans were caught off guard. Since then, with protests ringing across the country at town hall meetings and every other conceivable venue, it has become clear that Americans want a healthcare system bent on healing.

The immediate concern was over the now infamous end-of-life counseling provision, Section 1233, which would have authorized Medicare to pay for a consultation between a patient and doctor or nurse about how much or little medical care is desired in the event of incapacitation, informing patients about the benefits of hospice and palliative care. At first blush, there was nothing alarming here. Providers and payers have been wrestling to draw the line between aggressive care for the terminally ill, and the pointless, wasteful use of costly drugs that do little to improve or extend life in terminally ill patients. But there is an existing context for this language and the net effect of other provisions in the House bill that are intended to ration care, which would lead to the same result: an early and cost-effective death, all in the name of efficient healthcare resource allocation. (Note that there is all the difference in the world between a medically driven consultation with one's doctor and an agenda-driven consultation designed a priori to discourage care.)

Concern arose immediately over end-of-life counseling and rationing for the elderly, with fears that it signaled the start of limiting access to healthcare for our sickest, usually oldest, patients. Fueling this fear is the fact that a quarter of Medicare funds go to patients in the last year of their lives. Because policy must be drafted with an eye to clarity, the public wanted assurances that the government was not simply implementing a cost-saving measure designed to convince seniors to opt out of appropriate treatment when they are terminally ill. Evaluating the language within the context of political policy, the concern is that the bill is an incremental move toward replacing a progressive healthcare system with a regressive one, with the elderly as its first victims. The ensuing debate has helped to bring a central issue out in the forefront: will seniors receive the care they need?

It is important that we decide whether we are committed to a progressive healthcare system—one that aggressively pursues disease prevention, intervention, and innovation—or to a Brave New World of limited healthcare resources, concluding that the best years of healthcare are behind us. If the latter, then we must become adept at rationing care for the elderly, ultimately endorsing euthanasia, assisted suicide, and rationed care as practical remedies. Society must choose sides—it cannot finesse both ends of the spectrum, because the war on disease takes all the resolve of a true all-out war. As healthcare reform takes shape, we must take stock of how we treat our elderly, a fundamental measure of the decency of our society. And as we look at new initiatives for dealing with end-of-life care, we must ask if the United States will follow the lead of Great Britain and provide coverage based on quality-adjusted life-years, calculating coverage eligibility based on the cost of intervention measured against one's age. By encouraging hospice-oriented care for the elderly and the rationing of care, is government embracing a regressive healthcare system? Is government's healthcare vision one of reduced access to care for the elderly and infirm, coupled with reduced development of new life-saving drugs because payer coverage strategies are skewed against coverage of branded medications, the profits of which are needed for innovation? If this is the picture, would the affluent consent to the terms that a regressive healthcare system proffers to the public at large? Would the wealthy accept a government mandate that says it is your turn to die? Be it death counseling or rationing, the end goal is the same: death is good for the bottom line.

It has not escaped notice of policymakers that the major epidemiologic factor facing American healthcare is the aging of the baby boomers. The real crisis facing America's healthcare system is what will happen 10 years from now when baby boomers begin contracting geriatric disease states and consuming vast healthcare resources, if nothing is done to improve current efficiencies to healthcare. But it is the nature of a free people to reorder their circumstances to overcome challenges to their survival. In the face of the graying of America, some policymakers would have us encourage the elderly and infirm to die quickly and "will their estates" to the young. This is classical pessimism reincarnated 21st-century style under the guise of "death-with-dignity" allocation of resources. It is an easy guess that lawmakers and the wealthy endorsing this process for the public at large would exempt themselves from it. It is also an easy guess that most lawmakers do not want this to happen. If that is the case, it is imperative to insert language into the final healthcare bill that ensures the elderly have an "even playing field," where healthcare eligibility is not driven by age or productivity.

Visit the National Museum of the Marine Corps and you see testimony to patriots who faced down seemingly invincible armies by an unshakable resolve to win. Their approach was simple: the enemy was out to annihilate America, and surrender was not an option. As politicians set out to assist the healthcare system, it is imperative that they adopt the same strategy. Disease is not something to run from, but to address head on. Ultimate solutions for solving the entire picture do not constitute reform, just utopianism. In a recent appearance on *Charlie Rose*, Mayo Clinic CEO and president Denis Cortese advised we undertake healthcare reform one chunk at a time, not all at once. He also faulted the bill for its emphasis on cost-containment instead of balancing this with quality; combine them and you have value, not just cost-savings, he warned.

The ultimate abdication from quality of care is the restriction of access to care for the oldest and sickest, the facilitation of death via dehydration, starvation, avoidance of cardiac resuscitation or ventilator use, or simply rationing care. The concern over the aforementioned consultations in the healthcare reform bill stems from apprehension over realpolitik, where cost trumps quality and politics trumps cost. Is the bill the first stage of a strategy to entice seniors to sign boilerplate forms amounting to "do not resuscitate"? If so, it is placing American healthcare on the slippery slope to icy utilitarianism. If not, then the language must clearly forbid it.

The American spirit of can-do that the Marines showed at Belleau Wood and Iwo Jima in World War II is the proper approach to American healthcare system reform. But first, government must stop trying to dominate the triangle of sectors (clinical, business, regulatory) and instead support the clinical and business systems. Periodically, each of these three sectors regards itself as the one with the answers and seeks hegemony over the system, when it is balance of power that is needed. Enlightened government is measured not by its power over citizens, but its protection of their liberty.

Government healthcare policy must avoid domination of the healthcare process and policies that encourage—and eventually mandate—terminally ill patients to die quickly and inexpensively. The language of the healthcare bill must be crafted to pursue healing, not dying. It must keep the emerging American healthcare system true to our positive core values: life, liberty, and pursuit of happiness—not quality-adjusted life-years. To be progressive and effective, the American healthcare system must embrace prevention, intervention, and innovation, conspicuous by its absence is any fourth point called do not resuscitate. Instead of planning for an ultimate retreat from healthcare for seniors, policymakers should embrace strategies that encourage development of new drugs and devices that save lives and money spent when illness drives patients into nursing homes and hospitals. A society not committed to taking care of its elderly is essentially indecent and on its way out. We are better than that. We can and will take care of the sickest—not with foolhardy, reckless usage of costly medications that do little to prolong or improve life, but with new treatments and medications, and equally resourceful payer utilization processes that deliver quality on the high road of medicine.

We must continue to define our healthcare system as one befitting a free people, a system supportive of progress and the health of its citizens, a system confident in the ability of science and physicians to find the cures needed to sustain our healthcare system. The best is yet to come if we remain positive and avoid surrendering up our sickest out of fear that we do not yet have all the resources to treat them. As we codify our healthcare system, let us retain its noblest elements and reward our oldest citizens with the resolve to heal, not abandon them in their last years. ●

BY **ROBERT EMMETT HENRY**
Editor-in-Chief
American Health & Drug Benefits

Send comments on this and other topics to Karen@greenhillhc.com. All comments will be posted on our website www.theoncologynurse.com.

Nursing Shortages

Continued from cover

Medical Center, Nashville, Tennessee.

This shortage is especially troubling because, "As our aging baby boomers retire, they will consume roughly three to four times more healthcare than those under the age of 65," Buerhaus explained. "But as the demand for nursing goes up in the future, our supply will not increase fast enough to match it, resulting in delays in care, in less access to healthcare, and threats to quality and safety."

During his presentation, "The Future of the Nursing Workforce in the United States: Data, Trends, and Implications," at the Society of Critical Care Medicine's 38th Critical Care Congress in February, Buerhaus discussed current challenges facing all fields of nursing and the economic impact, long-running trends, and what can be done to improve the situation in the future. The trends and forecasting information from this presentation came from several sources, including Bureau of Census surveys.

As the demand for nursing goes up in the future, our supply will not increase fast enough to match it.

"Our estimates suggest that we have roughly 2.5 million nurses working today," Buerhaus said. Plus, as unemployment rates continue to increase during the current recession, he said that more nurses will be entering the workforce than ever before. "More people will want to become RNs [registered nurses] due to the job security that the recession-resistant nursing profession represents. In fact, from our studies of the American public, we have found that one in four at one point in their life thought about becoming a nurse."

He pointed out that current trends show more foreign-born RNs and an increasingly older workforce. "Not only are the currently working RNs getting older and not necessarily retiring in these uncertain economic times, but many retired RNs are also deciding to come back to work," said Buerhaus.

His team's projected age distribution of the RN workforce by the year 2012 shows that RNs in their 50s will comprise the largest age component, followed closely by those in their 40s. In addition, the number of those in their 60s will have tripled from 1990.

"I think this represents a workforce that is the most skilled and most knowledgeable of any in the nation's history. However, due to the heavy lifting and activity that takes its toll on the toes, ankles, knees, hips, back, necks, and eyes over the years, ergonomic remedies are going to be more important than ever before to ensure that older nurses can continue to do their jobs efficiently and safely."

He presented an overall deficit projection between nursing demand and supply through the year 2020 of approximately 285,000. Although this is a significant decrease from the 800,000 to 1,000,000 deficit estimate from just a few years ago, Buerhaus said that this number is still troubling. "There are currently 5.2 million people who work in hospitals and another 7.8 million who work in industries that supply goods and services to the healthcare industry. So if we let the nursing workforce unravel, it could definitely spill over into other sectors of the broader economy."

He said that plenty of people want to become nurses. The problem is getting them into programs and then graduated and out into the workforce. "We have been turning away 30,000 to 40,000 qualified applicants from nursing education programs each year since 2002 due to capacity issues such as limited faculty, a lack of classroom space, and a lack of clinical education sites,"

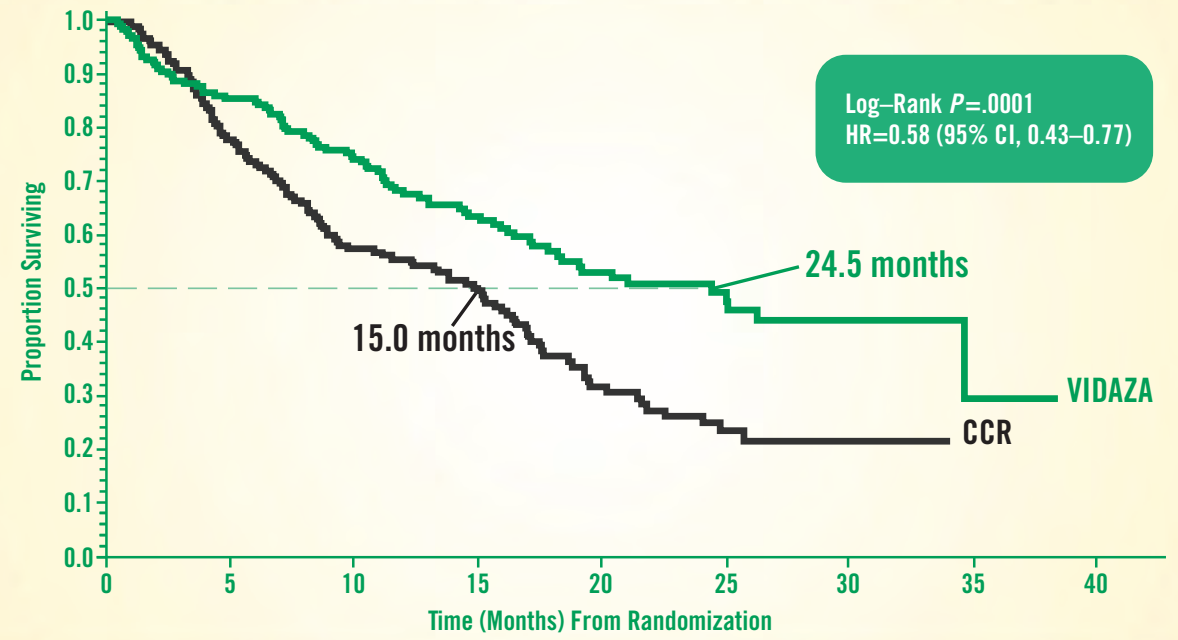
Continued on page 18

In the treatment of higher-risk MDS…*

A Breakthrough in SURVIVAL

VIDAZA® is the first and only agent proven to extend overall survival vs CCR[1]

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, noncrossover 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) + BSC (transfusions, antibiotics, G-CSF for neutropenic infection), or 1 of 3 CCR. CCR treatments included BSC alone; 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 preselected by study investigators. The primary end point of the study was overall survival.[1]

- In the Survival Study, median overall survival was 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])[1]
- VIDAZA nearly doubled the 2-year overall survival rate vs CCR[1,2]
  - 51% survival for VIDAZA vs 26% survival for CCR (24.6% difference, 95% CI, 13.1-36.1)[1,2]
- Patients continued treatment until disease progression, relapse after response, or unacceptable toxicity
  - Patients receiving VIDAZA were treated for a median of 9 cycles (range 1 to 39)[1]
  - Patients should be monitored for hematologic response and renal toxicities, with dosage delay or reduction as appropriate
- CCR included BSC or L-DAC or 7+3 chemotherapy[1]

Abbreviations: BSC, best supportive care; CCR, conventional care regimens; FAB, French-American-British classification for MDS; L-DAC, low-dose cytarabine; MDS, myelodysplastic syndromes.

*Higher-risk MDS is Intermediate-2– and High-risk MDS per International Prognostic Scoring System (IPSS).

†Bone marrow blast count ≥20% is classified by the WHO as AML.[3] The investigators in the Survival Study classified RAEB-T as blasts 21%-29%.[2]

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).

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.

References: 1. Fenaux P, Mufti GJ, Hellström-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232. **2.** Data on file, Celgene Corporation. **3.** Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee Meeting, Airlie House, Virginia, November, 1997. *Ann Oncol.* 1999;10(12):1419-1432.

Vidaza®

azacitidine for injection

Proven Results. Extended Survival.

Celgene

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% 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.

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Providing Survivorship Care

Continued from cover

Feuerstein put it, it is a "long and winding road."[1]

In 1985, Mullan, himself a survivor, wrote about the concept of being "cured" or not.[2] He declared the stages of survival as acute, extended, and permanent and began the discussion on the challenges faced by survivors. After this publication, others began looking at the phases of survivorship and how patients experience them. Ferrell and Grant organized the domains of quality of life in the cancer survivor, defining the physical, psychological, social, and spiritual perspectives (Figure). Patients and survivors continually move across these domains and from an acute phase to late and long-term effects. Aziz and Rowland, like Mullan, believe that recognizing the "concept" of survivorship provides an opportunity to build a definition that encompasses the "phenomenon" or "experience" of cancer survivorship.[3] Their definition includes diagnosis and treatment issues as well as long-term and late effects. The psychosocial and spiritual issues that coincide with a patient's physical response to the diagnosis and treatment are also considered.

Denice Economou, RN, MN, CNS, AOCN

There are 12 million cancer survivors in the United States today, and that number is expected to double by 2020. The 5-year survival rate for cancers overall increased from 50% in the period between 1975 and 1977 to 66% between 1996 and 2003.[4] Today, one in every seven survivors received their diagnosis more than 20 years ago. Improvements in screening, early detection, and treatment as well as better control of adverse effects are responsible for these gains. In addition, it is important to recognize that 60% of cancer survivors are aged 65 years or older.[4]

Survivorship resources

The National Coalition for Cancer Survivorship was founded by cancer survivors 20 years ago, when its members recognized the need to provide support for the different responses patients experience after active treatment. In 2006, the National Cancer Institute (NCI) established the Office of Cancer Survivorship. Its mandated role is to "improve the length and quality of life for all people diagnosed with cancer." This includes directing and supporting research and underwriting or advocating for training of researchers and clinicians dedicated to studying, treating, or caring for survivors.[5] The office also actively develops educational materials to provide cancer survivors and their caregivers support to reach optimal health after their diagnosis.

The American Society of Clinical Oncology (ASCO) recognizes the role oncologists play in the entire spectrum of care from diagnosis through treatment and beyond and has developed Cancer Survivors Care Summary and Treatment Plan templates. These forms provide a plan component to be completed before chemotherapy and a summary to be completed after chemotherapy. Oncologists can use them as guides when deciding how their patients will be seen after treatment. In 2008, ASCO made these templates available on its website to help meet the growing need.[6] ASCO has also launched Cancer.net, which provides resources, templates, and other materials to help transition patients into survivorship.[7]

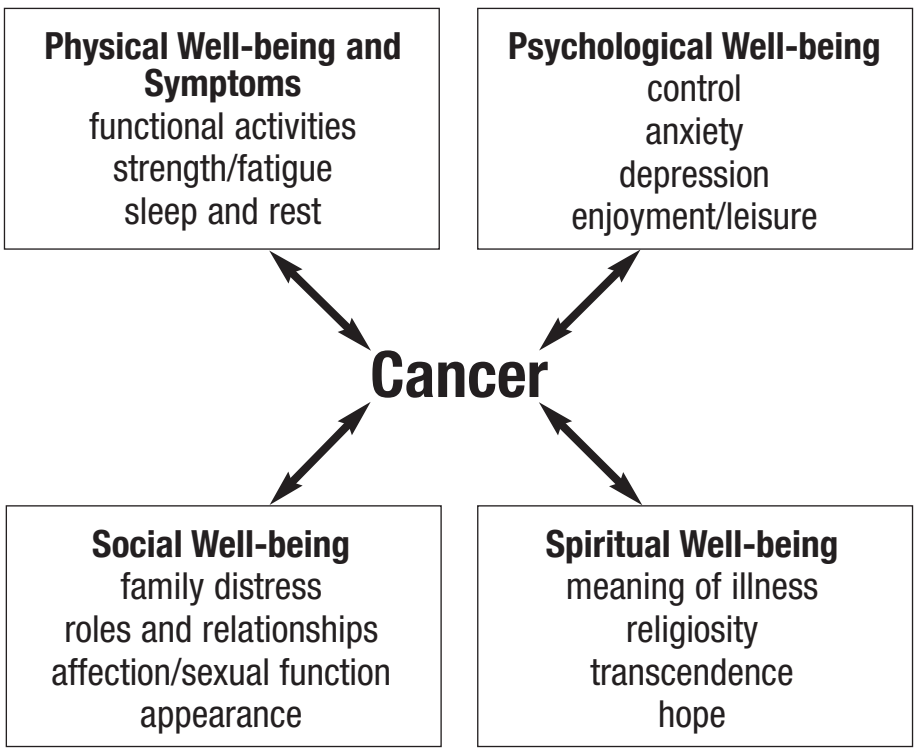

Figure. Quality-of-Life Model Applied to Cancer Survivors

Recently two web-based programs have been established. LiveStrongCarePlan.org has evolved from the Oncolink program and Journeyforward.org has been developed among the National Coalition for Cancer Survivorship, the UCLA Cancer Survivorship Center, WellPoint, Inc, and Genentech.[8,9] Both offer templates as well as cancer survivorship education materials for both professional and patient resources.

Recognizing the major role nurses play in survivorship care from diagnosis until death, the Oncology Nursing Society (ONS) recently launched its Survivorship Initiative. This initiative seeks to raise awareness among nurses across the healthcare community of their responsibility in caring for cancer survivors as well as their caregivers and families. ONS plans include providing critical resources to all nurses to help support these needs.

As knowledge evolves regarding long-term and late effects of cancer and its treatment, the role of oncology nurses must also evolve to provide the various components of survivorship care, which include (1) detection and health promotion, (2) surveillance for new or recurrent cancers, (3) interventions to deal with the consequences of cancer and treatment, and (4) coordination of care between specialists and primary care physicians. As you look at your own institution, you can begin to define different practices and see how these practices fit into the components of survivorship care, as identified by the Institute of Medicine report *From Cancer Patient to Cancer Survivor: Lost in Transition*.[10]

Survivorship program goals and services

City of Hope has been implementing an R25 cancer education grant by training two-person multidisciplinary teams in the components of survivorship care and then following the goals each team developed at 6, 12, and 18 months for percent of achievement. With 205 teams trained to date, we evaluated the goals developed using Donabedian's framework of structure, process, and outcomes to organize the primary areas of activity.[11]

Over the past 4 years, team goals have transitioned from raising awareness and educating administrators to designing specific programs and completing care summaries and plans for meeting an individual patient's needs. Cancer centers are reorganizing and coordinating services that go beyond their internal services and are developing relationships with community programs that can help provide additional services to their patients without requiring additional staffing and financial support.

Different institutions provide oncology care based on their particular areas of expertise. Institutions with strong academic and physical medicine staff support provide survivorship care that focuses on the physical symptoms patients may be experiencing, such as lymphedema, cardiovascular symptoms, endocrine symptoms, or osteoporosis. Institutions with strong psychological and social staffing focus on the psychosocial issues patients and families may be experiencing and provide support groups, anxiety- and depression-related services, as well as counseling on insurance or financial needs. Rehabilitative services or supportive care centers provide strength training and symptom-management strategies, such as fatigue-management interventions, and promote health and disease prevention. Spiritual well-being and helping survivors transcend through the meaning of illness to find hope in their uncertainty may be the center of some programs. Some part of all of these components will be available in an individual setting but programs will differ.

Oncology nurses must be familiar with the components of survivorship care and play a key role in directing patients and their families to the type of care needed. The cornerstones of survivorship care include monitoring physical health as well as assessing psychosocial well-being, detecting and preventing disease through health promotion and education, and coordinating care in a system that is fragmented and overwhelmed. Helping patients document their care and providing them with plans for future follow-up and coordination of long-term care needs is essential. Nurses can assist in the development of a model of care that fits their institution and care setting. It is important to evaluate the institution's supportive services, develop community relationships to help extend services, and use educational resources that are available through such organizations as the Lance Armstrong Foundation, The Wellness Community, CancerCare, the American Cancer Society, and ONS.

Cancer care settings range from large NCI-designated cancer centers or university-associated cancer centers to office practices with single or multiple practitioners. How each of these settings meets the needs of its cancer survivors varies, depending on staff expertise and the services available in their community agencies. Collaboration between the cancer center and the community agencies is essential for patients to get the services they need. For example, one team that attended our survivorship course coordinates their services with those of the local referring hospital. Breast cancer patients from the oncology office are referred directly to the breast health coordinator, an advanced practice nurse, at the hospital for education and follow-up after surgery. They work together to complete the care summary and treatment plan based on the physician's approved template. Some of the post-course teams in rural settings depend heavily on supportive services, such as

Continued on page 16

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Nursing Careers

ONS Award Winner Looks Back on Career

An Interview with **Marcia Grant, RN, DNSc, FAAN**

In recognition of her long and distinguished career, Marcia Grant, RN, DNSc, FAAN, was awarded the Oncology Nursing Society's Lifetime Achievement Award during the 34th Annual Congress in San Antonio, Texas. Dr Grant is director, Division of Nursing Research and Education, and professor, Department of Population Sciences at City of Hope (COH) in Duarte, California. Among her research interests are survivorship care, palliative medicine, pain management, and end-of-life care.


Marcia Grant, RN, DNSc, FAAN

How did you get started in oncology nursing?

I got started in oncology nursing when I went to work as a clinical research associate at COH in 1975. A couple of years later, Ruth McCorkle asked me if I would join the Oncology Nursing Society and become a part of a new research committee. Before that, I hadn't specialized in oncology nursing, but I was in a research department at the COH so it was a good match. I've been in oncology nursing ever since.

Where had you gone to nursing school?

I went to nursing school at Harper Hospital in Detroit and got my bachelor's and master's degrees from Wayne State University. I worked in many jobs and I taught for 7 years at the University of Hawaii School of Nursing. After I got to COH, I realized I needed a doctoral degree to get my research funded. I commuted to the University of California, San Francisco, where they had just stared an oncology specialist track for their doctoral program. Dr Marylin Dodd had just arrived to lead the program and also graduated from Wayne State, so I thought it would be a philosophical match.

What are some of the projects you've been involved in at COH?

We've gotten outside funding for our research projects since 1979 in areas including quality-of-life research, end-of-life care, palliative care, and survivorship care. It's very unusual for a hospital to have a nursing research department. COH is a National Cancer Institute (NCI)-designated comprehensive cancer center, and we contribute to the research of the full cancer center. COH is one of the few free-standing comprehensive cancer centers in the country.

How did the survivorship education program get started?

We have been concerned about cancer survivors for a long time in the department, and it has been a thread of our research program. We have looked at such questions as "What are the long-term effects of cancer not only on the patient but also on the patient's family?" and "How can we help the patient adjust after treatment is over to getting on with the rest of his or her life?" We have done educational courses to improve clinical care practice in pain management, end-of-life care, and palliative care, and we thought we should do the same thing for survivorship. So we submitted a grant to the NCI. About a year after we got our funding, the Institute of Medicine report *From Cancer Patient to Cancer Survivor: Lost in Transition* came out. So we were just a little ahead of the wave.

We find that bringing in teams of two is helpful. It seems to be easier to bring about institutional change when you have a partner helping you along. Multidisciplinary teams of cancer care professionals from across the United States come for a 3-day course. One person has to be a nurse, physician, or administrator, someone who has the power to make changes within the organization. The second person can be from one of those three disciplines or anyone else involved in survivorship care, such as a social worker, a pharmacist, or rehabilitation specialist. We use our quality-of-life model of physical, psychological, social, and spiritual well-being to organize the content as well as providing information about institutional change. We have the teams create goals when they are in the class and then we follow up with them at 6, 12, and 18 months to see what they have accomplished.

What are some of the major changes you have seen over the course of your career?

The population of cancer survivors is older, as is the general population. Cancer is a disease that affects older people more than younger people, so the number of people getting cancer is higher because the population is older. Also, the treatments we now have are better, and that's why more people are surviving. When we started the survivorship course, there were almost 11 million survivors in the United States. We are now in our fourth year, and there are more than 12 million, and that's going to keep increasing.

The services cancer survivors need relate to keeping their job, maintaining their insurance, making sure they are screened often enough so that recurrences are caught early, and making sure that they are in the line for new treatments that come up if they are not cured but in remission. It is important to keep in mind that when the oncology physician is through treating the patient, the patient often goes back to his or her primary care physician, who may not be familiar with the long-term effects of cancer treatment. They may not know how often the patient should go back to see the oncologist, what warning signs to be concerned about, or what cardiac or other side effects of cancer treatments may occur. A whole education is needed to pass this information on to primary care physicians. The best way to do that is to put together a care summary for each patient so that they have a record of exactly what treatment they have had. In addition, each patient should receive a summary of recommended follow-up care and what long-term effects to look for. ●

CANCER SURVIVORSHIP

Providing Survivorship Care

Continued from page 14

CancerCare and The Wellness Community, which offer web conferencing or teleconferencing to patients and families that cannot drive to a cancer center or support group easily or often. In addition to having internal expertise within your practice, it is essential to provide education and know your local community resources to meet the needs of cancer survivors.

Getting started

Starting survivorship activities at a cancer setting should begin by doing a needs assessment or simply adding a question or two to the institution's existing outcomes assessments. Knowing what disease type is most common among your patients will help you focus on the follow-up needs and long-term and late effects patients in this group may experience. Start small for better success. Define simple goals you can actually achieve. By re-evaluating programs you are already providing, you may find that some actually fall under the survivorship umbrella. Many institutions, for instance, provide support groups or special education sessions for breast cancer patients. Management of acute or late effects, such as lymphedema management programs or exercise programs for osteoporosis, can be added to the Breast Support group content, and, thus, be considered a survivorship program component. Psychosocial support for patients who fear cancer recurrence or have age-related employment issues is also a component of survivorship care.

No two centers offer the same programs in the same way. Each is unique to a setting and a patient population. It is not as difficult to provide survivorship care as many believe, and it is not something new or different from the quality care that all oncology nurses strive to provide. Survivorship care is already part of your practice. You just need to be sure it is integrated into the care you provide from diagnosis to end of life. ●

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Nursing Shortages

Continued from page 9

said Buerhaus. "We need to investigate these problems and then use this specific knowledge to identify the least costly and quickest options to expand capacity in nursing education programs for both the public and private sectors." He believes that reforming and expanding the nurse education system is going to be heavily influenced by public policy. "If it turns out that we will require public subsidies or taxpayer money to expand this capacity, we should think hard about asking for modifications to a program's curriculum. It may mean saying no dollars will go to any nursing education program that does not include more about geriatrics, have a rigorous upgrade in quality and safety, and teach an interdisciplinary and team-based approach that brings together medicine, nursing, management, and pharmacy in a cooperative environment."

Another recommendation for fighting the nursing shortage was working hard to retain the current workforce.

He also called on current nurses to help with this problem. "We need your support on efforts to expand the education capacity as well as your continuous discussions with politicians, patients, boards, executives, corporations, media, and your associations."

Another recommendation for fighting the nursing shortage was working hard to retain the current workforce by improving their ergonomic environment, helping nurses build up their physical strength, and figuring out how to use them more efficiently to prevent burnout. He also suggested specifically focusing on the retired nurses who have come back to work. "It's important to concentrate on retention so that once economic conditions improve, these nurses don't just want to leave again."

In an interview with *The Oncology Nurse*, Buerhaus said that today's smart hospital should not only talk to its older RNs about what it would take to keep them, but should also get them involved in some sort of mentorship program. "This allows the older RNs to provide guidance and help transfer some of their knowledge and wisdom to the younger generation of nurses."

He ended his presentation by recommending a shift in thinking about health reform. "Many people are interested in reforming healthcare by expanding insurance coverage, which is wonderful. But I would say to these people: how are we going to provide that access? How can a healthcare system be efficient if it is plagued by a chronic nursing shortage? The bottom line is that we need to increase our long-run supply of RNs."

Buerhaus said that the demand for oncology care is going to increase dramatically in the future. "I also think this is a great time for oncology nurses to think about becoming a nurse practitioner or a DNP [Doctor of Nursing Practice]. As we see the demand for oncology care increase, oncologists (who are already in short supply) are not going to be able to handle all these new patients." Plus, he said that the increased number of cancer survivors from the past 10 or 15 years "provides a great opportunity for nurse practitioners in oncology to triage and take care of survivors and get them in to see the oncologists when it's appropriate."

"So it's a bright future in a lot of ways for oncology nursing," Buerhaus concluded. "But we need to get the supply up so there isn't an overwhelming demand on the future nursing workforce." ●

—Deborah Brauser

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Important Role in Oncology Care

Continued from cover

school. I then got a bachelor's degree in healthcare administration, followed by an MBA from Johns Hopkins University, and I've been here for 26 years. I began in neurooncology on the surgery side, specializing in patients with neuroblastomas.

After my own diagnosis of breast cancer 17 years ago, I became interested in helping other women who were experiencing what I did. I began doing volunteer work in the breast center here, providing patients with one-on-one support and beginning a navigation process for them, recognizing how overwhelmed they feel when they are first diagnosed. I formally joined the breast center 12.5 years ago as the director of the program.

For 10 years, I was director of performance improvement utilization management and risk management for the entire institution. Looking at things from the utilization management perspective eventually led to the concept of navigation. A utilization review involved a retrospective chart review conducted by hospital nurses as well as nurses working for insurance companies and Medicare and Medicaid to identify when a patient had a barrier to treatment or to discharge that resulted in inefficient delivery of care. At that time, a huge problem for all hospitals was patients who were waiting for nursing home beds for anywhere from 5 days to 2 weeks. Hospitals would then receive a denial letter from the insurance company for those days of care because the patient could have been cared for at a lower level than the acute care setting. We then started doing concurrent chart reviews, because it certainly made more sense to review medical records while the patient was in the hospital and you could alert the physician that there may be some type of problem that would result in inefficient care.

The concept of case management was introduced in the early 1990s. With this approach, a nurse would work with the team caring for a particular patient population. The case manager was directly involved in the patient's care and could be proactive in identifying barriers to the patient's treatment and discharge from the hospital.

At the same time, Dr Harold Freeman was taking a look at the inability for people in underserved areas to access care, particularly cancer treatment, and gave birth to the term *navigation*. The original goal of navigation was to recruit patients in underserved communities to come in for cancer screening and then to give them access to care and facilitate their treatment so that more lives could be saved. We've expanded that concept to focus not just on underserved patients but any patient with a diagnosis of cancer.

The nurse navigator's role needs to dovetail with that of the other nurses involved. They have to communicate well with one another and work in a collaborative manner.

I am responsible for patients who have a diagnosis of breast cancer. I walk alongside the patient as she takes this journey. I want to be a couple steps ahead with my hand back holding her and guiding her through it. At the same time, I need to be looking forward a few steps to identify what is coming up next in her treatment regimen and assessing her for what barriers may exist that would impede our ability to deliver the care that she needs in an efficient and an effective way.

What are the typical responsibilities of an oncology nurse navigator, or do they vary in different settings?

They do vary in different settings. I've never seen two cancer centers function in the same way. The organizational structures are different and the geographic settings are different, which means that their patients are from various cultures, ethnicities, races, and financial status. However if we look globally at some of the more common functions that nurse navigators perform, the key one is patient education. We want to empower the patient so that he or she can participate in the decision-making regarding their treatment. So rather than doing things to him or her we need to be doing things with him or her. In doing so, we also are able to identify the patient's socioeconomic issues and psychological needs and learn what support systems she has to assist her with her treatment and recovery.

There are some areas where there can be a risk of duplication of effort if we haven't clearly outlined the roles and functions of the bedside nurse, the nurse navigator, and the social worker. The navigator needs to be well versed on what resources are available to tap into within her institution as well as within her community. For instance, there may be a social worker to help get the patient qualified for medical assistance while in another setting, there may not be a social worker and the nurse navigator may have to get involved with that aspect of care.

For a patient with cancer, there may be a surgical oncology nurse, a medical oncology nurse, and a radiation oncology nurse who is directly involved with the delivery of treatment. The nurse navigator's role needs to dovetail with that of the other nurses involved. They have to communicate well with one another and work in a collaborative manner, not see each other as a competitor.

Why do you think there has been a greater recognition of the need for nurse navigators in recent years?

Our healthcare delivery system, particularly in the area of cancer care, is incredibly fragmented. A patient may have surgery in one facility, chemotherapy in another, and radiation in yet another facility. Someone needs to help coordinate that and make sure that there is continuity of care and that a patient doesn't drop through the cracks or have long delays between one treatment regimen and another. I also think that the need for navigation has further intensified in the past 2 years because of our economy. It is becoming commonplace for a patient to be in the midst of her treatment when she loses her job and her health insurance. She is then in need of other resources to carry her through to complete her treatment.

Where can a nurse who is interested in becoming a nurse navigator learn more about the profession?

There are several opportunities. One is through the Academy of Oncology Nurse Navigators (AONN), which has a great website (www.aonnonline.org) that enables individuals to network with one another and learn from one another (see sidebar). The National Consortium of Breast Centers (NCBC) (www.breastcare.org) offers a certification program specifically for breast health and breast cancer navigators in various areas of the country as well as at their national meeting annually. They too provide navigators with ways to network with one another. A great deal of the training has to be on the job because, as I mentioned, no two facilities function in the same way. There is some basic knowledge though that nurse navigators need to have. For instance, they have to be intimately familiar with the diagnosis and treatment of the type of cancer that they are going to be navigating patients through. In addition, they need to have a very clear understanding of what it is like to travel through the patient experience. We have a tendency to assume that we know how a patient reaches our door, how they come in for a mammogram, what happens after that, and such. I

AONN™ Academy of Oncology Nurse Navigators

Your Voice Is Important

The Academy of Oncology Nurse Navigators (AONN) is a national specialty organization dedicated to improving patient care and quality of life by defining, enhancing, and promoting the role of oncology nurse navigators for patients and their families, as well as cancer centers, hospitals, and community practices. This fast-growing, grassroots organization, comprised of nurse navigators from a variety of clinical settings and disease states, strives to increase the role of and access to oncology nurse navigators, so that patients may benefit from their guidance and insight. AONN firmly believes that nurse navigators are critical to each patient's personal advocacy as he or she manages the complexities of the cancer care treatment continuum, including survivorship programs.

To help practicing navigators and those working to start up navigation programs, AONN's website (www.aonnonline.org) provides educational activities (including free CEUs for members), resources for patient education and grant opportunities, and social networking. This website has been specially designed to give all nurses a voice. AONN's online community provides a forum to exchange ideas with other oncology nurse navigators, oncology nurses, practice managers, patient care coordinators, and nursing administrators. In addition, through regular blog postings, members of the leadership council—both nurse navigators and non-nurse thought leaders in navigation—offer their insights on topics relevant to their clinical practice.

To raise awareness of the importance of certification for breast nurse navigators, AONN has partnered with the National Consortium of Breast Centers (NCBC). NCBC's Clinical Breast Examiner certification validates certificants' skill set and recognizes professionals who advance beyond basic knowledge in a field of specialty. To this end, AONN also advocates for certification of nurse navigators in other specialties within oncology.

Lung Cancer

Maintenance Pemetrexed Therapy Extends Survival in NSCLC

ORLANDO—Pemetrexed as maintenance therapy for patients with advanced non–small-cell lung cancer (NSCLC) led to an improvement in overall and progression-free survival (PFS) in patients enrolled in an international phase 3 trial.

Lead author Chandra Belani, MD, deputy director of the Penn State Cancer Institute, Hershey, Pennsylvania, said, "This is the first randomized, double-blind, placebo-controlled study to show the benefit of pemetrexed in the maintenance setting after initial therapy." He further predicted that the findings could "change the standard of care" and lead to a new treatment paradigm.

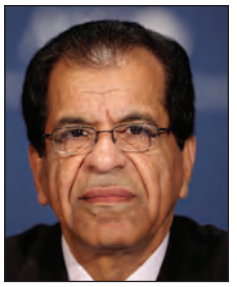
The phase 3 study included patients with advanced or metastatic (stage IIIB or IV) NSCLC that had progressed after four cycles of platinum-based chemotherapy. Investigators randomized 441 patients to treatment with pemetrexed 500 mg/m^2 every 3 weeks until further disease progression and 222 patients to placebo.

Overall survival was 13.4 months for the pemetrexed maintenance group compared with 10.6 months for the placebo group, representing a 21% reduction in risk (P = .012). Median PFS was 4.0 and 2.0 months, respectively, for a 40% reduction in risk with pemetrexed (P <.00001). Clinical benefit was attained by 51.7% and 33.3%, respectively (P <.001).

PFS was 15.5 months with pemetrexed, compared with 10.3 months with placebo.

Nonsquamous histology achieved benefit from pemetrexed

Benefit from pemetrexed maintenance was limited to patients with nonsquamous histology, as has been shown in previous trials of this agent, Belani said. For the nonsquamous histology group, PFS was 15.5 months with pemetrexed, compared with 10.3 months with placebo, for a 30% reduction in risk (P = .002). In those with squamous histology, PFS was similar at 9.9 and 10.8 months, respectively.


Chandra Belani, MD

Maintenance pemetrexed was relatively well tolerated, with 5% of patients requiring dose reductions. Pemetrexed-treated patients had more grade 3 and 4 neutropenia (3% vs 0%) and fatigue (5% vs 1%), Belani said.

After discontinuing the study, 67% of the placebo group received additional treatment, although only 19% got pemetrexed. Some NSCLC specialists believe that had more of these patients received pemetrexed at some point, the benefit for maintenance therapy may have been less.

Nasser Hanna, MD, of Indiana University, Indianapolis, discussed the presentation at the oral session. He noted that the use of pemetrexed did increase PFS, but he would like to see more data to determine whether overall survival is also increased. Although maintenance therapy in metastatic NSCLC may be preferable in some patients, he said, it is not a good idea for all patients.

"I will individualize my care," Hanna said. "Patients with more indolent disease or those with a strong response to treatment may be able to take treatment holidays. In these cases, you need close follow-up to avoid losing the opportunity to re-treat them effectively." ●

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

—Caroline Helwick

NURSE NAVIGATORS

Important Role in Oncology Care

coach people to assume nothing and advise them to follow one patient all the way through today and another patient tomorrow. I mean to follow the patient from being contacted to come in for a screening mammogram or coming in on her own and being by her side all the way through. You will identify barriers and issues that should result in performance improvement initiatives. It could be something as simple as making sure her phone number is correct in your database.

Another thing to look at is how long does it take to move from step A to step B to step C, and is that the ideal spacing or is there something to be improved regarding that? At our breast center, for example, we found that for a patient with breast cancer, there could be delays between appointments with the surgical oncologist, medical oncologist, and radiation oncologist. So now when we schedule the patients for surgery, we automatically contact the medical oncology office and schedule an appointment there as well. We carved off 3 weeks of waiting time and that reduced the patient's anxiety. It's fascinating when you stop and say let's assume nothing, let's step back and walk along with this patient and actually chart our current process to find what can we can do to deliver better care.

If a hospital or a clinic is interested in establishing a nurse navigator program, how can they get started?

One thing they can do is certainly to take advantage of the networking opportunities AONN and NCBC offer. You can learn from others by taking advantage of networking opportunities and trying to see how the navigation process works at an institution that is similar to yours. I have a book coming out in November called *Becoming a Breast Cancer Nurse Navigator* [Jones & Bartlett Publishing] that can serve as a guide for individuals interested in establishing a program.

What impact do you hope AONN will have on nurse navigation?

I'm hoping that it will provide a voice for nurses in this specialty, particularly recognizing that it is a new specialty and is still experiencing some growing pains. I think that it instills a sense of pride when you realize you are not the only one out there doing this type of work. I also feel confident that it will provide a way for performance improvement initiatives to take place. If a nurse navigator is just embarking on navigation at a particular cancer center, she will be able to network with others who specialize in that type of cancer and have already established a program.

An area that hasn't yet been explored but I am anticipating that it will be in the coming year regarding navigation is survivorship care navigation. We're anticipating a shortage of oncology specialists across the United States and yet we certainly aren't having any reduction in the number of individuals diagnosed with cancer. It is projected by the year 2020, there will be a 48% shortage of oncology specialists in the United States. At a minimum, that means that patients will no longer be able to be followed long term by the oncology team that took care of them. When patients finish their treatment, they are going to need to step out of that chair to make room for a newly diagnosed cancer patient. And yet we need to ensure that their long-term follow-up needs are being met. I anticipate that there will be a role for nurse navigators as we make this cancer paradigm shift away from follow-up care by the oncology specialist to the primary care physician. With an oncology nurse navigator as part of that team, I think we'll be able to do a better job of educating survivors about self-monitoring, what screening is needed, what symptoms to look for, and the importance of adhering to therapy now that they are no longer being closely monitored by the oncologist who initially prescribed it.

How do you see the profession and role of nurse navigators evolving in the next few years?

I think that it is going to increase in number as well as responsibility. We still have a bedside nursing shortage, so depending on the patient care setting, nurse navigators may very well have more responsibility associated with patient education due to time constraints that bedside nurses have in the clinic setting as well as in the inpatient setting. The need for coordination of care is going to continue to increase, and as we continue to have fragmentation of care, somebody has to be the glue that holds the treatment plan together. ●

—Karen Rosenberg

Newly Approved Pralatrexate

Continued from cover

points. The most common side effects in the clinical trial were mucous membrane inflammation, nausea, fatigue, and lowered levels of platelets.

T-cell lymphomas are a group of uncommon, biologically diverse hematologic malignancies comprising about 10% to 15% of all non-Hodgkin's lymphomas in North America.[1] Historically, PTCL patients have had a very poor outcome with conventional chemotherapy. Conventional chemotherapy treatments in PTCL patients have not been effective, and there were no pharmaceutical agents approved for use in the treatment of either first-line or relapsed or refractory PTCL. Overall 5-year survival is only about 25% after first-line therapy, and most patients relapse or become refractory after their initial combination chemotherapy.

Pralatrexate, designed to look like the natural B vitamin folic acid, inhibits DNA synthesis in tumor cells. The drug is designed to selectively accumulate in tumor cells, after which it induces apoptosis in the cancer cells. Pralatrexate is a novel folate analog designed to have high affinity for the reduced folate carrier, exhibiting improved internalization and efficacy over other aminopterin derivatives; it successfully disrupts DNA synthesis in tumor cells. In the trial, the most common grade 3/4 adverse events were thrombocytopenia, which was observed in 32% of patients; mucosal inflammation in 21%; neutropenia in 20%; and anemia in 17%.

Pralatrexate could change the natural history of PTCL

"Until now, these patients could only expect to survive for weeks to a few months," according to Owen A. O'Connor, MD, PhD, director of the Lymphoid Development and Malignancy Program, chief of the Lymphoma Service at the Herbert Irving Comprehensive Cancer Center at New York-Presbyterian Hospital/Columbia University Medical Center, and principal investigator and international study chair of the PROPEL [Pralatrexate in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma] trial, told *The Oncology Nurse*. "This study has shown us that it may now be possible to extend this benefit well over 9 months. I consider this to be spectacular, especially given the treatment-resistant nature of the disease in this study population. This drug could change the natural history of this PTCL, and hopefully put us on a path to cure more and more of these T-cell lymphoma patients every year."

Furthermore, he said, several patients who did not respond to chemotherapy but responded to pralatrexate became eligible for definitive and potentially curable bone marrow transplants. "If this holds up, it could be another significant benefit of pralatrexate."

For many patients in PROPEL, pralatrexate effectively did what conventional therapy could not—achieve a remission of the patient's lymphoma. "For some patients, this now means they may become eligible for autologous or allogeneic hematopoietic transplantation," O'Connor explained. "Performing a bone marrow transplant on patients in remission opens the door for curative therapy; for those with relapsed disease, pralatrexate allows patients to be bridged to a transplant, which has been definitive and curative in several patients."

When asked how he managed to assemble such a relatively large patient population for the PTCL study when it is a relatively rare cancer with 7100 cases annually, O'Connor said it was an international collaborative effort: "I tapped friends from around the world who have experience in this rare T-cell disease. I went to major international referral centers in different parts of the world; in this case, I went to friends in Italy, France, England, Canada. We brought everyone together for the benefit of the patients we are trying to help. Everyone was enthusiastic about being involved; it was a real team effort."

PROPEL took all comers

PROPEL took all enrollees, even those whose prognosis was exceedingly grim. O'Connor, who sees patients at

Newly Approved Pralatrexate

New York-Presbyterian Hospital/Columbia University Medical Center, stressed that the PROPEL trial is of particular significance because this study group was not limited in the number of prior chemotherapy treatments they could have received. Eligibility criteria included the requirement that the patient had recovered from the toxic effects of prior therapy. Patients treated with monoclonal antibody therapy were enrolled regardless of the timeframe of treatment if they had progression of disease (ClinicalTrials.gov Identifier: NCT00364923).

O'Connor said every enrollee had a reasonable chance of achieving remission: "Our patient population had no limit on the number of prior chemotherapy treatments; most of them were refractory to their prior line of chemotherapy, and, when you look at our response rate, the median number of prior therapies was three with a range of one to 12—that's a very high number."

He noted that he and his colleagues intentionally selected patients who had had poor outcomes with conventional chemotherapy: "The fact that there was no limit of prior chemotherapy is very unusual in registration-directed clinical trials. Most studies state, 'No more than two prior lines of treatment,' so many trials don't want patients that have already failed twice. And if you go back to our patient population, those patients who never responded to chemotherapy, the median number was three; one of four patients never responded to any chemotherapy program; 20 of those responded to pralatrexate. That shows you that pralatrexate works in a way that is unique and distinctly different from our conventional chemotherapy."

O'Connor continued: "If you look at the patients who were refractory to their prior line of chemotherapy, 53% of patients on PROPEL did not respond to the chemotherapy regimen immediately prior to receiving pralatrexate, whereas 25% of patients on PROPEL never responded to any chemotherapy regimen. One other piece of information is the duration of response—9.5 months is the median duration of response. I consider this to be an exciting feature of this trial; most new drugs in this disease are looking for overall response rates of 20% with a duration response of 2 to 3 months."

Combination regimens being studied

Allos Therapeutics has agreed to undertake additional clinical studies to further verify and describe the clinical benefit of pralatrexate in patients with T-cell lymphoma. O'Connor, said that it was the encouraging data from PROPEL that provided substantial evidence for expanding the current promising results into new disease-management strategies with a variety of combined biological drug therapies. "In this study, pralatrexate was given alone. Now we're working on combining it with a number of other drugs; right now it almost doesn't matter what drug you combine it with, because most of the ones we have tested have shown mathematical synergy when combined with pralatrexate. We're doing a phase 1/2 study to figure out how to best combine pralatrexate and gemcitabine [ClinicalTrials.gov Identifier: NCT00481871], and we will soon begin a study with pralatrexate and bortezomib in a phase 1 trial."

He said: "We need to find new ways to get patients into remission, and, to do that, we need to look at unique drugs. If we're at 27% by itself with pralatrexate, and if we combine it with bortezomib or gemcitabine, or the histone deacetylase inhibitors, we can possibly get up to 70%; each of these classes of drugs alone produces response rates of about 20% to 30% in patients with T-cell lymphoma, so conceivably, we could have 30% increases to 60%, which increases to a 90% response." He summed it up, "At that point, we would be changing the natural history of a challenging disease." ●

Reference

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—*Kristina Rebelo*

Pediatric Cancers

Experimental Immunotherapy Increases Overall Survival in Children with Neuroblastoma

Combining a chimeric antibody known as ch14.18 with interleukin-2 (IL-2) or granulocyte macrophage colony-stimulating factor (GM-CSF) and then adding the vaccine to standard therapy improves overall survival by 20% and reduces the risk of relapse when compared with standard therapy alone for children with high-risk neuroblastoma, according to results from a phase 3 trial presented at the annual meeting of the American Society of Clinical Oncology.

In a statement, coauthor John M. Maris, MD, The Children's Hospital of Philadelphia, reported that this is the first substantial increase in cure rate for neuroblastoma for more than a decade. "This experimental immunotherapy is poised to become part of the new standard of care for children with the aggressive form of neuroblastoma."

Lead investigator Alice L. Yu, MD, PhD, University of California and UCSD Moores Cancer Center, San Diego, presented the study results on behalf of the Children's Oncology Group. "Even though we treat neuroblastoma with aggressive therapy, it often returns, and only 30% of patients survive," said Yu.

In this study, 226 newly diagnosed high-risk neuroblastoma patients (who had already gone through induction chemotherapy, surgery, and stem-cell transplant) received a standard treatment of 13-cis-retinoic acid for six cycles, and of those, 113 patients also received five concomitant cycles of the ch14.18 antibody combined with GM-CSF or IL-2 in alternating cycles.

With a median follow-up of 2.1 years, event-free survival for the vaccine group was 66% compared with 46% for the standard treatment group (P = .01155). "This means these patients were 20% more likely to be alive without any sign of cancer after 2 years," Yu explained.

Overall survival was also significantly higher at 86% for patients treated with the antibody vaccine and 75% for those treated with standard care only (P = .0223).

Subgroup analysis of stage IV patients older than 1 year (n = 179) showed significantly higher event-free survival for the vaccine group at 63% compared with 42% of patients in the standard-care group (P = .0155), and a trend for higher overall survival at 84% versus 76% (P = .1006).

However, the vaccine-treated patients also experienced grade 3 pain (21%), vascular leak syndrome (7.3%), and allergic reactions (7.2%, which appeared to occur more frequently in the courses containing IL-2). "Overall, the immunotherapy was associated with more toxicities," Yu said. "But they were usually controllable and reversible."

She concluded, "This is the first clinical trial to document that combining an anticancer antibody with cytokines is an effective anticancer therapy. This is also the first time that an antibody targeting a glycolipid is shown to be effective for immunotherapy of cancer." ●

—*DB*

Breakthrough cancer pain

Closing the Gap by Opening the Dialogue

Although breakthrough cancer pain is becoming more widely recognized among healthcare professionals as a serious healthcare problem, there is still a gap between *identifying* it and actually *treating* it. This gap may be due partly to the variable and complicated nature of breakthrough cancer pain itself. But, more likely, this gap can be attributed to the limited dialogue that exists between the patient and the clinician.

Patient-related barriers to the conversation

Identifying and addressing the patient-related barriers to the dialogue about pain and talking about them *proactively* with patients is a positive step toward effectively managing breakthrough cancer pain. In actual clinical practice, translating a patient's description of various breakthrough cancer pain episodes—often described as "burning, aching, sharp, searing, throbbing, excruciating, relentless, or intolerable"[1,2]—into effective pain management can be challenging. It is a process that requires an open dialogue.

Barriers to the dialogue may manifest themselves in a number of ways. For instance, patients may fail to report breakthrough cancer pain to their healthcare provider for emotional or personal reasons and do not want to complain or bother the doctor.[1,3]

Some patients believe that an admission of pain indicates a worsening of their disease.[1] Other patients may be reluctant to distract the physician from treating the cancer.[1] Many patients have a fear of drug addiction and do not want to be thought of as addicts.[2] They are afraid to use opioids,[1,3] often failing to fill prescriptions. Concern about unmanageable side effects—such as mental confusion and analgesic addiction—may be an issue for some patients.[4] Also, some patients may be unable to assess pain levels or understand treatment regimens.

Most patients and caregivers do not understand the difference between *persistent* and *breakthrough* cancer pain or the difference between the types of medications used to treat them.[5] This lack of knowledge causes a disconnect that can influence the way a patient takes pain medication.[5] For example, a patient with chronic pain may decide not to take extra medicine during episodes of increased pain (breakthrough cancer pain) because he/she is concerned about the number of pills taken per day.[5]

One survey of 40 patients with terminal cancer found that 60% believed that being given drugs for pain was harmful to them and that they should refrain from taking such therapy too often.[3]

Supportive Care

5-FU Overdose: Antidote Becomes Available

ORLANDO—Overexposure to 5-fluorouracil (5-FU) has been a safety concern in oncology. Until recently, there was no way to reverse its potentially lethal adverse effects, but now a novel antidote that has been granted orphan drug status by the US Food and Drug Administration (FDA) has been shown to be lifesaving.

At the 2009 annual meeting of the American Society of Clinical Oncology, investigators from Wellstat Therapeutics Corporation (Gaithersburg, MD) reported success with the orally administered agent vistonuridine as an antidote to 5-FU overdose. The study, which involved 17 patients, was reported by Reid von Borstel, PhD, vice president of discovery research at Wellstat Therapeutics, the company that developed vistonuridine.

Vistonuridine is a prodrug of uridine, a direct biochemical antagonist of 5-FU toxicity. Uridine nucleotides dilute intracellular fluorouridine nucleotides derived from 5-FU, reducing their lethal incorporation into RNA.

According to the investigators, overexposure to 5-FU typically occurs for one of three reasons:

- The drug's narrow therapeutic index
- Individual genetic differences that cause some patients to metabolize the agent more quickly than most
- Miscalculation of the proper dose by administering staff.

A doubling of the dose or the infusion rate of 5-FU is often fatal, the investigators noted. Some 275,000 cancer patients in the United States receive 5-FU annually, and approximately 3% of them develop serious toxic reactions, which result in death for more than 1300 persons (NIH. *Fed Regist*. 2008; 73(129):38233).

Some 275,000 cancer patients in the United States receive 5-FU annually, and approximately 3% of them develop serious toxic reactions.

Although most cases of 5-FU overdose may not be publicly disclosed (as they may be due to medication error, a sensitive area), von Borstel and colleagues uncovered 11 cases in the medical literature, all of which were treated solely with best supportive care and all of which resulted in death.

They used these cases as comparators for the 17 patients who suffered overdoses but received vistonuridine in their study. The total dose of 5-FU ranged from 2940 mg, given over 17 hours in one patient, to 8960 mg, infused over 4.5 hours in another.

Wellstat was contacted by physicians of patients who had received 5-FU overdoses, mostly due to infusion pump errors. Permission for the drug's emergency use was obtained from the FDA, and vistonuridine was immediately flown or couriered to the clinics to be administered as soon as possible, generally 8 to 96 hours after overdose.

In all 17 cases, the patients recovered, including the 14 patients whose overdose was severe enough that the expected outcome was death, von Borstel reported.

The company is continuing its discussion with the FDA and with the European Medicines Agency, which also approved orphan drug designation, to obtain marketing approval. ●

—Caroline Helwick

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Prediction and Promise: *KRAS* and Colorectal Cancer

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LEARNING OBJECTIVES

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

- Explain the rationale for studying the effect of *KRAS* mutations in patients with metastatic colorectal cancer
- Discuss how *KRAS* mutations affect response to epidermal growth factor receptor (EGFR) inhibitor therapy in patients with metastatic colorectal cancer
- Describe common toxicities associated with use of anti-EGFR monoclonal antibodies and measures that can be taken to prevent and manage them
- Explain how use of biomarkers such as *KRAS* mutations to select therapy can lead to more cost-effective treatment of patients with cancer

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.

Cancer remains a major cause of death and disability in the developed world. As we enter the new millennium, the promise of improved cancer biology knowledge leading to new cancer treatments is being realized. We want to be able to offer these breakthrough treatments to patients who will benefit from them. Moreover, we would like to avoid initiating therapy in patients who have little chance of responding, and hence eliminate the toxicity of ineffective therapy and enable other treatment approaches to be pursued. Up until recently, however, there were no such predictors of response and benefit to guide our management approach to advanced colorectal cancer. Chemotherapy drugs with or without bevacizumab were tried and changed when treatment failure was observed. The results of the CO.17 trial have helped to change the treatment paradigm for metastatic colorectal cancer when using monoclonal antibodies that target the epidermal growth factor receptor (EGFR).[1]

Why did we look at *KRAS*?

Study CO.17 was initiated by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) in collaboration with the Australasian Gastro-Intestinal Trials Group (AGITG). This multicenter, prospective, open-label, randomized, phase 3 trial compared cetuximab plus best supportive care (BSC) with BSC alone in patients with pretreated metastatic colorectal carcinoma.[2] All the patients had received previous chemotherapy, and the treating physician considered that further chemotherapy would not help the patient. The only remaining standard therapy for patients entering this study, as recommended by the investigator, was BSC. Patients in the cetuximab arm received the agent as a once-per-week intravenous infusion.

The trial demonstrated that cetuximab when used as a single agent improves overall survival and prolongs progression-free survival in patients with colorectal cancer after failure of chemotherapy, but the majority of patients did not respond to cetuximab in this setting, with more than 50% of patients showing disease progression at the time of the first disease-response assessment.[2]

Cetuximab is a monoclonal antibody that binds to the EGFR with high affinity and inhibits the subsequent activation of downstream signaling pathways.[3] Kirsten rat sarcoma (*KRAS*), a small protein downstream of EGFR, is an essential component of the EGFR signaling cascade and may represent a bottleneck in the pathway.[4] Mutations in the *KRAS* gene can lead to constitutive activation of the pathway, and this may render inhibitors of components of the cascade upstream of *KRAS*

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ineffective. *KRAS* mutations, therefore, may predict for lack of efficacy of inhibitors that target the EGFR.[5] *KRAS* gene mutations occur early in the stages of carcinogenesis, as the colorectal adenoma progresses to develop into a carcinoma.[6] *KRAS* mutations are found in 30% to 50% of colorectal cancers.[7-10]

Examination of tumor tissue is crucial

For the current study, colorectal cancer tumor samples were collected from 394 patients involved in the CO.17 trial, representing 69% of all the patients in that trial. Mutation analysis for the *KRAS* gene was performed by direct gene sequencing to examine the tumor DNA in detail and look specifically at the DNA that codes for the *KRAS* gene. We effectively divided the tumor samples into two groups, those that exhibited *KRAS* mutations and those that did not. *KRAS* genes without mutations are called "wild type." We found that 42% of the tumor samples examined exhibited mutations of the *KRAS* gene, and this frequency is in keeping with previously published reports. We then set out to see whether *KRAS* mutation status was associated with differences in patient outcome.

The results: *KRAS* does matter

We observed a significant difference in survival times, but only for one of the *KRAS* groups. Overall survival was almost doubled for patients treated with cetuximab if the tumor did not have a *KRAS* mutation (ie, the *KRAS* wild-type subgroup). In the *KRAS* wild-type subgroup, median survival was 9.5 months in those receiving cetuximab and 4.8 months with BSC alone (Figure). Similarly, progression-free survival was also prolonged with cetuximab therapy in patients with *KRAS* wild-type tumors (3.7 months vs 1.9 months). In contrast, the survival time was not prolonged with cetuximab treatment in patients whose tumors had *KRAS* mutations. For those patients, median survival was the same in the cetuximab-treated and BSC arms, 4.5 and 4.6 months, respectively. Progression-free survival was also the same in the two arms for patients with *KRAS*-mutant tumors. *KRAS* mutation status was found to be correlated with overall survival, progression-free survival, and radiologic response. Quality-of-life analysis also demonstrated that patients with *KRAS* wild-type tumors derived the greatest benefit.

Overall, the benefit obtained with cetuximab in the setting of advanced colorectal cancer previously treated with chemotherapy was isolated to patients with tumors that do not exhibit *KRAS* gene mutations. No benefit was observed from using cetuximab in patients whose tumors had *KRAS* mutations. This correlation of *KRAS* mutation status and treatment effect has also been observed in other published retrospective series.[10-13]

Is *KRAS* also a prognostic factor?

The presence of a *KRAS* mutation may predispose to more aggressive biological behavior of the cancer, but the prognostic significance of *KRAS* mutations has varied in reported series.[7-9,14,15] In our study, we were able to examine the survival of patients who did not receive any cancer treatment, because these patients were in the BSC arm. In this way, we could examine the impact of *KRAS* on survival without having to consider a possible effect of treatment. We did not observe that the presence of a *KRAS* mutation predicts for a more aggressive cancer and a poorer prognosis.

We found no difference in the survival of patients according to *KRAS* mutation status in the BSC group. Median survival was 4.6 months in patients with *KRAS*-mutant tumors on BSC and 4.8 months in those with *KRAS* wild-type tumors on BSC, with 1-year survival of 19.6% and 20.1%, respectively. This analysis provides the best assessment of the influence of *KRAS* mutation status on survival without the effect of another variable such as treatment with cetuximab.

Where to now?

Although *KRAS* mutations may represent a common genetic aberration involved in cancer development, other gene mutations can also lead to unrestricted cancer cell growth. Some of these are already being examined, including loss of *PTEN* activity,[16] gene expression of the EGFR ligands amphiregulin and epiregulin,[17] and *PI3KCA* mutations.[18]

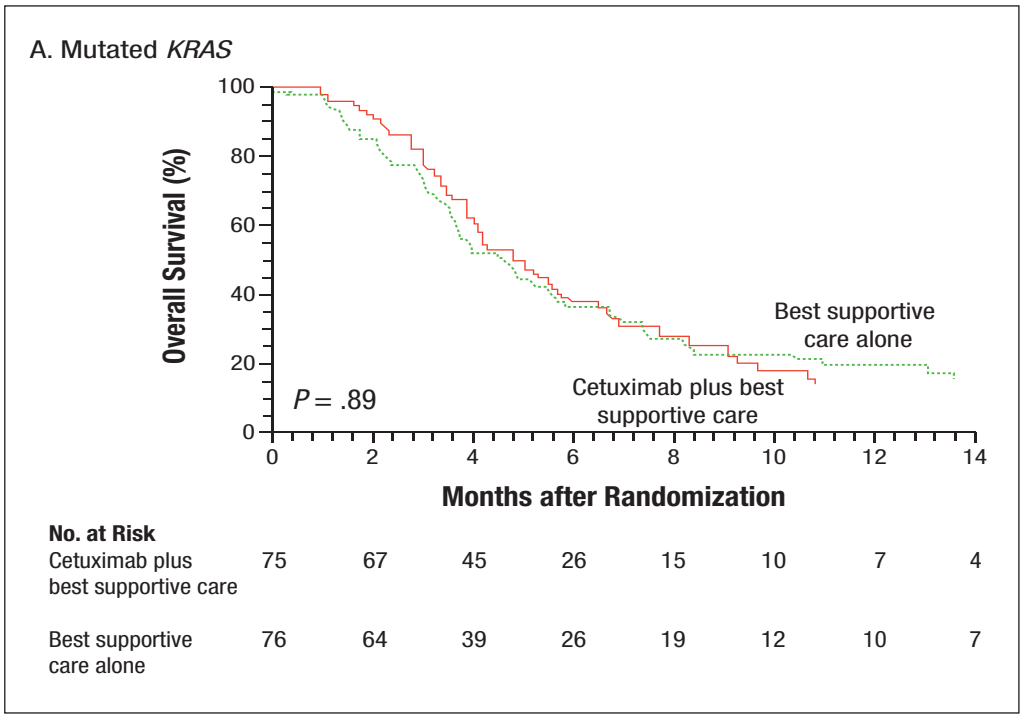
Over the past decade, there has been a paradigm shift in the way we manage patients with advanced colorectal cancer. Multiagent chemotherapy and multiple lines of therapy are now part of optimal treatment strategies. Antiangiogenic therapy has contributed further to improving the outcome of such patients, particularly in progression-free survival, with an associated prolongation of overall survival. The benefit of antiangiogenic therapy has been observed when bevacizumab is used as part of either first- or second-line therapy. EGFR-directed therapy, particularly using cetuximab and panitumumab, has also prolonged survival and progression-free survival, but this prolongation is restricted to patients with *KRAS* wild-type tumors.

In the future, cost-benefit analysis may become a major factor in deciding on wider availability of these agents. Cetuximab is a relatively expensive pharmacologic therapy. The cost-effectiveness of this treatment approach improves when the treatment can be delivered to those patients with a higher chance of benefiting. The major challenge is the identification of appropriate predictors of response to these drugs. Low response rates, short survival times, and relatively expensive new drugs have provided an understandable impetus to discover predictors of benefit from therapy. Avoiding therapy in patients who have little chance of responding can help to eliminate toxicity of ineffective therapy and allow other treatment approaches to be pursued.

The results of the CO.17 study have identified a biomarker that can effectively exclude a significant proportion of patients with colorectal cancer, approximately 40% with tumors that have *KRAS* mutations, from a therapy

Continued on page 28

Figure. Kaplan-Meier Curves for Overall Survival According to Treatment



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Continued from page 27

that has very little prospect of providing a benefit. An accurate and reliable biomarker that allows selection of a subpopulation of patients with advanced colorectal cancer who will benefit from new therapies represents a significant advance in the clinical management of this disease. *KRAS* has now been proved to be such a biomarker and should be routinely examined and used to select patients for treatment with EGFR-directed monoclonal antibodies such as cetuximab and panitumumab.

The ideal predictive biomarker is one that identifies all of those patients who will benefit from therapy before initiation of treatment, and excludes the patients who will not respond. Although *KRAS* has a significant predictive effect, it is not perfect. In our study, some patients with *KRAS* wild-type tumors did not respond to cetuximab and had rapid cancer progression. Other prognostic and predictive variables that can be reliably and easily measured need to be identified. ●

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COMMENTARY

KRAS and Colorectal Cancer: A Pharmacist's Perspective

BY **BETTY M. CHAN, PHARMD, BCOP**

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Recent advances with chemotherapeutic agents (ie, oxaliplatin, irinotecan) and targeted biologic agents (ie, anti–epidermal growth factor receptors [EGFRs] cetuximab, panitumumab; anti–vascular endothelial growth factor bevacizumab) have greatly expanded our treatment options for patients with colorectal cancer. Recent findings on use of Kirsten rat sarcoma (*KRAS*) mutational status to predict response to anti-EGFR monoclonal antibodies further demonstrated our need to streamline patient selection to those likely to derive the greatest benefit (ie, those with *KRAS* wild-type tumors only) from treatment so as to minimize treatment toxicities and provide cost-effective treatment.

In the article by Karapetis, the author reported that results from the CO.17 trial have helped change the treatment paradigm for metastatic colorectal cancer. In the study, overall survival and progression-free survival were significantly improved in patients with *KRAS* wild-type tumors who received treatment with cetuximab compared with best supportive care.[1] In addition to the findings reported by Karapetis and colleagues, several other recent publications have reported greater improvement in response rates, progression-free survival, and overall survival when an anti-EGFR monoclonal antibody (ie, cetuximab or panitumumab) is used as monotherapy or in combination with chemotherapy agents in patients with advanced colorectal cancer who have *KRAS* wild-type tumors.[2-6]

Although treatment with an anti-EGFR monoclonal antibody (cetuximab or panitumumab) is much better tolerated by patients compared with chemotherapy, most patients receiving treatment do experience toxicities.[7,8] As with other monoclonal antibodies, infusion-related symptoms include fever, chills, urticaria, flushing, fatigue, headache, bronchospasm, dyspnea, angioedema, and hypotension. Incidence rates are higher in patients receiving cetuximab, a chimeric monoclonal antibody, than in those receiving panitumumab, a fully humanized IgG2 monoclonal antibody. Premedication is needed in patients before treatment with cetuximab because the incidence of infusion reactions is higher with the first infusion (40%-50% reported) than with subsequent infusions (<1%). Close monitoring for all infusions is recommended, however, to minimize infusion reactions and to provide supportive care if infusion reactions develop.[7,8]

Skin toxicity, although often considered a surrogate marker for clinical activity, is, nevertheless, another common toxicity associated with anti-EGFR monoclonal antibodies. Commonly observed skin toxicities include acneiform skin rash with papulopustular eruption on the face and upper trunk, dry skin with pustular eruptions, and pruritus. Management includes educating patients to avoid sun exposure, which may exacerbate skin reactions, and to apply a para-aminobenzoic acid-free sunscreen with a sun-protection factor of 15 or higher before sun exposure. Dosage adjustment may be necessary, depending on the severity of skin toxicity. Topical antibiotics with clindamycin or its derivatives (ie, clindamycin phosphate 1% gel for isolated lesions and clindamycin phosphate 1% lotion for scattered lesions) can be used for mild skin toxicity. For moderate-to-severe skin toxicity, systemic oral antibiotics (ie, minocycline or doxycycline 100 mg orally twice a day for 10-14 days) can be used. For dry skin, applying emollient twice a day may provide relief of symptoms. Pruritus can be managed with diphenhydramine or hydroxyzine 25 mg to 50 mg orally every 6 hours as needed.[9-12]

Electrolyte abnormalities such as hypomagnesemia and hypocalcemia have also been reported. Hypomagnesemia has been observed as early as 3 weeks into treatment with cetuximab.[13,14] Close monitoring of magnesium and calcium levels before treatment is recommended, providing electrolytes supplementation as needed.

Pulmonary toxicity including interstitial lung disease, although rare (<1%), has been reported with anti-EGFR monoclonal antibodies. Patients with acute-onset or worsening pulmonary symptoms (eg, increased cough, dyspnea, and pulmonary infiltrates) must be carefully monitored, and holding or discontinuing treatment may be necessary in patients with pulmonary toxicities.[7,8]

Generalized malaise and asthenia have been observed (with cetuximab more than panitumumab).[7,8] Paronychial inflammation and swelling of lateral nail folds of fingers and toes has also been reported in patients receiving treatment for a prolonged period of time. Management options include topical antibiotics or topical corticosteroids.[11,12]

Although toxicities associated with anti-EGFR monoclonal antibody therapy are generally mild and manageable, frequent assessment and close monitoring are still required to minimize toxicities and patient discomfort. Nurses and pharmacists can assist with the assessment and monitoring of these toxicities, and develop management guidelines in their institution for the treatment of skin toxicities and the management of hypomagnesemia.

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COMMENTARY

KRAS and Colorectal Cancer: A Nurse's Perspective

BY **SANDRA E. KURTIN, RN, MS, AOCN, ANP-C**
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The search for the silver bullet in cancer treatment has long been the elusive coup de grâce. We envision a time when treatments are selected based on clearly defined targets with little or no collateral damage. With the advent of molecular profiling and advanced tissue analysis, which can identify key components of signaling pathways, we are moving toward this future.

Signaling pathways are present in both normal and abnormal cellular function and provide attractive targets for manipulation of abnormal pathways. Inhibition of the epidermal growth factor receptor (EGFR) and its downstream pathways using targeted monoclonal antibodies has provided a unique treatment strategy in patients with colorectal cancer. EGFR upregulation is present in 25% to 80% of colorectal cancers, making it an attractive target.[1] Blocking EGFR pathways may interrupt the pathologic effects of EGFR overexpression, including cell cycle progression, apoptosis, angiogenesis, tumor cell motility, and metastasis.[2]

Recently, the role of the Ras/Raf/mitogen-activated protein kinase pathway has elucidated the critical role of the Ras oncogene in colorectal tumorigenesis and response to EGFR-inhibiting agents.[3] *KRAS*, an intracellular signal transducer, is the gene that codes for the Ras signaling pathway. Mutations in *KRAS* are present in approximately 40% of colorectal tumors, with a high concordance (90%) between primary and metastatic sites at the time of diagnosis.[4] *KRAS* mutations are thought to alter protein activity, leading to unregulated cellular proliferation and malignant transformation.[5] *KRAS* mutations in codon 12 and 13 have been extensively analyzed in phase 2 and 3 clinical trials using EGFR inhibitors either as monotherapy or in combination with other agents.[3,6-8] In all studies, patients with *KRAS* mutations did not derive benefit from treatment with EGFR-inhibiting monoclonal antibodies (cetuximab and panitumumab). Despite the retrospective and subset-analysis techniques used in the majority of these studies, the strength of the data has been largely undisputed by clinicians.

As a result of these studies, the American Society of Clinical Oncology (ASCO) issued a Provisional Clinical Opinion[7]: "Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations in a [Clinical Laboratory Improvement Amendments] CLIA-accredited laboratory, according to ASCO. If *KRAS* mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR antibody therapy as a part of their treatment." Importantly, the group did offer qualifications that *KRAS* mutational status has not been validated as a prognostic factor in the analyzed studies. *[Editor's note: On July 17, 2009, the US Food and Drug Administration approved class labeling changes to cetuximab and panitumumab, noting that these agents are not recommended for treatment of colorectal cancer with* KRAS *mutations in codons 12 and 13.]*

These findings have changed the treatment paradigm for colorectal cancer, mandating comprehensive and accurate tissue testing at the time of diagnosis for all newly diagnosed colorectal cancers, testing of existing tissue blocks for those who have recurrent or progressive disease when testing has not already been done, and effectively eliminating a treatment option for a large number of patients with metastatic disease who test positive for the *KRAS* mutation.

The mandate for clinicians and researchers is clear: We must work diligently to enroll patients in clinical trials that may provide new treatment options for this disease. Proactive and aggressive management of disease and treatment-related toxicities is essential to optimal clinical outcomes and necessary to avoid the elimination of future treatment options because of residual toxicities or secondary organ damage. This applies to effective management of EGFR inhibitor–associated toxicities for those patients who are fortunate enough to have *KRAS* wild-type tumors. Strategies for evaluation of treatment response and grading of toxicities will need to be refined to avoid premature discontinuation of therapies. Analysis of the sequencing of the seven commonly used US Food and Drug Administration–approved agents for this disease may be required to achieve optimal outcomes with the limited treatment options for metastatic colorectal cancer. Personalized medicine through molecularly driven treatment selection is definitely a double-edged sword.

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Oncology Drug Codes

Medications Used for the Treatment of Breast Cancer

The following sections include:

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

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

174 Malignant neoplasm of female breast
Use additional code to identify estrogen-receptor status (V86.0, V86.1)
Includes: breast (female)
connective tissue
soft parts
Paget's disease of:
breast
nipple
Excludes: skin of breast (172.5, 173.5)
174.0 Nipple and areola
174.1 Central portion
174.2 Upper inner quadrant
174.3 Lower inner quadrant
174.4 Upper outer quadrant
174.5 Lower outer quadrant
174.6 Axillary tail
174.8 Other specified sites of female breast
Ectopic sites
Inner breast
Lower breast
Malignant neoplasm of contiguous or overlapping sites of breast whose point of origin cannot be determined
Midline of breast
Outer breast
Upper breast
174.9 Breast (female), unspecified

175 Malignant neoplasm of male breast
Use additional code to identify estrogen-receptor status (V86.0, V86.1)
Excludes: skin of breast (172.5, 173.5)
175.0 Nipple and areola
175.9 Other and unspecified sites of male breast
Ectopic breast tissue, male

Generic (brand) name	HCPCS code: code description	FDA-approved for breast cancer	*NCCN Drugs & Biologics Compendium* off-label use for breast cancer	Current code price (AWP-based pricing), effective 10/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
anastrozole (Arimidex)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
anastrozole (Arimidex)	S0170: anastrozole, oral, 1 mg	?		$13.04	S0170: not payable by Medicare	N/A
bevacizumab (Avastin)	J9035: injection, bevacizumab, 10 mg	?		$68.75	$57.48	96413, 96415
capecitabine (Xeloda)	J8520: capecitabine, oral, 150 mg	?		$7.76	$5.79	N/A
capecitabine (Xeloda)	J8521: capecitabine, oral, 500 mg	?		$25.85	$19.09	N/A
carboplatin (Paraplatin)	J9045: injection, carboplatin, 50 mg		?	$85.10	$4.60	96409, 96413, 96415

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Generic (brand) name	HCPCS code: code description	FDA-approved for breast cancer	*NCCN Drugs & Biologics Compendium* off-label use for breast cancer	Current code price (AWP-based pricing), effective 10/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
cisplatin (Platinol AQ)	J9060: cisplatin, powder or solution, per 10 mg		?	$4.33	$2.07	96409, 96413, 96415
cisplatin (Platinol AQ)	J9062: cisplatin, 50 mg		?	$21.66	$10.34	96409, 96413, 96415
cyclophosphamide oral (Cytoxan)	J8530: cyclophosphamide, oral, 25 mg	?		$2.09	$0.81	N/A
cyclophosphamide injection (Cytoxan)	J9090: cyclophosphamide, 500 mg	?		$30.34	$21.51	96409, 96413, 96415
cyclophosphamide injection (Cytoxan)	J9091: cyclophosphamide, 1.0 g	?		$54.62	$43.03	96409, 96413, 96415
cyclophosphamide injection (Cytoxan)	J9092: cyclophosphamide, 2.0 g	?		$98.30	$86.06	96409, 96413, 96415
docetaxel (Taxotere)	J9170: injection, docetaxel, 20 mg	?		$456.53	$345.54	96413
doxorubicin HCl (Adriamycin)	J9000: injection, doxorubicin HCl, 10 mg	?		$13.20	$3.69	96409
doxorubicin HCl liposome (Doxil)	J9001: injection, doxorubicin HCl, all lipid formulations, 10 mg		?	$559.32	$459.18	96413
epirubicin (Ellence)	J9178: injection, epirubicin HCl, 2 mg	?		$8.16	$2.59	96409, 96413
estradiol (Estrace)	J8499[a]: prescription drug, oral, nonchemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
etoposide (Vepesid)	J8560: etoposide, oral, 50 mg		?	$47.64	$0.46	N/A
exemestane (Aromasin)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
exemestane (Aromasin)	S0156: exemestane, 25 mg	?		$12.38	S0156: not payable by Medicare	N/A
fluorouracil (Adrucil)	J9190: injection, fluorouracil, 500 mg	?		$3.30	$1.52	96409
fluoxymesterone (Androxy)	J8499[a]: prescription drug, oral, nonchemotherapeutic, not otherwise specified		?	NDC level pricing	NDC level pricing	N/A
fulvestrant (Faslodex)	J9395: injection, fulvestrant, 25 mg	?		$96.33	$82.18	96402
gemcitabine (Gemzar)	J9201: injection, gemcitabine HCl, 200 mg	?		$169.46	$141.77	96413
goserelin acetate (Zoladex 3.6 mg ONLY)	J9202: goserelin acetate implant, per 3.6 mg	?		$451.19	$196.73	96372, 96402
ixabepilone (Ixempra)	J9207: injection, ixabepilone, 1 mg	?		$73.76	$63.74	96413, 96415
lapatinib ditosylate (Tykerb)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
letrozole (Femara)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
leuprolide (Eligard, Lupron Depot)	J9217: leuprolide acetate (for depot suspension), 7.5 mg		?	$352.56	$214.57	96402
leuprolide (Lupron)	J9218: leuprolide acetate, per 1 mg		?	$27.44	$5.40	96402
megestrol (Megace)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A

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Generic (brand) name	HCPCS code: code description	FDA-approved for breast cancer	*NCCN Drugs & Biologics Compendium* off-label use for breast cancer	Current code price (AWP-based pricing), effective 10/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
megestrol (Megace)	S0179: megestrol acetate, oral, 20 mg	?		$0.66	S0179: not payable by Medicare	N/A
methotrexate	J8610: methotrexate, oral, 2.5 mg	?		$3.56	$0.12	N/A
methotrexate sodium	J9250: methotrexate sodium, 5 mg	?		$0.27	$0.21	96372, 96374, 96401, 96409, 96450
methotrexate sodium	J9260: methotrexate sodium, 50 mg	?		$2.73	$2.12	96372, 96374, 96401, 96409, 96450
paclitaxel (Abraxane)	J9264: injection, paclitaxel protein-bound particles, 1 mg	?		$10.97	$9.26	96413
paclitaxel (Taxol)	J9265: injection, paclitaxel, 30 mg	?		$19.89	$9.11	96413, 96415
prednisone	J7506: prednisone, oral, per 5 mg		?	$0.05	$0.04	N/A
tamoxifen (Nolvadex)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
tamoxifen (Nolvadex)	S0187: tamoxifen citrate, oral, 10 mg	?		$1.89	S0187: not payable by Medicare	N/A
testolactone (Teslac)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
thiotepa (Thiotepa)	J9340: injection, thiotepa, 15 mg	?		$138.00	$99.57	51720, 96409
toremifene citrate (Fareston)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified	?		NDC level pricing	NDC level pricing	N/A
trastuzumab (Herceptin)	J9355: injection, trastuzumab, 10 mg	?		$74.49	$64.73	96413, 96415
vinBLAStine	J9360: injection, vinblastine sulfate, 1 mg	?		$3.18	$0.96	96409
vinorelbine (Navelbine)	J9390: injection, vinorelbine tartrate, per 10 mg		?	$42.60	$12.18	96409

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

References

• *HCPCS Level II Expert, 2009* • *CPT 2009;* 2008 • *ICD-9-CM for Professionals Volumes 1 & 2*; 2009 • *The Drug Reimbursement Coding and Pricing Guide,* Vol 6, No 4; RJ Health Systems International LLC; 4th Quarter 2009 • FDA-approved indication (from products' prescribing information) • NCCN • National Cancer Institute • www.ReimbursementCodes.com powered by RJ Health Systems International, LLC, Wethersfield, Connecticut • CMS-Medicare allowable 4th Quarter 2009 (effective dates 10/1/09-12/31/09).

Prices listed herein are effective as of October 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.

Nursing Practice

APRN Regulations: Implications for Your Practice

SAN DIEGO—The executive director of Oncology Nursing Certification Corporation (ONCC) said the expanding role and capabilities of the Advanced Practice Registered Nurse (APRN) has made it all the more important that a uniform APRN regulation model be built across the United States and its territories to align the education, accreditation, certification, and licensure for all involved to ensure patient safety and access.

Cynthia A. Miller Murphy, RN, MSN, CAE, executive director, ONCC, reviewed current APRN topics in the advanced practice role for a group of nurses at the Scripps 6th Annual Oncology Nursing Advanced Practice: Innovation through Practice conference.

"The reason we regulate is so that people without competence aren't out there practicing," said Miller Murphy. "This is important because unprepared and incompetent individuals who practice pose risk of harm to the public."

Looking back, it was in 1995 that the ONCC first launched the first advanced practice certification examination for oncology nurses. The competencies of oncology clinical nurse specialists (OCNSs) and oncology nurse practitioners (ONPs) were tested. Around this time, Miller Murphy said, state boards of nursing started to tighten the reins of regulation on APRNs. "However, this did not result in consistent regulations across the states; the number of APRNs continued to expand both in terms of numbers and capabilities; yet each state continued to independently determine the roles and specialties that were recognized, the criteria for entry into advanced practice, and advanced scopes of practice."

Ten years later, the ONCC introduced role-specific certifications for both OCNSs and ONPs. Still, ONCC certification examinations continued to have widely disparate recognition by state boards of nursing. Miller Murphy said that all areas of APRNs were affected, including clinical nurse specialists, nurse practitioners, nurse anesthetists, and nurse midwives.

A relatively large number of APRNs specialize in oncology; however, a small number of graduate programs are specifically dedicated to the specialty.

No current uniform model of APRN regulation

Licensing boards, which are governed by state regulations and statutes, are the final arbiters of who is recognized to practice in a given sate, Miller Murphy said. These licensing boards develop the rules and regulations consistent with their state's nurse practice act, which has the force and effect of law. Each state independently determines the legal scope of practice for APRNs—the roles that are recognized, the criteria for entry into advanced practice, and the certification examinations accepted for entry-level competence assessment. Currently, however, there is no uniform model of regulation of APRNs across the states.

"There are very different and disparate requirements across the United States and territories," said Miller Murphy. "Some states, for instance, don't require a master's degree; some require certification and some do not; some require specific education and others do not. They also provide different privileges and scope of practice. Each state independently recognizes different roles—there's a huge variety in what they can do and in what privileges they have. This has created a significant barrier for APRNs to easily move from state to state and has decreased access to care for patients," Miller Murphy continued.

Still struggling to agree on an APRN definition, specialization, subspecialization, education, certification, and licensure, 32 organizations convened in 2004 and hatched a smaller group, Miller Murphy explained, which was charged with "envisioning a future model for APRN regulation by establishing a set of standards that protect the public, improve mobility, and improve access to safe, quality APRN care."

Final consensus

The final consensus document produced by the group was released in July 2008 and has been formally endorsed by the Oncology Nursing Society (ONS) and the ONCC Boards of Directors.

The specialty of oncology may serve as a prototype for the model, Miller Murphy noted. "A relatively large number of APRNs specialize in oncology; however, a small number of graduate programs are specifically dedicated to the specialty," she said.

Nursing's leading professional organizations produced a document that was the collaborative work of the APRN Consensus Work Group and the National Council of State Boards of Nursing APRN Committee (currently known as the APRN Joint Dialogue Group) that once and for all established guidelines for licensure, accreditation, certification, and education for all APRNs. The target date for complete implementation is December 31, 2015, although the model is slowly being phased in. Miller Murphy said a subgroup of the APRN Joint Dialogue Group, with representatives from each of these facets, has been formed to assure that these groups work together to implement the model.

In the APRN model of regulation, there are four roles:

- Certified Registered Nurse Anesthetist (CRNA)
- Certified Nurse Midwife (CNM)
- Clinical Nurse Specialist (CNS)
- Certified Nurse Practitioner (CNP).

There are also six population foci:

- Neonatal
- Pediatric
- Adult
- Family
- Women's health
- Psychiatric/mental health.

All APRNs will be required to attain education and certification in one of the roles and one of the population foci for regulatory purposes. Specialties, such as oncology, will not be part of the regulatory process. However, certification in a specialty is highly encouraged in the model and will be overseen by professional organizations and required in the workplace rather than by the regulatory bodies.

"ONS will also continue to offer continuing education programs to assist APRNs to attain and maintain the advanced practice knowledge and skills necessary to competently provide care to patients with cancer," Miller Murphy explained, "while ONCC will continue to administer certification examinations for oncology nurse practitioners and oncology clinical nurse specialists who are sound, reliable, valid, and representative of current practice."

According to Miller Murphy, a specific challenge in the area of oncology is a "need to demonstrate the value of specialty certification." Oncology APRNs must be encouraged to attain and demonstrate specialty competencies; and employers and others must be encouraged to require certification for specialty practice.

"We need to encourage employers to recognize the need for APRNs with specialty certification in the workplace—nurses will drive recognition," said Miller Murphy.

Existing certification

Miller Murphy said that anyone who is already credentialed and working will not have to meet new criteria for education or certification in the state where they are practicing. "Anyone already practicing will be grandfathered in." ●

—Kristina Rebelo

More Information

- **Consensus Model for APRN Regulation: Licensure, Accreditation, Certification & Education**
  www.nursingworld.org/DocumentVault/APRNs/ConsensusModelforAPRNRegulation.aspx
- **Oncology Nursing Society: Oncology Nurse Practitioner Competencies**
  www.ons.org/clinical/Professional/QualityCancer/documents/NPCompentencies.pdf
- **Oncology Nursing Society: Clinical Nurse Specialist Competencies**
  www.ons.org/clinical/professional/QualityCancer/documents/cnscomps.pdf

Did you **Know?**

Patients Want to Know about Costly Cancer Drugs

Ninety-one percent of respondents would want their doctor to tell them about an expensive anticancer drug if it could prolong survival by an additional 4 to 6 months, and 51% would be willing to pay for it, a survey of a random sample of the Australian general public showed. Of the 1255 respondents, 137 (11%) had a prior cancer diagnosis. Respondents were more willing to pay for an expensive drug if it could improve quality of life (71%) or if there was no effective standard treatment (76%). A previous survey of Australian oncologists found that up to 41% would not tell patients about new cancer treatments if they were not government-subsidized (Mileshkin L, et al. *J Clin Oncol.* 2009; Sep 28. Epub ahead of print).

The Patient's Voice

Ovarian Cancer National Alliance Works to Increase Awareness of Ovarian Cancer Patients' Needs, Concerns

Ovarian cancer, the deadliest of gynecologic cancers, is the fifth leading cause of cancer-related deaths among American women. The symptoms of ovarian cancer (Table) are subtle and nonspecific and are often not recognized by women or their physicians. When diagnosed early, nine out of 10 women will survive more than 5 years. But there is no reliable early detection test, and fewer than 20% of patients are diagnosed in the early stages before the disease has spread beyond the ovaries. As a result, the overall survival rate is only about 46%.

Table. Symptoms of Ovarian Cancer

- Bloating
- Pelvic or abdominal pain
- Difficulty eating or feeling full quickly
- Urinary symptoms (urgency or frequency)
- Additional symptoms may include fatigue, indigestion, back pain, pain with intercourse, constipation, and menstrual irregularities

Ovarian Cancer National Alliance

The Ovarian Cancer National Alliance (OCNA), a patient-led umbrella organization of 45 national, regional, and ovarian groups, was founded in 1997 "to conquer ovarian cancer and save women's lives." Chief executive officer Karen Kaplan, MPH, ScD, says, "Talking about it is the key. We have to raise awareness among women and the men who care about them."

Nurses, she said, are ovarian cancer patients' "secret weapon." She explained, "It is the nurses who have the first contact and ongoing contact with the patients. Nurses are the gatekeepers, the main communicators. Patients often feel more comfortable talking to a nurse, and often it is the nurse or physician assistant who alerts the physician to the possibility of an ovarian cancer diagnosis."

The alliance's activities fall into three broad areas:

Awareness: OCNA seeks to increase awareness of the symptoms of ovarian cancer and the importance of early recognition and treatment.

Education: OCNA serves as a resource for survivors and works to educate healthcare professionals about the diagnosis of ovarian cancer and the importance of referral to a gynecologic oncologist.

Advocacy: OCNA focuses on legislative issues of importance to the ovarian cancer community. It advocates at the federal and state level for (1) adequate funding for ovarian cancer research and awareness programs, and (2) legislation that will improve quality of life and access to care for cancer patients.

A central part of OCNA's educational efforts is its Survivors Teaching Students: Saving Women's Lives program, which is supported by the Entertainment Industry Foundation. In this program, ovarian cancer survivors of diverse backgrounds go into medical school classrooms to share their experiences with cancer diagnosis and treatment with third-year medical students during their gynecology rotation. The program has been expanded to include nurses, nurse practitioners, physician assistants, and residents.

The Oncology Nurse recently spoke with participants in the Survivors Teaching Students program.

Survivors share their stories

Five-year survivor

Annie, a 5-year survivor, was 40 years old when she was diagnosed with stage 2C ovarian cancer. She was first treated in an academic medical center and then at a comprehensive cancer center. Based on her experiences, she has become a firm believer in the importance of doctor-patient communication and the need to involve patients in decision making.

Her medical treatment was excellent, but she felt that communication between doctors and patients and between doctors in different specialties could be improved. "I find that when people are dissatisfied with their care, it often comes down to communication," she observed. At the academic medical center, she had a nurse who explained everything clearly and was the person to contact if she had any questions. At the comprehensive cancer center, however, "the lines of communication were not so clear." Although she understands the need to prioritize patients' calls, she said she sometimes felt that "you have to make your pitch to get attention, to get someone to call you back." She also noted that different practices and different departments have different ways of doing things, which can make it difficult to keep track of whom to contact in different practices. "Having one point person to go to would make life a lot easier," she said.

She also felt that patients with ovarian cancer were not referred to other services, such as pain management and nutrition, as readily as patients with other cancers. "It seems that referrals are not made quickly enough. You shouldn't have to wait 7 months for a referral for pain management," she said.

On the other hand, she felt her doctor was too quick to refer her to a social worker when she cried during an office visit. "He's a great doctor, a great explainer, and very patient with me, but he was uncomfortable with the strong emotions I was feeling. I don't expect everyone to hold my hand every time I fall apart, but at least he should be sensitive to it. Acknowledge it and then give me the referral."

Becoming involved in patient support and advocacy groups, such as the Ovarian Cancer National Alliance, has helped Annie cope with the ovarian cancer experience and overcome the isolation she felt when she was first diagnosed. Ovarian cancer survivors have unique needs she has found. "Not everyone gets their 5-year clean bill of health and not everyone will live happily ever after. A lot will have recurrences. There are a lot of survivorship issues, and I don't want us to be left out. We have a lot of the same needs and we have a lot of different needs as other survivors, but we are still survivors."

2.5-year survivor

Peg had an eye-opening encounter with Western medicine when she was diagnosed with stage 1 ovarian cancer just before her 60th birthday. She had no medical insurance, so, in addition to her medical issues, she had to learn to deal with the intricacies of getting coverage through county and state resources. "Most of my adult life, I turned to alternative healing," she said, and at first attributed the symptoms she was feeling to a recent fall. She was fortunate to find a surgeon who not only scheduled surgery immediately but also helped her get insurance and referred her to a gynecologic oncologist. "I have learned how important timely referral to a gynecologic oncologist is. Patients with ovarian cancer have better outcomes when they are treated by a specialist."

Peg says, "I was stressed into this Western medical world in about 6 months. Now I've become a strong advocate for ovarian cancer awareness." She helped launch the Survivors Teaching Students program at the University of California, San Diego and continues her efforts to raise awareness among the public and healthcare professionals. "Women tend to rationalize and delay seeking treatment. Women need to be empowered. The silence needs to be broken. Medical professionals need to think of ovarian cancer first instead of last. If a woman says there is something going on, believe her because we tend to listen to our bodies."

A lasting impression

Joanna Hofmann, RN, EdD, ANP/GNP-BC, a professor at the Hunter-Bellevue School of Nursing in New York, says that participating in the Survivors Teaching Students program was "an amazing experience" for her graduating nurse practitioner students. "Students remembered what they heard and kept getting information on their own afterward. Hearing the survivors' stories was a thousand times better than teaching with a case study…. I think it has made a lasting impression. It will work throughout their careers and will help a lot of people." ●

For more information about ovarian cancer and the Survivors Teaching Students program, go to the Ovarian Cancer National Alliance website, www.ovariancancer.org.

Recent FDA Approvals

- **MammoSite ML to Help Prevent Recurrences of Breast Cancer**

The US Food and Drug Administration (FDA) has approved a new version of the MammoSite system, the MammoSite ML (Hologic). MammoSite devices deliver radiation seeds to prevent recurrences of breast cancer. According to the company, the new version allows physicians to better target specific areas of tissue than the original version, allows therapists to treat patients who are not otherwise good candidates for radiation seeding, and is usable in more typical cases.

- **Zevalin for First-line Treatment of Follicular Non-Hodgkin's Lymphoma**

The FDA has approved an expanded label for Zevalin (Spectrum Pharmaceuticals) as part of first-line treatment of follicular non-Hodgkin's lymphoma. The label extends the agent's use to patients with previously untreated follicular non-Hodgkin's lymphoma who achieve a partial or complete response to first-line chemotherapy. This approval was based on data from the FIT Study presented at the 2008 annual meeting of the American Society of Hematology.

International Oncology News

Reports from International Meetings and Researchers

Renal Function Rapidly Worsens in Cancer Patients

MILAN—Researchers have documented a rapid deterioration in renal function in cancer patients, with an annual decrease in the glomerular filtration rate (GFR) exceeding 3.5 mL/min/1.73 m^2.

Nicolas Janus, MD, with the Pitié Salpêtrière Hospital in Paris, and colleagues conducted a study to examine the evolution of renal function in 4945 cancer patients seen at 19 centers throughout France.

In an earlier analysis, the group had reported a high prevalence of renal insufficiency in cancer patients.

In the present study, GFR measurements obtained every 6 months were reviewed over a 2-year period.

Results showed that the mean GFR decreased from 90.8 mL/min/1.73 m^2 to 83.7 mL/min/1.73 m^2 over the follow-up period. The prevalence of renal insufficiency increased, with 62.9% and 17.5% of patients having a GFR <90 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2, respectively, at the end of follow-up.

Of 641 patients who had their serum creatinine level determined at the start and end of follow-up, 41.6% of those with an initial GFR >90 mL/min/1.73 m^2 had a GFR <90 mL/min/1.73 m^2 after 2 years.

Janus said that the results provide a strong rationale for close monitoring of renal function in cancer patients, with GFR measured at least every 6 months, which is not currently standard practice. It may also be necessary to convert patients from potentially nephrotoxic agents to less nonnephrotoxic drugs, if possible.

He reported the findings at the World College of Nephrology 2009.

Sunitinib Shows Promise as Treatment for Advanced Pancreatic Islet Cell Tumors

BARCELONA—The multikinase inhibitor sunitinib doubles progression-free survival (PFS) in patients with advanced pancreatic islet cell tumors, researchers announced at the 11th World Gastrointestinal Cancer Congress of the European Society for Medical Oncology.

Eric Raymond, MD, with Beaujon Hospital in Clichy, France, and associates randomized patients to sunitinib, 37.5 mg/day as a continuous oral dose, or placebo.

The target enrollment in their trial was 340 patients, but the study was stopped after 145 patients had been enrolled because the primary end point of PFS had been met. Patients were then given the option to receive sunitinib treatment.

The analysis found a PFS of 11.1 months in sunitinib-treated patients and 5.5 months in placebo-treated patients. Overall survival results are not yet available.

The 37.5-mg dose of sunitinib produced fewer adverse side effects than the 50-mg dose used in other clinical trials. The most frequent grade 1/2 side effects were diarrhea, nausea, vomiting, asthenia, and fatigue. The most frequent grade 3/4 side effects included neutropenia, hypertension, abdominal pain, diarrhea, hypoglycemia, and hand-foot syndrome. ●

—Jill Stein

Nursing Life

Roasted Root Vegetables with Walnut Pesto

This fall take advantage of nutrient-dense root vegetables. These vegetables will not just add color to your meals but also increase the nutritional value. Root vegetables are packed with cancer-fighting phytonutrients and carotenoids as well as potassium, calcium, vitamins A and C, folic acid, and fiber. These low-fat, high-fiber vegetables can help increase satiety and aid in weight loss. The complex carbohydrates provided can also give you a needed energy boost during the day. Root vegetables can be sautéed, roasted, baked, or boiled. They can be used as a side dish, added to salads or stews, or eaten just by themselves. Try one of these root vegetables today: rutabaga, sweet potato, parsnip, fennel, turnip, beet, and carrot. The following recipe takes advantage of a variety of root vegetables. Another added bonus is the omega-3 fatty acids you will get from the walnut pesto. This dish can be incorporated into any diet to increase heart health and provide anticancer benefits.

Ingredients

For the vegetables:

3 cups (1-inch-thick) sliced carrot (about 1 pound)

3 cups (1-inch-thick) sliced parsnip (about 1 pound)

3 cups (1-inch-thick) cubed peeled turnip

3 cups (1-inch-thick) sliced rutabaga

2 shallots, peeled and quartered

1 large onion, cut into 8 wedges

Cooking spray

½ teaspoon salt

¼ teaspoon freshly ground black pepper

For the pesto:

2 cups basil leaves

¼ cup (1 ounce) grated fresh Parmigiano-Reggiano

¼ cup coarsely chopped walnuts, toasted

4 teaspoons extra virgin olive oil

2 tablespoons water

1 tablespoon fresh lemon juice

½ teaspoon salt

1 garlic clove, peeled

Preheat oven to 425 degrees

To prepare vegetables, place first six ingredients in a single layer on a jelly-roll pan coated with cooking spray. Lightly coat vegetable mixture with cooking spray. Sprinkle evenly with ½ teaspoon salt and ¼ teaspoon black pepper; toss. Bake at 425 degrees for 1 hour or until browned. Transfer vegetable mixture to a large bowl.

To prepare pesto, combine basil leaves and remaining ingredients in a food processor; process until smooth, scraping sides. Spoon basil mixture over vegetable mixture, and toss to coat.

Nutritional Information
10 servings (serving size: 1 cup)

Calories 128 (30% from fat); Fat 4.3 g (sat 0.8 g, mono 1.7 g, poly 1.5 g); Iron 1.5 mg; Cholesterol 2 mg; Calcium 101 mg; Carbohydrate 20.5 g; Sodium 277 mg; Protein 4.3 g; Fiber 5.1 g

Recipe courtesy of Peter Pascale, CCC Executive Chef, Somerville, New Jersey

What's Your Favorite Healthy Recipe?

With a little creativity, healthy foods can be delicious as well as nutritious. Do you have a favorite healthy recipe that you would like to share with your colleagues and patients? Send your recipe and its source (family recipes are welcome) to Karen@greenhillhc.com.

Your Financial Future

BY **SILVIA MAURIN**

This article is the first in the series that will focus on retirement plans. More information at your disposal will help lessen worries about a secure retirement and build confidence in your future.

Employer-sponsored plans. For purposes of this writing, I will assume that you are an employee and that your employer offers you the opportunity to participate in a retirement plan. Unless it is absolutely impossible to do so, participation in the plan can create the cornerstone for your retirement savings. In fact, participating by contributing the highest amount possible is your surest course to future financial stability. And if your company matches a percentage of your contribution, think of the match as a bonus you cannot afford to miss. For example, if your company matches up to 4% of your contributions, make sure you contribute enough to take full advantage of the match. In these very difficult economic times, some companies have temporarily suspended matching contributions. If your company has temporarily suspended its contributions, do not suspend yours, for you will lose the value of time [compounded earnings over time], and lost time will equal fewer dollars for your retirement.

Employee contributions. We all know that if we don't have money in hand, we tend not to miss it. When you enroll in your company's plan, money is deducted automatically from your pay, so think of it as money going into another pocket, labeled "future retirement earnings." Until you have maxed out on your annual contribution, you should strive to increase your contribution over time so as to reach the goal of contributing the maximum allowable amount. The opportunity for increasing your contribution may come along as you receive raises or other salary adjustments. Although most people are not inclined to defer the use/enjoyment of the entire amount of their raises, begin to think in the following terms. If you get a 4% raise, think about not only how much extra will be in your paycheck but also how much more you can contribute to your retirement plan. If you only increase your contribution by 1% or 2%, the money will add up over time, and chances are very good that you will never miss the additional contributions. If you have not been accustomed to looking for ways to increase your plan contributions, the process of integrating this behavior change will not be much different from any other change you decide to make.

Understanding the rules governing retirement plans. Variances from plan to plan can create uncertainty, but some rules are common to most plans. The federal government sets those rules, and by gaining a grasp of the fundamentals, understanding the plan your company offers will become significantly easier. If you work for a nonprofit organization, the Internal Revenue Service code section under which your plan is governed is 403(b); if you work for a for-profit organization, the section is 401(k).

Following are some basics regarding the federal rules governing employer-sponsored 403(b) and 401(k) plans:

- Money contributed grows tax-deferred until used; that means you pay no income tax on the annual earnings so long as the money stays in the plan

"PAY NO ATTENTION TO HIM, DOCTOR. HE'S JUST MY MALPRACTICE LAWYER."

- Money withdrawn before age 59½ will create an income tax on the previously untaxed portion of the sum withdrawn, and you will owe a penalty of 10% for early withdrawal—so tapping retirement plans for cash is very expensive and should be avoided
- Maximum allowable contribution amount changes from year to year. For 2009, the contribution limit is $16,500; if you reach age 50 by December 31, 2009, you can contribute an additional $5500, for a total contribution of $22,000
- **Caveat**—an employer's restrictions may cause your individual contribution limit to be somewhat lower: possible causes for a lower-than-allowable rate include a cap on the percentage of pay you are eligible to contribute and/or your employer not yet allowing for catch-up contributions. Ask your employer if its contribution limits are lower than the maximum allowable amount
- Most but not all plans allow hardship distributions; if your plan provides for hardship distributions, it must provide the specific criteria used to make the determination of hardship; for example, a plan may provide that a distribution can be made only for medical or funeral expenses, but not for the purchase of a principal residence or for payment of tuition and education expenses
- **Hardship distributions**—a hardship distribution request must be based on an immediate and heavy financial need; such a request may also be based on the need of your spouse or dependent; in some instances, employer plans may also include nonspouse and/or nondependent beneficiaries; a distribution is not considered necessary to satisfy an immediate and heavy financial need of an employee if the employee has other resources available to meet the need, including assets of the employee's spouse and minor children, and the hardship usually has to be unforeseeable
- **Caveat**—whether a need is immediate and heavy depends on the facts and circumstances; certain expenses are deemed to be immediate and heavy, including: (1) certain medical expenses; (2) costs relating to the purchase of a principal residence; (3) tuition and related educational fees and expenses; (4) payments necessary to prevent eviction from, or foreclosure on, a principal residence; (5) burial or funeral expenses; and (6) certain expenses for the repair of damage to the employee's principal residence
- Most but not all plans allow for loans; if your plan allows loans, it may limit the loan amount; the maximum amount that the plan can permit as a loan is (1) the greater of $10,000 or 50% of your vested account balance; or (2) $50,000, whichever is less

Plans that provide for loans must specify the procedures for applying for the loan and its repayment terms; repayment of the loan must occur within 5 years, and payments must be made in substantially equal payments that include principal and interest and that are paid at least quarterly

More than one outstanding loan at a time is allowable; however, any new loan, when added to the outstanding balance of all loans from the plan, cannot be more than the plan maximum amount

- **Caveat**—if a plan loan is not repaid according to its terms, the loan becomes in default and the entire outstanding balance of the loan is treated as a taxable distribution; each plan providing for loans will specify how it handles loan defaults; when leaving your current job, loans must be paid in full.

Maximum allowable contribution amount changes from year to year. For 2009, the contribution limit is $16,500.

Upcoming issues will cover stages of retirement, investing retirement assets, and retirement and medical coverage during retirement. If you have questions, please let us know, and we will make an effort to answer as many as possible in coming issues. ●

Sylvia Maurin 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.

Medical Minutes

BY **JOHN SCHIESZER**

Oncology Nurses May Soon Be Seeing More Older Patients

Researchers at The University of Texas M.D. Anderson Cancer Center are predicting that many more cancer patients in the future will be geriatric and nonwhite. Over the next 20 years, the number of new cancer cases diagnosed annually in the United States will increase by 45%, from 1.6 million in 2010 to 2.3 million in 2030, with a dramatic spike in incidence predicted in the elderly and minority populations.


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"In 2030, 70% of all cancers will be diagnosed in the elderly and 28% in minorities, and the number of older adults diagnosed with cancer will be the same as the total number of Americans diagnosed with cancer in 2010," according to senior study author Ben Smith, MD, adjunct assistant professor of radiation oncology at M.D. Anderson Cancer Center, Houston, Texas. "Also alarming is that a number of the types of cancers that are expected to increase, such as liver, stomach, and pancreas, still have tremendously high mortality rates."

This new study predicts a 67% increase in the number of adults aged 65 years or older with cancer, from 1 million in 2010 to 1.6 million in 2030. In nonwhite individuals over the same 20-year span, the incidence is expected to increase by 100%, from 330,000 to 660,000.

Smith and his team accessed the US Census Bureau statistics, updated in 2008 to project population growth through 2050, and the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) registry. The SEER registry is the country's premier population-based cancer registry, representing 26% of the population. Cancer incidence rates were calculated by multiplying the age-, gender-, race-, and origin-specific population projections by the age-, gender-, race-, and origin-specific cancer incidence rates.

The researchers found that the rates of cancer in African Americans will increase by 64% and in Hispanics by 142% during this time period. Regarding disease-specific findings, the researchers found that the leading cancer sites are expected to remain constant: breast, prostate, colon, and lung. However, cancer sites with the greatest expected increase in incidence are the stomach, liver, plasma cells, pancreas, and bladder.

Smith said these findings highlight two issues that must be addressed simultaneously: clinical trial participation and the increasing cost of cancer care. Historically, both older adults and minorities have been underrepresented in such studies, and therefore are vulnerable to suboptimal cancer treatment. Simultaneously, the cost of cancer care over the past 10 years has grown at a rate that is not sustainable.

"The fact that these two groups (older adults and minorities) have been underrepresented in clinical research participation, yet their incidence of cancer is growing so rapidly, reflects the need for therapeutic trials to be more inclusive and address issues that are particularly relevant to both populations," said Smith.

Two Reproductive Factors May Be Important Predictors of Death from Ovarian Cancer

Researchers at the US Centers for Disease Control and Prevention (CDC) report that survival among women with ovarian cancer is influenced by age of menarche and total number of lifetime ovulatory cycles. The findings suggest that hormonal activity over the course of a woman's lifetime may influence the prognosis after an ovarian cancer diagnosis.

Results from previous studies indicated that fewer lifetime ovulatory cycles, oral contraceptive use, hysterectomy, and tubal ligation are associated with decreased risk of developing this form of cancer, according to the researchers. However, little is known about the influence of these factors on a patient's survival after a diagnosis of ovarian cancer.

"Ovarian cancer is the fifth leading cause of cancer mortality in women. It accounts for more deaths than any other gynecologic cancer," said study investigator Cheryl Robbins, PhD, an epidemiologist at the CDC, Atlanta, Georgia. "Although we have relatively good knowledge about the influence of reproductive factors on the risk of developing ovarian cancer, knowledge is rather limited regarding the reproductive factors that may influence survival after diagnosis with this serious disease."

She and her colleagues conducted a longitudinal study of 410 women aged between 20 and 54 years with ovarian cancer. After a follow-up of about 17 years, 221 women had died, and overall 15-year survival among the study population was 48%. Lifetime ovulatory cycle and age at menarche were found to be the two factors that played a key role in predicting death from ovarian cancer.

Women with the most lifetime ovulatory cycles had poorer survival compared with those who had fewer lifetime ovulatory cycles. Robbins said that the number of lifetime ovulatory cycles a woman has is affected by her use of oral contraceptives, pregnancy, and breastfeeding, all of which temporarily cause ovulation to cease and reduce the total number of cycles. The researchers also found that after diagnosis of ovarian cancer, women whose menarche began before age 12 were more likely to die compared with those whose menarche began at age 14 or older.

Cardiovascular Fitness May Not Be Affected by Cancer Treatment

The cardiovascular fitness level of cancer survivors does not appear to be affected by many standard cancer therapies, according to researchers at Georgetown University Medical Center.

The researchers conducted a chart review of 49 women who attended a physician-directed fitness clinic for cancer survivors, founded and run by Priscilla Furth, MD, one of the study's authors. The data included demographics, physical activity levels, cancer treatment type, cancer duration, and time since cancer treatment. Fitness assessments were conducted using a 3-minute step test during a clinic visit. The purpose of the study was to assess the step test as a way of determining a patient's current cardiovascular fitness level.


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"We know physical activity is a critical component of cancer survivorship, both during and after cancer treatment," said Jennifer LeMoine, PhD, a postdoctoral research fellow at Georgetown University's Lombardi Comprehensive Cancer Center, Washington, DC. "In order to prescribe an exercise program, it's critical that we understand our patient's fitness level and whether or not treatment has had an impact on their cardiovascular health."

All the patients in this study were women, but there was diversity in age and body mass index (BMI). Their cancer diagnoses and treatments varied. Overall, 33% of survivors were sedentary and 67% reported being physically active. A total of 35 women (71%) completed the step test. The researchers found that test completion and heart rate recovery were not affected by treatment, BMI, or age.

"What's really exciting to us is that we found that cardiovascular fitness was not affected by the expected culprits: cancer treatment, type, duration, or time since last treatment," said LeMoine. "That isn't to say there aren't side effects of some treatments that may hinder physical activity, but when it comes to actual cardiovascular fitness as measured in our clinic, many of the standard treatments didn't have a role."

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Books and Media

Putting Evidence Into Practice: Improving Oncology Patient Outcomes

Edited by **LINDA H. EATON, MN, RN, AOCN**, and **JANELLE M. TIPTON, MSN, RN, AOCN**

Oncology Nursing Society, Pittsburgh, PA; ONS Publishing Division; 2009. 324 pages. Soft cover. $50.00 ONS members; $70.00 nonmembers.

Reviewed by
PAMELA HALLQUIST VIALE, RN, MS, CS, ANP, AOCN

The movement for evidence-based practice in nursing is growing, reflecting the desire to critically assess available data and then apply the information to guide clinical decision making and nursing practice. Evidence-based practice is also important because it addresses the preferences and values of patients and their families in this process (Gobel BH, et al. *Clin J Onc Nursing.* 2006;10:621-624). The Oncology Nursing Society (ONS) is committed to promoting excellence in oncology nursing and improving the care of patients with cancer and their families. To this end, ONS has developed nursing-sensitive patient outcomes resources. Among these are the Putting Evidence into Practice (PEP) resources, which provide evidence-based interventions for important aspects of patient care in the form of easily carried pocket-sized reference cards. Originally a set of four symptoms, the PEP cards have grown to encompass 16 different side effects or complications of cancer, which can be a lot to carry in one's pocket. The newly published *Putting Evidence Into Practice: Improving Oncology Patient Outcomes* by the ONS, and edited by Eaton and Tipton, combines all of the resources in one volume along with helpful measurement tools and references.

This useful text gives oncology nurses access to the most recently updated PEP card information printed in the familiar color format to allow for easily recognized levels of evidence: recommended for practice; likely to be effective; benefits balanced with harms; effectiveness not established; effectiveness unlikely; and not recommended for practice. The text also includes assessment and measurement tools, ideas for patient care and organization use, and helpful case studies, all in one handy volume printed with a soft cover. The case studies are useful in illustrating how to use the tools provided in the text and can help oncology nurses understand the application of interventions in nursing practice. The information in the text can be used to develop evidence-based practice in the hospital or clinic setting and provides useful clinical examples. The ultimate goal is to improve patient outcome and satisfaction, and this new ONS publication is an excellent comprehensive resource to assist oncology nurses in providing evidence-based care and document the impact of nursing interventions on patient outcomes. ●

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- 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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