NURSING CAREERS
Rose Virani receives ONS Making a Difference Award

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CANCER CENTER PROFILE
University of Pittsburgh Medical Center Cancer Centers and Cancer Institute provide high-quality care

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HEALTH POLICY

REMS for Opioids: What Will They Mean for Oncology Nurses and Patients?

An interview with Leslie Greenberg, RN, MSN, OCN

On May 27, 2009, the US Food and Drug Administration (FDA) heard testimony on its proposed Opioid Analgesic and Risk Evaluation & Mitigation Strategies (REMS). In this interview, Leslie Greenberg, RN, MSN, OCN, health policy manager for the Oncology Nursing Society (ONS), discusses her testimony and the possible implications of REMS for opioids for oncology nurses and their patients.

What are REMS and what type of drugs are they used for?

REMS stands for Risk Evaluation and Mitigation Strategies. In September 2007, the Food and Drug Administration Amendments Act gave the FDA expanded authority, including the ability to require companies to submit REMS when deemed necessary to ensure that a product's benefits outweigh its risks. REMS are a step between issuing a warning letter and pulling a drug off the market. The FDA wanted to

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CANCER SURVIVORSHIP

Fertility Preservation before Cancer Treatment: Too Little, Too Late?

ORLANDO—Cancer patients who wish to preserve their fertility after treatment may be getting short-changed, according to a study presented at the 2009 annual meeting of the American Society of Clinical Oncology (ASCO) that found oncologists to be less than proactive.

Surveys of cancer patients show that loss of fertility is an immense concern, one that often does not surface until treatment has been completed and options for

Continued on page 18

GENITOURINARY CANCERS

The Changing Kidney Cancer Treatment Landscape. Part 1. New Opportunities, New Challenges

SEATTLE—Advances in the detection and treatment of cancer in recent years bring new hope for patients, but they also challenge the medical community to keep up with rapid changes in the landscape. One very dramatic example is the quiet and slow revolution that has taken place with kidney cancer.

Renal cell carcinoma (RCC), the most common type

Continued on page 9

SUPPORTIVE CARE

Treatment Options for Chemotherapy-induced Nausea and Vomiting Increasing

BY **PAMELA HALLQUIST VIALE, RN, MS, CS, ANP, AOCNP**
ONCOLOGY NURSE PRACTITIONER AND CONSULTANT, SARATOGA, CALIFORNIA, AND ASSISTANT CLINICAL PROFESSOR, UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

The treatment of patients receiving chemotherapy has become vastly more complex in the past 25 years, particularly with the introduction of many new chemotherapy and targeted therapy agents. Supportive care for patients receiving these treatments includes the management of chemotherapy-induced nausea and vomiting (CINV) and, although considerable advances have been made in the management of this side effect, some patients still rank CINV as one of

Continued on page 11

When treating patients with HER2+ breast cancer

No one touches their

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

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

Adjuvant indications

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

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

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

Metastatic indications

Herceptin is indicated:

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

Boxed WARNINGS and Additional Important Safety Information

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

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

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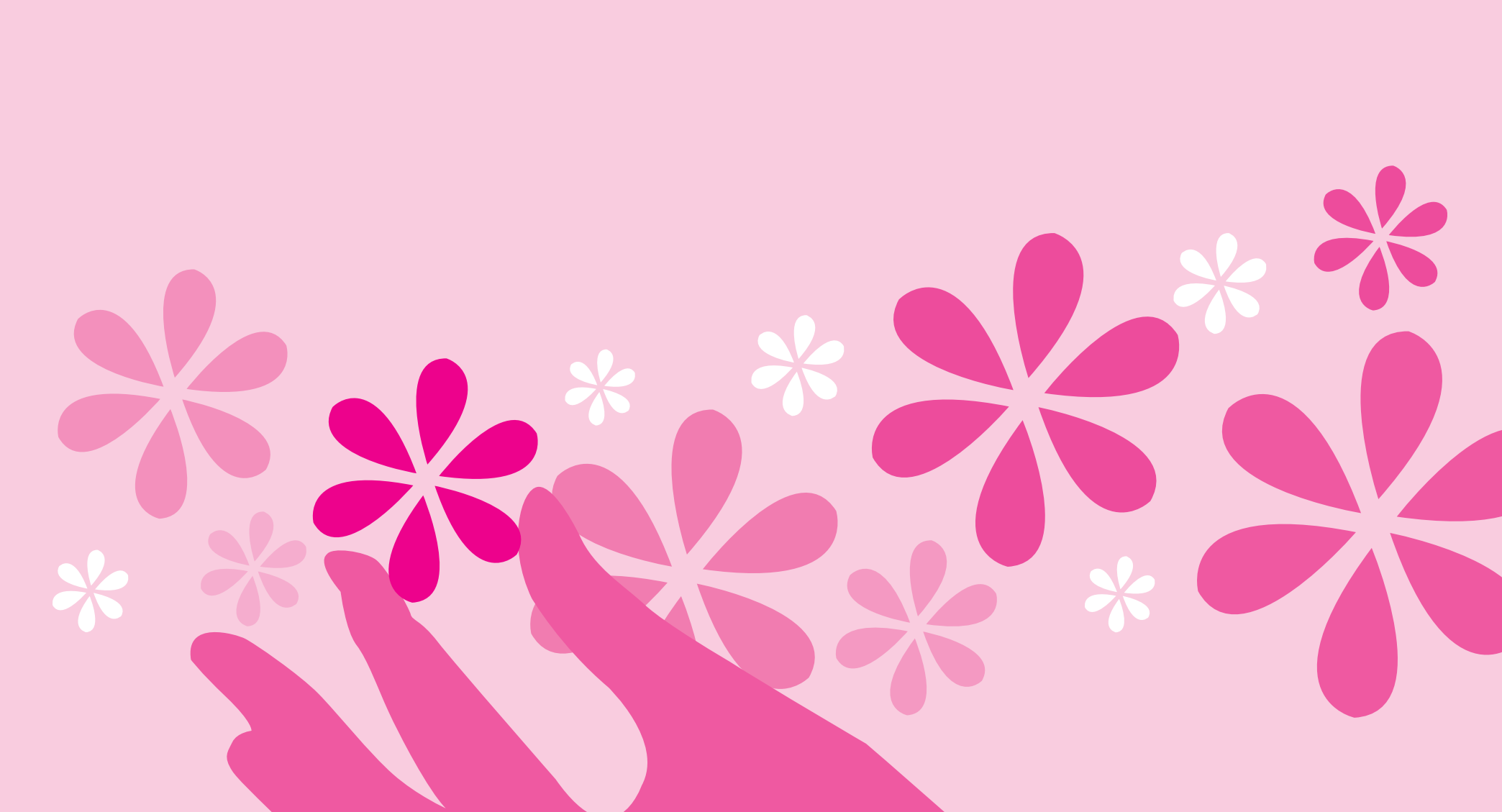


withheld in patients who develop significant left ventricular cardiac dysfunction. In one adjuvant clinical trial, cardiac ischemia or infarction occurred in the Herceptin-containing regimens.

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

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

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

www.herceptin.com

Herceptin®
trastuzumab
Targeted on HER2, Focused on Living

9568900 01/09

HERCEPTIN® (trastuzumab)

Brief Summary For full Prescribing Information, see package insert.

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, and PULMONARY TOXICITY

Cardiomyopathy

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

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

Infusion Reactions; Pulmonary Toxicity

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

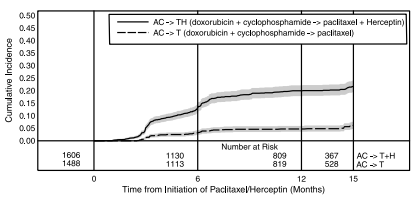
the AC-T arm, 24 months in the AC-TH arm. In Studies 1 and 2, 6% of patients were not permitted to initiate Herceptin following completion of AC chemotherapy due to cardiac dysfunction (LVEF <50% or ≥15 point decline in LVEF from baseline to end of AC). Following initiation of Herceptin therapy, the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

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

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

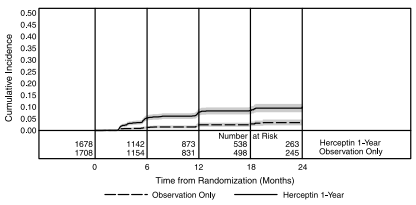
[a] For Studies 1, 2 and 3, events are counted from the beginning of Herceptin treatment. For Study 4, events are counted from the date of randomization. [b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC→T) or paclitaxel plus Herceptin (AC→TH)
[c] Study 4 regimens: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

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



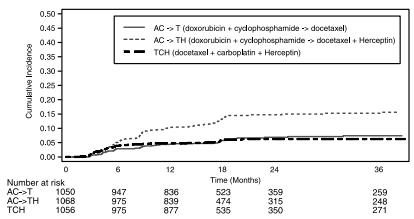
Time 0 is initiation of paclitaxel or Herceptin + paclitaxel therapy.

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



Time 0 is the date of randomization.

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



Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials the probability of cardiac dysfunction was highest in patients who received Herceptin concurrently with anthracyclines. *Infusion Reactions* During the first infusion with Herceptin, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of Herceptin infusion); permanent discontinuation of Herceptin for infusional toxicity was required in <1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusional toxicity occurred in 21% and 35% of patients, and was severe in 1.4% and 9% of patients, on second or subsequent Herceptin infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting, severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported. *Anemia* In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2–5 anemia (12.5% vs. 6.6% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. Following the administration of Herceptin as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was <1%. *Neutropenia* In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4–5 neutropenia (2% vs. 0.7% [Study 2]) and of selected Grade 2–5 neutropenia (7.1% vs. 4.5 % [Study 1]) were increased in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. *Infection* The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2–5 infection/febrile neutropenia (22% vs. 14% [Study 1]) and of selected Grade 3–5 infection/febrile neutropenia (3.3% vs. 1.4%) [Study 2]), were higher in patients receiving Herceptin and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract. In study 4, the overall incidence of infection was higher with the addition of Herceptin to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC grade 3-4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms. In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving Herceptin in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. *Pulmonary Toxicity* Adjuvant Breast Cancer Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2–5 pulmonary toxicity (14% vs. 5% [Study 1]) and of selected NCI-CTC Grade 3–5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 1% [Study 2]) was higher in patients receiving Herceptin and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2–5: 12% vs. 4% [Study 1]; NCI-CTC Grade 2–5: 2.5% vs. 0.1% [Study 2]). Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving Herceptin compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving Herceptin, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone. In Study 3, there were 4 cases of interstitial pneumonitis in Herceptin-treated patients compared to none in the control arm. Metastatic Breast Cancer Among women receiving Herceptin for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions. Thrombosis/Embolism* In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving Herceptin and chemotherapy compared to chemotherapy alone in three studies (3.0% vs. 1.3% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]). *Diarrhea* Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2–5 diarrhea (6.2% vs. 4.8% [Study 1]) and of NCI-CTC Grade 3–5 diarrhea (1.6% vs. 0% [Study 2]), and of grade 1-4 diarrhea (7% vs. 1% [Study 3]) were higher in patients receiving Herceptin as compared to controls. In Study 4, the incidence of Grade 3–4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1–4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving Herceptin. Of patients receiving Herceptin as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving Herceptin in combination with chemotherapy for treatment of metastatic breast cancer. *Glomerulopathy* In the postmarketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18 months from initiation of Herceptin therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure. **Immunogenicity** As with all therapeutic proteins, there is a potential for immunogenicity. Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to Herceptin was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer. The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Herceptin with the incidence of antibodies to other products may be misleading. **USE IN SPECIFIC POPULATIONS Pregnancy Teratogenic Effects: Category D [*see Warnings and Precautions*]** Herceptin can cause fetal harm when administered to a pregnant woman. Post-marketing case reports suggest that Herceptin use during pregnancy increases the risk for oligohydramnios during the second and third trimester. If Herceptin is used during pregnancy or if a woman becomes pregnant while taking Herceptin, she should be apprised of the potential hazard to a fetus. In the postmarketing setting, oligohydramnios was reported in women who received Herceptin during pregnancy, either alone or in combination with chemotherapy. In half of these women, amniotic fluid index increased after Herceptin was stopped. In one case, Herceptin was resumed after the amniotic fluid index improved, and oligohydramnios recurred. Women using Herceptin during pregnancy should be monitored for oligohydramnios. If oligohydramnios occurs, fetal testing should be done that is appropriate for gestational age and consistent with community standards of care. Additional intravenous (IV) hydration has been helpful when oligohydramnios has occurred following administration of other chemotherapy agents, however the effects of additional IV hydration with Herceptin treatment are not known. Reproduction studies in cynomolgus monkeys at doses up to 25 times the recommended weekly human dose of 2 mg/kg trastuzumab have revealed no evidence of harm to the fetus. However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mutant mice lacking HER2, embryos died in early gestation. Placental transfer of trastuzumab during the early (Days 20-50 of gestation) and late (Days 120-150 of gestation) fetal development period was observed in monkeys. [*See Nonclinical Toxicology*] Because animal reproduction studies are not always predictive of human response, Herceptin should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. *Registry* Pregnant women with breast cancer who are using Herceptin are encouraged to enroll in MotHER- the Herceptin Pregnancy Registry: phone 1-800-690-6720. **Nursing Mothers** It is not known whether Herceptin is excreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the breast milk of lactating cynomolgus monkeys given 12.5 times the recommended weekly human dose of 2 mg/kg of Herceptin. Infant monkeys with detectable serum levels of trastuzumab did not have any adverse effects on growth or development from birth to 3 months of age; however, trastuzumab levels in animal breast milk may not accurately reflect human breast milk levels. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from Herceptin, a decision should be made whether to discontinue nursing, or discontinue drug, taking into account the elimination half-life of trastuzumab and the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Herceptin in pediatric patients has not been established. **Geriatric Use** Herceptin has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of Herceptin in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of Herceptin in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of Herceptin treatment in older patients is different from that observed in patients <65 years of age for metastatic disease and adjuvant treatment. **OVERDOSAGE** There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested. **PATIENT COUNSELING INFORMATION** • Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness [*see Boxed Warning: Cardiomyopathy*]. • Advise women with reproductive potential to use effective contraceptive methods during treatment and for a minimum of six months following Herceptin [*see Pregnancy*]. • Encourage pregnant women who are using Herceptin to enroll in MotHER- the Herceptin Pregnancy Registry [*see Pregnancy*].

HERCEPTIN® [trastuzumab]

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Initial US Approval: Sept. 1998
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News Notes

News Updates of Relevance to Everyday Oncology Practice

■ NCCN Updates NHL, Cervical Cancer Screening, and Breast Cancer Guidelines

Following US Food and Drug Administration approval of pralatrexate injection as the first single-agent therapy for relapsed or refractory peripheral T-cell lymphoma (PTCL), the National Comprehensive Cancer Network (NCCN) has updated its *Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas* to include pralatrexate as a second-line therapy option for relapsed or refractory PTCL. The therapy is a category 2A recommendation for patients who are not candidates for high-dose therapy and a category 2B recommendation for patients who are candidates for high-dose therapy.

The NCCN has also updated its *Clinical Practice Guidelines in Oncology: Cervical Cancer Screening* to include a section of recommendations for women who have positive results for the human papillomavirus (HPV) high-risk DNA test but negative cervical cytology screen/Pap smear. Options cited include having a more specific HPV 16/18 DNA test or proceeding to colposcopy.

In addition, the NCCN *Clinical Practice Guidelines in Oncology: Breast Cancer* now discourages prophylactic mastectomy except in women considered at high risk. Although a recent study showed that the number of women with cancer in one breast choosing to have the other breast removed has increased, the NCCN guidelines caution that the small benefits must be balanced with the risk of recurrent disease and recommend that a high-risk woman considering a prophylactic mastectomy should be counseled on the risks of the procedure. Another update replaces the recommendation for a full axillary lymph node dissection as an option for woman with clinically negative lymph nodes with the recommendation that women with stage I or II invasive breast cancer with clinically negative lymph nodes undergo sentinel node mapping and excision. These guidelines have also added a new regimen for adjuvant chemotherapy for invasive breast cancer—fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel.

■ Metastatic Lobular Breast Cancer Tumor DNA Sequenced

Canadian researchers, in an attempt to precisely characterize all somatic coding mutations that occur during the development and progression of an individual cancer, have sequenced all 3 billion letters in the DNA sequence of one estrogen receptor α–positive metastatic lobular breast cancer tumor. With the recent advances in next-generation sequencing, the researchers were able to sequence the genome in just weeks. They found 32 somatic nonsynonymous coding mutations in the metastatic tumor. On comparison with the patient's primary tumor

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A Letter from the Editor

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

EDITOR-IN-CHIEF

It is not every day that actress Suzanne Somers and Dr Otis Brawley, chief medical officer of the American Cancer Society, have an opportunity to exchange views on medical matters. But in recent appearances on the *Larry King Live* show, the two discussed their sharply differing views on alternative medicine. In Ms Somers' new book, she not only endorses alternative medicine but also urges readers to avoid conventional treatment. Dr Brawley responded that used wisely in conjunction with conventional medicine, alternative and complementary therapies can be helpful in making patients feel better, but he emphasized that it is essential for patients to talk to their doctors about what they are taking.

Patients may be more comfortable about talking to their nurses about alternative/complementary therapies, and we have a responsibility to learn more about these treatments so that we can answer their questions and counsel them on safe and effective use of any medications or nutritional supplements they are taking. The article by Amanda Saldivar on use of soy products by patients with breast cancer is an excellent example of the type of balanced information we should provide.

Appropriate use of pain medications is also a huge concern for patients with cancer and their caregivers, and any restrictions on their use, as for instance in the plan under consideration by the US Food and Drug Administration to require Risk Evaluation and Mitigation Strategies for opioid analgesics, could have a major impact on clinical practice. Leslie Greenberg discusses the Oncology Nursing Society's stance on this matter.

Peripheral neuropathy is a common cause of pain in patients receiving chemotherapy. This month's continuing education article by Constance Visovsky and Rhonda Moore provides a comprehensive overview of the epidemiology, prevention, and treatment of chemotherapy-induced peripheral neuropathy.

Also in this issue are a review by Pamela Viale of treatment options for the common problem of chemotherapy-induced nausea and vomiting and a discussion of the less-discussed but important issue of fertility preservation in patients with cancer.

We hope these articles will help you in your practice, and we would like to hear from you about what you would like to see in coming issues. ●

News Notes

News Updates of Relevance to Everyday Oncology Practice

Continued from page 3

from 9 years prior, five of those mutations were prevalent, six were present at lower frequencies, 19 were not present, and two were undetermined. The five mutations were not previously known to researchers as being involved in cancer, thus identifying new avenues to pursue for the development of personalized medicines for patients (*Nature*. 2009;461:809-813).

■ PV-10 Compassionate Use Program Extended to United States

PV-10, an investigational agent being developed as a therapeutic for a broad spectrum of cancers, is now available to patients under the US Food and Drug Administration's compassionate use guidelines. The agent will be available for indications that do not involve visceral organs and are not subject to enrollment in ongoing clinical trials. Cancers that meet these indications include certain breast cancers, basal cell carcinoma, squamous cell carcinoma, certain head and neck cancers, and melanoma. The agent is currently available through St. Luke's Hospital & Health Network, Bethlehem, Pennsylvania, and will be extended to more sites in the upcoming months (Provectus Pharmaceuticals).

■ UnitedHealthcare Offers Free Access to *NCCN Drugs & Biologics Compendium*

UnitedHealthcare now provides its in-network physicians and their staff free access to the *NCCN (National Comprehensive Cancer Network) Drugs & Biologics Compendium*. The Centers for Medicare & Medicaid Services recognizes the NCCN compendium as a mandated reference for oncology coverage policy. In January 2008, UnitedHealthcare began basing its benefit coverage for chemotherapy drugs used in outpatient settings on the compendium as well. The free access reflects the company's ongoing commitment to ensuring physicians and patients have access to evidence-based care. The access will also help save time by eliminating time spent on phone calls for coverage confirmation (UnitedHealthcare).

■ HD Colonoscopy Use Increases Adenoma Detection; Adding Colored Dye Does Not

Two studies presented at the American College of Gastroenterology annual scientific meeting focused on the clinical benefits of high-definition (HD) colonoscopy technology. DeVault and colleagues conducted a retrospective study of 2011 patients who had screening, surveillance, or diagnostic colonoscopies to determine if the HD colonoscopy scopes lead to better detection of subtle mucosal changes and, therefore, adenomas. Standard-definition scopes were used on 1188 patients; HD scopes on 823. Mean age was 63 years; 54% were male. The researchers found that adenomas less than 5 mm, as well as those 6 mm to 9 mm, were detected significantly more frequently with HD technology. Lesions greater than 1 cm were detected at the same rate. The researchers noted that monitoring these smaller lesions over time may present a challenge (ACG 2009; Abstract 60).

Kahi and colleagues randomized 660 patients to chromocolonoscopy (the addition of colored dye to HD colonoscopy) or HD white-light colonoscopy to determine if chromocolonoscopy increased detection of adenomas in average-risk patients undergoing routine screening. Only patients undergoing their first colonoscopy were evaluated. Patients were excluded if they had risk factors such as family history. The researchers found no significant difference between the groups in number of patients with at least one adenoma (55.5% vs 48.4%, respectively), in the number of adenomas per patient (1.3 vs 1.1, respectively), nor in the number of advanced adenomas under 10 mm (0.02 vs 0.01, respectively). Chromocolonoscopy did detect more flat adenomas per patient (0.6 vs 1.2; $P = .01$) and more adenomas under 5 mm in diameter (0.8 vs 1.3; $P = .03$). The researchers concluded that the marginal increase in detection did not meet statistical significance (ACG 2009; Abstract 12). ●

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Viewpoint

How the US Government Rations Health Care

The agency that would likely run the "public option" was slow to pay for implantable cardiac defibrillators.

President Barack Obama deflects criticism that his health-care plan will bring on government rationing of medical care by arguing that insurance companies ration care. Everyone knows private payers limit access to some health care. But government does it in far more byzantine and arbitrary ways.

Consider the $450 billion Medicare program. It provides a model for—indeed its bureaucracy could well end up running—the "public option" health plan that Mr. Obama wants to offer all Americans under the age of 65. In recent years, Medicare's staff has been aggressively restricting coverage for costly treatments. Looking for ways to control spending on medical products—and preserve the illusory "trust fund" that pays Medicare claims—is what shapes the culture of the organization and motivates the agency's staff.

This often means limiting access to the costliest technologies. To do this Medicare relies on its rationing and pricing systems. National coverage decisions (NCDs) are assessments issued by Medicare's medical staff that define who is eligible for new but often expensive treatments. Medicare then assigns medical products and procedures with "codes" that determine which regulated category they fall into. Finally, price "schedules" are developed by Medicare's staff each year to assign each unique code with its own updated payment rate. The process for getting a favorable code on a new product is a source of intense lobbying. It can make or break a technology.

For a remote agency like Medicare, far removed from clinical practice, it's easier to try and manage the use of a high-cost but specialty treatment than a much lower-cost but very widely used product. Yet cheaper, more commonly used products can still be mispriced and account for more total cost to the agency. For example, low-tech orthotic devices and other "durable medical equipment" are a known source of wasteful spending. These medical products often evade Medicare's attention in favor of less used but more expensive items such as a biological cancer drug.

Take the agency's tortured decisions concerning the use of implantable defibrillators that jump-start stopped hearts during cardiac arrest. Medicare sharply restricted their use in the 1990s. Mounting research proved that the $30,000 devices could be saving many more lives. So in 2003 Medicare adopted a novel theory to expand coverage to some, but not everyone, who needed one. The agency said only patients with certain measures on their electrocardiograms (called "wide QRS") seemed to benefit.

It was an easily measurable but ultimately imprecise way to allocate the devices. After another major study firmly refuted the QRS theory, Medicare expanded coverage again in 2005, potentially saving 2,500 additional lives according to a press release issued with that decision.

That experience wasn't unique. From 1999 to 2007, Medicare denied access in a third of the treatments it evaluated through its coverage process, taking an average of eight months to complete its reviews. When coverage was granted, in 85% of cases the treatments were restricted, usually to patients with more advanced illnesses.

Medicare is lately increasing its use of the national coverage process and is becoming more tightfisted. Since 2008, according to my review of Medicare data, it conditioned access in 29% of its reviews and denied new or expanded coverage in fully 53% of cases.

Medicare's methods can also be arbitrary. Take the travails of the pharmaceutical company Sepracor and its drug Xopenex, an innovative respiratory medicine that competes with the chemically distinct and much cheaper generic albuterol. Both are inhaled aerosols used to treat asthma and chronic obstructive pulmonary disease. Xopenex has the same benefits as albuterol, but some believe fewer of its cardiac side effects. Medicare didn't agree.

The agency tried to make a "national coverage decision" on Xopenex but couldn't come up with a clinical justification to limit the drug's usage. So Medicare manipulated its payment process, saying it would pay Xopenex a price equivalent to the "least costly alternative" form of generic albuterol, 10 cents a treatment compared to about $2.50 for Xopenex. Then Medicare was sued by a patient, and a Federal court recently ruled the agency exceeded its authority.

Medicare finally succeeded in reigning in the use of Xopenex with its coding system. By issuing Xopenex the same classification as generic albuterol, it was able to pay both products the same "blended" price—an average of the cost of each individual drug. That lowered the price on Xopenex, but ironically increased what Medicare paid for the generics.

It's not a stretch to say that Medicare spent hundreds of cumulative man-hours focusing on Xopenex while other priorities languished. The question is why? There weren't safety concerns. Xopenex may have been used in lieu of a cheaper alternative, but at peak Medicare sales of about $300 million it represented far less than one one-thousandth of the agency's budget. Simply put, a few staffers inside Medicare were consumed with the drug and its higher price—revealing a process that is capricious and often disconnected from science.

Worse still is how impenetrable these programs have become. Drug and device companies spend millions of dollars trying to influence Medicare decisions. The hundreds of consultants they hire to advise them typically command $20,000-a-month retainers.

Formal patient and provider appeals to Medicare took an average of 21 months, according to a report issued in 2003 by the Government Accountability Office (using 2001 data), with delays in "administrative processing" due to "inefficiencies and incompatibility" of data systems eating up 70% of the time spent processing appeals.

There's nothing inherently wrong with a program like Medicare seeking value for taxpayers. But it shouldn't make up the rules as it goes. When private plans ration care, patients can appeal directly to an insurer's medical staff. Only a small fraction of Medicare's denied claims—about 5%—are ever formally appealed because its process is so impenetrable. People can also switch insurers, and in many cases patients chose a policy because it matched their preferences in the first place. These options don't exist in a government health program. ●

—*Scott Gottlieb*

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

FDA's Safe Use Initiative

The US Food and Drug Administration (FDA) has launched the Safe Use Initiative, a program that intends to collaborate with healthcare professionals and other stakeholders to reduce the likelihood of preventable harm from medication use. The initiative will identify drugs and drug classes that are linked to preventable harm, cross-sector interventions for reducing that harm, and the metrics for success. Millions of people are harmed each year from inappropriate medication use, or as a result of incomplete access to information about a drug, patient, or the patient's condition. In a report on the program, the FDA highlights several risk-reduction projects that may benefit from Safe Use collaborations, notably those addressing these problems.

New Opportunities, New Challenges

Continued from cover

of kidney cancer, currently affects more than 200,000 people in the United States. Historically, it has been among the most treatment-resistant tumors. Until just recently, patients with advanced kidney cancer had limited treatment options. That is no longer the case. Today's treatment strategies are altering the approach to kidney cancer, posing new opportunities and challenges for oncology nurses.

"There are two main drug categories, and the good thing for us as nurses is that the newer agents have some different side effects and some of them are pretty predictable. If you know the side effect profile to look for, and develop a comfort level with dealing with these side effects, you can pass that knowledge on to patients and tell them what to look for. Also, you can tell them when to be concerned, and give them interventions on what to do," said Patricia Creel, RN, a clinical cancer research coordinator at Duke University, Durham, North Carolina.

Recent approvals of new agents have dramatically changed how RCC is managed by oncology nurses as well as physicians. New biologic therapies for the treatment of advanced metastatic RCC are now available, including the vascular endothelial growth factor receptor-tyrosine kinase inhibitors sunitinib and sorafenib, the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus, and the monoclonal antibody to the vascular endothelial growth factor bevacizumab.

Patient education and communication important

"For oncology nurses, the big shift is that a large portion of these drugs are oral agents, which certainly has presented challenges to how we present education and management of them," said Creel in an interview with *The Oncology Nurse*. "We have been accustomed to working with patients in an infusion chair and having the luxury of that interaction and education time. Now, it has shifted because when the patient gets an oral agent, if it is not given with an infusion agent, that time in the infusion chair for medication teaching does not exist. So, there has been a shift in the time and place where patient education goes on."

Creel said, traditionally, a physician would explain the medications to the patient, but there was an opportunity for the infusion nurse to reinforce that education and do more detailed teaching than the physician gave. "It was a very concrete way to carry out this process. Now that upfront teaching is not going on with oral agents," Creel explained.

She said the optimal time for teaching patients about their medications is when they receive their prescriptions, but many patients are not ready to ask questions at that time. Creel said some cancer centers are now offering oral therapy teaching sessions, but that is not the case at all institutions.

Creel noted that many cancer patients are reluctant to discuss the side effects or problems they may be having with various medications, because they are worried the treatment might be stopped. She said this is an issue that needs to be addressed upfront. "We emphasize this in our practice, and we tell the patients exactly when to call us. If I see a patient who I think will be hesitant to call, I call them. I put it on my planner to call certain patients at certain times and that helps develop that relationship. If you

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New Opportunities, New Challenges

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call them, it opens the door for them. You want them to feel comfortable about calling. That is essential," Creel said. "Patients need to be in close communication with their clinicians at all times; it may be the nurse, such as an office nurse. In our practice, we have nurse practitioners, but there needs to be a close communication with them for close monitoring and frequent follow-up. Patients need to know how to get through the system to reach someone to speak to, and they need to feel they can be open and honest about their side effects."

Managing side effects

The new oral therapies for RCC have distinct side effect and adverse event profiles. The mTOR inhibitors may cause rash, fatigue, diarrhea, and mucositis with painful swallowing. "You need to explain to your patient what mucositis is and how to manage it. The same with diarrhea," said Laura Wood, RN, MSN, a renal cancer research program coordinator at the Cleveland Clinic, Ohio. "While class effect toxicities exist, specific side effect profiles vary by agents. We want to maintain the highest doses so they are effective and beneficial."

She said with the mTOR inhibitors, close monitoring of blood glucose levels is required, and the other oral agents for RCC may result in hypertension, hand-foot skin reactions, rashes, fatigue, and nausea. "Fatigue is a big problem. Approximately 50% of patients may have it, and it affects their quality of life," Wood said. "We want to give nurses some tips and tricks."

She recommends a full patient assessment at the initiation of therapy, meeting with the patient at the beginning of each treatment cycle, and emphasizing that the patient should call at the first sign of any adverse event. She said it is important that patients with RCC are encouraged to stay active and maintain a normal schedule. She also advocates that oncology nurses discuss nutritional intake as well as hand and foot conditions, which are very common reactions to some therapies for RCC.

"We recommend getting a pedicure before treatment to get your feet in the best possible condition," Creel said. She noted that painful areas on the palms and soles can impair functional ability and significantly impair quality of life. Both Creel and Wood said it is important to discuss these issues before treatment as well as what topical agents are available for hand and foot conditions.

Another important issue is for nurses to get family members involved as much as possible. Creel noted that patients suffer fatigue and have a host of problems, so they may not be able to remember all they need to know about their treatments. "It is good to educate adult children or the person who is helping," she said. "I also ask patients to keep notes or a journal on their side effects."

She said there is no one drug in the treatment of RCC that is the worst in terms of side effects, and that most of the newer agents are highly tolerable, but it often depends on the patient.

Wood said the primary goals for nurses managing patients with RCC should be to reduce discomfort, avoid dose modification, improve patient compliance, and support optimal clinical outcomes. ●

—John Schieszer

Part 2 of this article on the role of oncology nurses in improving patient outcomes will appear in the January/February 2010 issue.

Treatment Options for CINV

Continued from cover

the most problematic adverse events associated with cancer treatment.[1]

CINV is usually described as acute-onset (occurring within a few minutes to several hours after chemotherapy administration, resolving within 1 day) or delayed-onset (beginning more than 24 hours after drug administration).[2] Delayed-onset CINV can last 5 to 7 days or longer. Anticipatory CINV can occur before the patient receives a treatment. It can affect the patient the night before therapy and is a learned response from previous poorly controlled CINV. Breakthrough emesis is vomiting that occurs despite antiemetic treatment, requiring "rescue" antiemetics. Refractory emesis is emesis that occurs during subsequent cycles of therapy when antiemetic therapies or rescue therapy has failed previously.[2]

The emetogenic potential of chemotherapy agents is generally ranked as minimal (accounting for most targeted therapy agents), mild, moderate, or high. Most guidelines agree that when agents are given in combination, the most emetogenic agent in the combination should guide the choice of antiemetic regimen. Additional factors can increase the risk of CINV, and clinicians should assess each patient for these factors to determine increased risk associated with cancer therapies (Table 1).[2-4]

Pathophysiology and treatment

The pathophysiology of CINV is complex and involves several neurotransmitters. Although dopamine transmitters were the focus of early antiemetic therapy, the serotonin receptor antagonists (5-hydroxytryptamine type 3 [5-HT_3]) and substance P have attained prominence in CINV, and many of our newer therapies target these neurotransmitters. The introduction of 5-HT_3 receptor antagonists (RAs) in the early 1990s contributed significantly to better control of CINV. These agents are now included in most regimens for antiemetic control.[5] Substance P is the most recently identified neurotransmitter with activity in CINV. It is one of a group of peptides called tachykinins located throughout the central nervous system and found in the gastrointestinal tract along with 5-HT_3 receptors.[5,6] Substance P is mediated through the neurokinin-1 (NK_1) receptor and, with the development of novel agents, such as the NK_1-RA and palonosetron (an extended-action 5-HT_3), patients have more options for management as well as improved control of CINV.[6] The first NK_1-RA, aprepitant, and the long-acting agent palonosetron were approved by the US Food and Drug Administration (FDA) in 2003 for the treatment of CINV. In addition, recently FDA-approved new formulations of older agents, such as nabilone (2006) and transdermal granisetron (2008), have added new tools to the armamentarium of therapeutic agents available to control CINV (Table 2).[7-12]

Transdermal granisetron is a new 5-HT_3-RA delivery medium and allows clinicians to treat patients with a single transdermal system that can be applied up to 48 hours before chemotherapy.[13] It can be left on the skin for up to 7 days, depending on the type and duration of chemotherapy agent, and its longer action avoids the need for oral dosing. Nabilone, an oral cannabinoid that targets the cannabinoid receptors CB1 and CB2, is approved to treat CINV in patients who have failed to respond to conventional antiemetic agents. Its duration of action allows for twice-a-day dosing.[14,15]

With the increased number of agents currently approved to treat patients receiving chemotherapy and/or targeted therapy drugs, clinicians may be confused about the most optimal way to treat CINV. Existing guidelines can help to educate oncology nurses and other healthcare providers regarding the available choices and most efficacious combinations to improve control of CINV.[16] There are many guidelines that refer to treatment of CINV, but in the United States, the most commonly used guidelines/recommendations are those of the American Society of Clinical Oncology, the Multinational Association for Supportive Care in Cancer, the Oncology Nursing Society, and the National Comprehensive Cancer Network (NCCN).[2-4,17] The NCCN guidelines have been updated to incorporate transdermal granisetron and fosaprepitant, the intravenous form of aprepitant. In addition, the NCCN guidelines call for the consideration of an H2-blocker or proton-pump inhibitor to prevent dyspepsia, which can be a side effect associated with steroids used in the treatment of CINV and can present as emesis in some patients. For the most part, the four different organizations agree on management of CINV; however, there are some subtle differences (Table 3).

Table 1. Risk Factors for Emetogenicity

Emetogenic potential of chemotherapy agents

- High—90% risk
- Moderate—30% to 90% risk
- Mild—10% to 30% risk
- Minimal—<10% risk

Patient risk factors

- Patient age, <50 years
- Female gender
- Lower alcohol intake history
- Emesis during pregnancy
- Previous CINV experience

CINV indicates chemotherapy-induced nausea and vomiting.
Sources: References 2-4.

Although the previous iteration of the NCCN guidelines called for use of a 5-HT_3-RA (in general) in patients receiving moderately and highly emetogenic chemotherapy, the most recent update has added a preferred designation to palonosetron (category 2B evidence) for prevention of highly emetogenic chemotherapy based on a publication by Saito and colleagues.[18] In this double-blind, double-dummy, randomized, comparative phase 3 study, palonosetron was found to be noninferior to granisetron in the acute phase of CINV with highly emetogenic chemotherapy and superior to granisetron in the delayed phase (56.8% complete response in the palonosetron group vs 44.5% in the granisetron group, P <.0001). However, the study dose of palonosetron was 0.75 mg as compared with the 0.25-mg FDA-approved dose for administration in the United States.

At the Multinational Association for Supportive Care in Cancer (MASCC)/European Society of Medical Oncology (ESMO) 2009 International Symposium, MASCC/ESMO announced that the combined regimen of palonosetron and multiday dexamethasone is recommended to prevent acute- and delayed-onset nausea and vomiting following chemotherapy of moderate risk.

Delayed-onset CINV is still ranked as a significant adverse event associated with chemotherapy treatments.[19] The incidence of delayed nausea and vomiting is high following administration of chemotherapy agents such as cisplatin. In one study, following a peak intensity on day 1, cisplatin-induced nausea and vomiting subsided slightly on day 2, but then peaked again on day 3.[20] Knowledge of the patterns of emesis for individual chemotherapy agents is important in choosing appropriate antiemetic therapies. Use of the NK_1-RA aprepitant can alleviate delayed-onset CINV, but in patients not receiving an NK_1-RA, symptoms can affect quality of life.[19] Dexamethasone, an important component of management of acute emesis, has a role in the management of delayed-onset CINV as well. It has been shown to be effective both as monotherapy and in combination with other antiemetics.[21]

Pamela Hallquist Viale, RN, MS, CS, ANP, AOCNP

Adjunctive treatments

Nonpharmacologic adjunctive treatments have also been studied to determine their role in the treatment of CINV. A recently published meta-analysis suggested that acupressure may be effective in the treatment of CINV and called for additional trials to confirm this.[12] In a study of 160 women with breast cancer, acupressure was shown to have a statistically significant effect on the amount of vomiting and the intensity of nausea when compared with the placebo group. The study showed that acupressure at the P6 point is a beneficial technique when applied in addition to optimal pharmaceutical management for women undergoing therapy for breast cancer.[22] Once taught the appropriate strategy, acupressure is inexpensive and easy to implement. Other nonpharmacologic adjunctive therapies, some of which can be nurse-initiated, are described in Table 2.

Costs of treatment

The costs of supportive therapy agents are often a concern. Inadequate control of CINV, however, can lead to undesirable consequences, such as increased hospitalization and use of hospital resources, which can increase costs and decrease quality of life.[23-25] In a study of 2018 patients, the cost of treating CINV was estimated at $1300 higher per month for patients of working age. The researchers concluded that despite the use of 5-HT_3-RAs, patients receiving moderately or highly emetogenic chemotherapy agents suffered higher expenses related to uncontrolled CINV.[24] In a Canadian study, ondansetron significantly reduced emesis-management costs from those incurred before ondansetron was available. The savings were achieved through a reduction in the use of hospital days and other costs associated with treatment of CINV.[26]

Role of oncology nurses

Oncology nurses are ideally positioned to assess and intervene with patients who are suffering from CINV. From the initial assessment to identify the risk factors that increase patients' risk for CINV to the evaluation of patients at mid and later cycles to determine the effectiveness of antiemetic combination therapies, oncology nurses are on the front line of patient care. Oncology nurses should be aware of new therapies and options for patients with CINV and familiar with the current armamentarium of agents for this side effect. They should understand that oral and intravenous forms of antiemetics have equivalent efficacy, and therefore individual patient needs should be taken into account.[2] Knowledge of potential drug-drug interactions is important when administering aprepitant, and nurses should counsel patients taking warfarin regarding the need for a blood test to monitor the anticoagulant ratio within 7 to 10 days of initiating this antiemetic.[27,28] Although chemotherapy is associated with nausea and vomiting, other potential causes of emesis should also be assessed and evaluated in patients with this common side effect.[2] In addition, nurses should carefully monitor patients with CINV for nutritional and hydration problems and impact on quality of life.[29] Although higher drug costs are associated with many of the newer antiemetic agents, the ultimate cost of inadequately treated CINV is to the

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Treatment Options for CINV

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Table 2. Treatment of CINV

Drug class	Agents (route of adminstration)	Side effects	Comments
5-HT_3 receptor antagonists	Ondansetron (oral/IV) Granisetron (oral/IV/transdermal) Dolasetron (oral/IV) Tropisetron (oral/IV) Palonosetron (oral/IV)	All drugs in class: • headache, constipation (most common), diarrhea, dizziness, fatigue, hypotension, drowsiness Dolasetron/ondansetron: • acute changes in echocardiogram, usually reversible Granisetron: • syncope, atrial fibrillation (rare) IV dolasetron • tachycardia, ventricular fibrillation (rare)	Headache not noted as a side effect with transdermal granisetron Tropisetron not available in United States Palonosetron is long-acting preparation (40 h half-life) In general, the guidelines agree that all 5-HT_3 receptor antagonists are essentially interchangeable with similar side effects
NK_1 receptor antagonists	Aprepitant (oral) Fosaprepitant (IV)	Hiccups, asthenia, fatigue, anorexia, constipation, diarrhea, dehydration, headache, dizziness	Potential for drug-drug interactions
Corticosteroid	Dexamethasone (oral/IV)	Hyperglycemia may occur (monitor patients with diabetes), anxiety, sleeplessness, skin changes (eg, acne), increased appetite may occur	Not FDA-approved as an antiemetic, but all guidelines recognize the role of corticosteroids in combination with other antiemetics, and as single-agent therapy for delayed-onset CINV
Cannabinoids	Nabilone (oral) Dronabinol (oral)	Sedation, euphoria, feeling of being "high," some reports of dysphoria	Not first-line therapy but may be appropriate for breakthrough treatment per NCCN guidelines
Substituted benzamide	Metoclopramide (oral/IV)	EPR reactions, particularly in younger patients; recommended to give with diphenhydramine to reduce EPR effects	Not first-line therapy but may be appropriate for breakthrough treatment per NCCN guidelines
Benzodiazepines	Lorazepam (oral/IV/sublingual)	Sedation, orthostatic hypotension, dizziness, ataxia	Not FDA-approved as an antiemetic, but all guidelines recognize the role of benzodiazepines as a useful adjunct to other antiemetics; particularly noted to be helpful with anticipatory CINV
Atypical psychotropic	Olanzapine (oral)	Asthenia, dizziness, drowsiness or sedation, constipation, dry mouth, dyspepsia, weight gain, hypotension, cough	Not first-line therapy but may be appropriate for breakthrough treatment per NCCN guidelines; not FDA-approved for CINV
Typical antipsychotic	Haloperidol (oral)	EPR reactions	Not first-line therapy but may be appropriate for breakthrough treatment per NCCN guidelines; not FDA-approved for CINV
Dopamine antagonists	Prochlorperazine (oral/IV) Promethazine (oral/IV)	EPR reactions (diphenhydramine may ameliorate these effects), sedation, akathesia, orthostatic hypotension	Not first-line therapy but may be appropriate for breakthrough treatment per NCCN guidelines

Nonpharmacologic treatments

Therapy	Comment
Acupuncture	Found to be effective in one review of 11 studies via electroacupuncture for first-day vomiting, but not on successive days; all patients also received antiemetic agents
Acupressure	Found to be effective in one review of 10 studies; overall effect strongly suggestive but not conclusive; authors strongly recommend as an effective adjunctive therapy with pharmacologic management of CINV if effects can be reproduced in future trials
Guided imagery	Found to produce a more positive experience with chemotherapy in one study; authors suggest that these implications can increase patient coping abilities and can be independently initiated
Music therapy	Found to act as an effective adjunct to pharmacologic regimen for decreasing CINV; authors suggest that this intervention can be initiated independently by nurses and individualized for each patient, producing beneficial effect
Progressive muscle relaxation	Found to improve CINV and QOL in patients with breast cancer; can be initiated independently by nurses

5-HT_3 indicates 5-hydroxytryptamine type 3; CINV, chemotherapy-induced nausea and vomiting; EPR, extrapyramidal; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network; NK_1, neurokinin-1; QOL, quality of life.
Sources: References 7-12.

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Medtronic

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MICHELSON TECHNOLOGY AT WORK

Nursing Careers

ONS Recognizes Outstanding Nursing Careers

Two nurses honored at the 34th Annual Oncology Nursing Society (ONS) Congress in San Antonio, Texas, recently spoke with *The Oncology Nurse* about their long and distinguished careers.

Rose Virani, RN, MHA, OCN, received the Pearl Moore "Making a Difference" award. Ms Virani is a senior research specialist in the Division of Nursing Research and Education at City of Hope, Duarte, California. Her research projects focus on cancer pain, and end-of-life/palliative care. She has served as project director of the End-of-Life Nursing Education Consortium (ELNEC) and is past president of the Inland Empire chapter of ONS.

How did you get into oncology nursing?

I got into it by chance. Throughout nursing school, I did not even think about oncology nursing. I always wanted to go into maternal and child health, but at the time of graduation, there was a medical strike going on in California over malpractice issues and only teaching institutions were hiring staff as they were not affected by the malpractice incident. I thought I would work at City of Hope for a year just to get experience. Once I started oncology nursing, I loved it, and I've stayed with it ever since.

What is the most satisfying aspect of your work? The most challenging?

Most satisfying is the fact that there are always new therapies in oncology and something new to learn. The most challenging aspect is finding better management of symptoms and assisting patients and their families to achieve a better quality of life.

Rose Virani, RN, MHA, OCN

You have been involved in ELNEC for quite a while. Please tell us about that.

Working in oncology, especially in the earlier years, end-of-life care was always an issue. Especially now with our aging population, we see more cancer and other chronic diseases. In the late 1990s, Dr Betty Ferrell, principal investigator, and I conducted a study examining end-of-life content in textbooks commonly used in nursing schools and found that only 2% of content in nursing textbooks was related to end of life. As a result of the study, ELNEC (www.aacn.nche.edu/elnec) was developed in 2000, and it's been very gratifying to see the impact it has had on nursing education and on helping healthcare professionals realize that you can achieve quality of life at the end of life.

ELNEC is a national effort to train nurses and provides programs on palliative care to undergraduate and graduate faculty, and continuing education providers for hospitals, hospices, oncology, pediatrics, geriatrics, and critical care nurses. ELNEC teaches nurses how to talk to patients and their families at the end of life and the importance of pain management. To date, ELNEC has trained more than 10,000 nurses and healthcare providers in the United States and internationally. ●

Breakthrough cancer pain

A Closer Look at Identifying the Problem

Cancer pain is a serious healthcare problem

A number of studies conducted over the past 20 to 25 years have demonstrated that pain is undertreated in nearly half of patients with cancer.[1-5] Recently, the Global Results Presentation conducted by European Pain in Cancer (EPIC) reported that many patients with cancer experience moderate-to-severe pain every day. Pain so severe, it is often described as "intolerable."[4] This type of cancer pain can be enduring and relentless.[5]

In addition to its severity, cancer pain is common throughout the entire course of disease. About a third of cancer patients experience pain at diagnosis, more than half experience pain during active treatment, and the majority experience pain with advanced disease.[6] Relatively low utilization rates of opioids have been reported among patients with metastatic cancer in their final year of life. Although published clinical guidelines recommend the use of opioids in this setting, this suggests that for many patients with advanced cancer, pain may be suboptimally treated.[5]

Cancer pain is one of the most feared consequences of cancer. Pain is believed to be part of "having cancer."[4] Although family members are supportive, they cannot fully comprehend the intensity of the pain or the patient's suffering.[4]

Untreated or undertreated pain has a profound impact on emotional distress.[3] Patients with pain have an increased incidence of psychological factors (ie, depression and anxiety), which intensify the pain experience, and patients with cancer pain who present with psychiatric symptoms might actually be showing symptoms of uncontrolled pain.[3]

Unrelieved, cancer pain destroys quality of life.[4] It adversely affects psychological and physical well-being.[7] Pain interferes with functioning, forces some patients to stop working, interferes with thinking or concentration, requires patients to rely heavily on other people, and prevents patients from caring for themselves or others.[4] Patients who experience persistent pain report a significant reduction in their ability to sleep, perform daily activities, engage in relationships with others, and enjoy life.[5] Pain also affects the family's ability to provide appropriate support.[2]

According to the National Cancer Institute, there is a low priority given to cancer pain treatment.[8] Physicians are trained to focus on prolonging life and achieving a cure, rather than assessing pain[8] or alleviating suffering.[3]

Deena Damsky Dell Receives Cancer Nursing Education Award

Deena Damsky Dell, MSN, RN-BC, AOCN, received the Mary Nowotny Excellence in Cancer Nursing Education Award at the 2009 ONS Congress. Ms Dell is clinical nurse specialist and director of the Graduate Nurse Transition Program at Fox Chase Cancer Center in Philadelphia.

How did you get involved in nurse education?

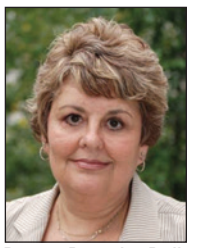
I began my career as a critical care nurse and started teaching medical/surgical nursing at the Massachusetts General Hospital nursing school in the 1970s. I then taught at Gwynedd-Mercy College in Philadelphia for several years. When I decided I wanted to get back into critical care, I chose Fox Chase because it offered me 2 weeks of orientation instead of the 2 days provided at other hospitals. After a few years here, I was asked to start a transition program for new graduate nurses.

Please tell us about the transition program.

The program was started because we realized that with the nursing shortage, we were going to have to hire new graduates unlike the experienced nurses we had been able to hire up to that point. We pride ourselves on the nursing care we give, and we didn't feel that new graduates would be ready to give the kind of nursing care we provide. We also didn't want to "eat our young" by throwing them into situations that they were not prepared for. So we had two goals—to have excellent nursing care and to support the new nurses and nurture them.

The program is three-tiered with different competencies along the way, starting with medical/surgical competencies, then getting into oncology-specific competencies, and finally leadership competencies. It includes both classroom education and working with a preceptor.

Was your award from ONS specifically for the transition program?



Deena Damsky Dell, MSN, RN-BC, AOCN

I also work with patients. In addition to the new graduate program, I run the advanced life support and telemetry courses and I work with another clinical nurse specialist doing pre- and post-operative teaching with breast cancer patients. When women come to our breast evaluation clinic, we hold a general educational session with one of the social workers and then we give them our names so they can call us with specific questions. We also do discharge teaching with them. I am also on the patient education committee at the hospital, so I am very involved in developing the educational materials we give patients.

What do you find the most satisfying aspect of your work? The most challenging?

It is very gratifying when nurses give me feedback about how I helped shape their career or when I see nurses giving excellent care to patients because of the classes I have taught. It is also satisfying to spend time with the patients and provide them with education and especially to see their anxiety melt away when I can answer their questions and teach them how to help themselves.

The most challenging part of my work is getting people to accept change. Patients are pretty good; they will accept change when they need it. But trying to get nurses, doctors, and others in the hospital to change the way they have been doing things can be difficult.

What advice would you give a young oncology nurse who is starting out a career?

Oncology nursing is a broad spectrum. An oncology nurse can be an inpatient nurse, an operating room nurse, an intensive care unit nurse, an outpatient nurse, a research nurse, a radiation nurse, an infusion room nurse, or a community educator. A depth of skills is required from basic physical care to emotional support and compassion. So oncology nursing is a career that is never boring. Oncology is not for people who don't want to keep on learning because an oncology nurse has to stay on top of things. For those who like to constantly be challenged and learn new things, it is a great field. ●

—Karen Rosenberg

Treatment Options for CINV

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Table 3. Recommendations for Antiemesis Agents

Treatment for Highly Emetogenic Chemotherapy Agents		
Organization (last updated)	**Acute-onset CINV**	**Delayed-onset CINV**
ASCO (2006)	5-HT_3-RA with dexamethasone plus aprepitant	Dexamethasone plus aprepitant
ONS (2005)	5-HT_3-RA with dexamethasone plus aprepitant with consideration of lorazepam	Dexamethasone plus aprepitant with consideration of lorazepam
MASCC (2008)	5-HT_3-RA with dexamethasone plus aprepitant or fosaprepitant	Dexamethasone plus aprepitant
NCCN (2009)	5-HT_3-RA[a] (palonosetron preferred, category 2B) with dexamethasone plus aprepitant or fosaprepitant with consideration of lorazepam and H2-blocker or proton-pump inhibitor	Dexamethasone (days 1 to 4) plus aprepitant (days 2 and 3) with consideration of lorazepam (days 1 to 4)
Treatment for Moderately Emetogenic Chemotherapy Agents		
Organization (last updated)	**Acute-onset CINV**	**Delayed-onset CINV**
ASCO (2006)	AC regimen, 5-HT_3-RA with dexamethasone and aprepitant; non-AC regimens, 5-HT_3-RA with dexamethasone	AC regimen, aprepitant alone; non-AC regimens, dexamethasone or a 5-HT_3
ONS (2005)	5-HT_3-RA with dexamethasone plus aprepitant with consideration of lorazepam	Consideration of dexamethasone, 5-HT_3-RA (ondansetron, granisetron, or dolasetron), metoclopramide ± diphenhydramine
MASCC (2008)	AC regimen, 5-HT_3-RA with dexamethasone plus aprepitant or fosaprepitant; non-AC regimens, 5-HT_3-RA with dexamethasone	AC regimen, aprepitant or dexamethasone; non-AC regimen, dexamethasone alone preferred, if not able to use consider 5-HT_3-RA
NCCN (2009)	Selected patients,[b] 5-HT_3-RA[a] with dexamethasone plus aprepitant or fosaprepitant with consideration of lorazepam and H2-blocker or proton-pump inhibitor; non-AC or selected patients, 5-HT_3-RA with dexamethasone with consideration of lorazepam and H2-blocker or proton-pump inhibitor	Selected patients,[b] aprepitant (days 2 and 3) with consideration of dexamethasone, or 5-HT_3-RA,[c] lorazepam, H2-blocker or proton-pump inhibitor (if used on day 1)

[a]5-HT_3 agents may include: ondansetron (oral/IV), granisetron (oral/IV/transdermal), dolasetron (oral/IV) or palonosetron (oral/IV).
[b]Selected chemotherapy regimens for consideration of aprepitant or fosaprepitant include: carboplatin, cisplatin, doxorubicin, epirubicin, ifosfamide, irinotecan, or methotrexate.
[c]Ondansetron, granisetron, or dolasetron.
5-HT_3-RA indicates 5-hydroxytryptamine type 3 receptor antagonist; AC, doxorubicin and cyclophosphamide; ASCO, American Society of Clinical Oncology; CINV, chemotherapy-induced nausea and vomiting; MASCC, Multinational Association for Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; ONS, Oncology Nursing Society.

patient, who may subsequently develop anticipatory and delayed-onset CINV, rendering further therapies for CINV less effective and possibly leading to withdrawal from treatment.[27]

Conclusion

CINV remains a significant problem for patients and, although treatment has improved considerably, more effective therapies for this adverse event are needed.[5,27] Clinicians can improve treatment of CINV by increasing awareness of therapeutic options and by incorporating existing clinical guidelines. Baseline assessments to determine increased risk of CINV should be conducted before chemotherapeutic treatments, and appropriate antiemetics should be selected according to individual risk and choice of chemotherapy agents. Oncology nurses play a key role in the initial and ongoing assessment of patients receiving chemotherapy who experience CINV. Further research is needed to identify best practice strategies for CINV. ●

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REMS for Opioids

Continued from cover

have authority to proactively evaluate the risks and mitigate them with high-risk medications.

Why has there been so much attention to opioids lately?

There is a large outcry in the general public health community regarding people who have been misusing or abusing opioids. Because they are such powerful drugs and are so widely used, some people can't handle them properly or don't understand their benefits. ONS is concerned about opioid misuse, but obviously our concern is that no undue burden be placed on our patients with cancer because they need their pain controlled.

Is opioid misuse a major concern among cancer patients?

There seems to be no quality data on this. The FDA did a study at the beginning of the REMS process, trying to determine the extent of misuse, but I don't think their data were particularly rigorous. Its study didn't separate cancer patients from others with chronic pain. I am not aware of any study that found misuse a huge problem among cancer patients. I think misuse is a small issue, but there are some patients who do not take the drugs as prescribed. A bigger concern of the cancer community is that pain isn't being adequately treated.

Could you summarize the ONS position on REMS for opioids?

ONS does not have an official position on REMS, but we have a position on cancer pain management. It states that pain needs to be adequately treated and with both pharmacologic and nonpharmacologic means. We think that untreated or undertreated pain is an issue for patients with cancer, and we want to decrease barriers so that patients can get the pain control they need.

We are sympathetic with what the FDA is trying to do. Opioid abuse and misuse is a real problem. Our bottom line is that if the FDA is going to take action, it needs to better define the problem. We don't know who is misusing the drugs or how the drugs are getting to people who are misusing them. We not only need to better define the problem but also the specific outcomes we hope to achieve.

We have recommended that the FDA test the program on a pilot basis before doing a nationwide rollout. Using the pilot program, the FDA can capture the needed data. That way, when the strategy rolls out nationwide, the FDA will be able to implement it well and patients with cancer won't be adversely affected.

What role can nurses play in education and in making sure that opioids are used safely and effectively?

Education is going to be a huge factor in making sure that both healthcare professionals and patients are well-informed. Patient education especially will be widely needed to make sure that the strategy goes well and there are no unintended consequences.

ONS has advocated with the FDA that oncology nurses be used in this effort. In my conversations with the FDA, it seems that it is focusing on healthcare provider education. Another important piece is patient education, and nurses can play that role. If the FDA tries to regulate education about REMS, it will have to determine how to keep track of it. I would like to see a nonprofit organization in the nursing community develop the patient education guidelines, but no organization can do that until it is known what the FDA plans to do.

Is there concern that if REMS are cumbersome to implement opioids will be less prescribed and patients' pain won't be adequately controlled?

That is a concern. If REMS are cumbersome, certain prescribers will choose not to go through the process and will just stop prescribing opioids. Then if an area has fewer providers prescribing the medications, it is going to be harder for patients to get adequate pain control.

We need to see how REMS play out. The worst case scenario is that patients can't get the medication they need, but if it is done properly, REMS will not have unintended consequences and patients will be able to access the drugs that they need. The FDA has implemented REMS for other medications, but those have never been this far-reaching. ONS just wants to do its part to advocate for patients and make sure that if the FDA does do something this far-reaching, it is as scientifically based as possible. ●

Fertility Preservation

Continued from cover

preserving fertility have greatly diminished, said Gwendolyn Quinn, PhD, MPH, an investigator in the health outcomes and behavior program at the H. Lee Moffitt Cancer Center, Tampa, Florida.

Some 40% to 80% of female cancer patients of childbearing age become infertile after chemotherapy or radiotherapy, and 30% to 75% of male cancer patients become sterile. The risks vary by patient age and treatment regimen (Table 1), with the patient's age at the time of chemotherapy being the greatest determinant of permanent gonadal failure, Quinn said.

Gonadal failure occurs when the body fails to produce sufficient amounts of sex hormones to suppress luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels to normal.

Risk according to cancer type and treatment regimen can be easily calculated on the Fertile Hope website (www.fertilehope.org/tool-bar/risk-calculator.cfm).

Survey shows oncologists are falling short

Considering these risks, the need for pretreatment fertility counseling would seem obvious, but a study by Quinn and colleagues at Moffitt raises concerns. In a national survey of oncologists' practice patterns, most physicians said they do discuss fertility preservation, but one quarter never or only rarely refer patients to infertility specialists or reproductive endocrinologists, and nearly one half never or rarely consult with specialists themselves, on behalf of their patients.

In addition, only one quarter distribute educational materials to their patients, and more than one third are unaware of current ASCO guidelines regarding fertility preservation, Quinn reported.

In 2006, ASCO issued guidelines recommending that oncologists address the risks of infertility and be prepared to discuss fertility preservation options or refer appropriate and interested patients to reproductive specialists. The guidelines include an algorithm for triaging fertility preservation referrals (*J Clin Oncol.* 2006;24:2917-2931).

"We found that the majority of physicians may not be following ASCO guidelines or consulting specialists about fertility preservation. We see this as a physician responsibility, but we understand there may be significant barriers to having this discussion," Quinn said during a press briefing at the meeting.

For one thing, oncologists note that fertility preservation seems far less important than saving a life. According to Quinn, one clinician said, "I'm very uncomfortable saying to a patient, 'You have a 20% chance of survival, and by the way, have you ever thought about having kids?'"

Survey of oncologists reveals interesting practices

The aim of the Moffitt survey was to determine practice patterns and characteristics that may impact referral to specialists.

The population included 1979 physicians recruited through the American Medical Association database stratified by board specialty related to oncology. Of these, 613 (33%) responded to the 58-item survey of knowledge, attitudes, perceptions, barriers, and practice behaviors (Table 2).

Making the Case for Fertility Preservation

- A 30-year-old childless woman is diagnosed with breast cancer and is scheduled to receive dose-dense doxorubicin plus cyclophosphamide followed by paclitaxel.
- It is estimated that this chemotherapy regimen will result in the loss of 10 years' worth of oocytes, giving this 30-year-old woman an egg reserve of a 40-year-old woman.
- After chemotherapy, the patient is prescribed tamoxifen for 5 years, during which time she must forego pregnancy; this reduces her already diminished egg reserve to that of a 45-year-old woman.
- As a result of her cancer treatment and the lack of fertility preservation, this woman has near-zero probability of achieving a pregnancy and bearing even one child.

—Kutluk Oktay, MD
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Chemotherapy-induced Peripheral Neuropathy: Prevention and Treatment

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LEARNING OBJECTIVES

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

- Review the epidemiology of chemotherapy-induced peripheral neuropathy (CIPN)
- Explain the causes of CIPN
- Describe the symptoms of CIPN
- Compare available pharmacologic and nonpharmacologic therapies for CIPN

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.

Chemotherapy-induced peripheral neuropathies (CIPNs) present an increasingly common neuropathic and pain syndrome in cancer survivors.[1,2] Peripheral neuropathy is the end result of peripheral, motor, sensory, and autonomic neuron damage secondary to neurotoxic chemotherapy agents that inactivate the components required to maintain the metabolic needs of the axon. The damage caused by chemotherapeutic agents can cause subsequent and long-term functional abnormalities of structural lesions in the peripheral and central nervous systems (CNS).[3-5] CIPN is sensory, dose-related, and cumulative. It is usually delayed and may appear weeks to months after the initiation of therapy. The chemotherapeutic agents most often associated with CIPNs are the platinum-based compounds, taxanes, vinca alkaloids, thalidomide, and bortezomib.[3-10] Although the incidence of peripheral neuropathy resulting from a single agent can be significant, the administration of two neurotoxic agents is not uncommon and results in higher grades of overall neurotoxicity.[11] At this time, no standard or evidenced-based therapies exist to prevent or treat CIPNs. This article aims to provide an understanding of CIPNs and to review the evidence for both its prevention and treatment.

Case study

A 56-year-old right-handed woman, a 2-year survivor of a stage IIIB adenocarcinoma of the left lung (Pancoast tumor) previously treated with cisplatin-gemcitabine-paclitaxel, presented to the clinic with left shoulder pain radiating into the left arm and hand, grade 3 CIPN, weight loss, hand weakness, poor appetite, and cough. She was clinically diagnosed with stage IV adenocarcinoma. During her previous treatment, she had developed grade 3 CIPN. She articulated the dominance of CIPN and pain on her quality of life (QOL):

> I no longer remember what it is like to not be in pain. I can't think of anything else but the pain and I can't concentrate at all. It has been like this for over 5 months. I have pain all over, under the cuff of my left arm, the doctor calls it subclavicle pain, and on my arm. I have lost time because of pain. I have pain that increases when I have chemotherapy, and I have pain that increases when I don't have chemotherapy. I am damned. I am so tired, I hurt, and I can't walk without the pain. I can't feel my feet anymore or my fingers. I can't drive, and I have lost my independence.

Pancoast tumors of the lung are relatively rare. The pain associ-

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ed with a Pancoast tumor can extend along an ulnar nerve distribution of the arm to the elbow and is frequently relentless and unremitting. Although a relatively unique scenario, this case illustrates the potential for severe complications from cancer and CIPN.

Pathopysiology and epidemiology

It has been hypothesized that neurotoxic chemicals directly damage nerve fibers by inactivation of components required to maintain the metabolic needs of the axon. The longer and larger distal axons are affected first and this may result in interruptions of axonal transport and degeneration of myelinated nerve fibers and unmyelinated axons.[8-10] In a recent animal-model study of paclitaxel-induced CIPN, abnormalities in the axonal mitochondria of sensory nerves were found to contribute to paclitaxel-induced neuropathic pain.[12] Under normal circumstances, large sensory neurons do not conduct noxious stimuli. These large myelinated sensory fibers are preferentially injured by neurotoxic chemotherapeutic agents. Injury or damage to large sensory fibers by chemotherapeutic treatments can also result in the paresthesias, dysesthesias, and decreased proprioceptive abilities. These stimuli can be detected by nerves within the body as well as by the semicircular canals of the inner ear. Thus, CIPNs induce a type of neuropathic pain and represent a serious yet understudied consequence of cancer treatment. The sensory and motor symptoms and signs of CIPNs are potentially disabling and can have a significant impact on QOL for patients with cancer.[13,14] Moreover, even when CIPN is not a dose-limiting side effect, its onset may severely affect QOL and cause chronic discomfort and pain.[6-11]

Risk factors include prior use of chemotherapies (particularly prior treatments with platinum-based therapies), older age, and female gender.

Prevalence and incidence

The prevalence of CIPNs is not known because of a lack of adequate standardized assessment, measurement, and reporting mechanisms.[3,9,11] Toxicity-grading scales used to detect CIPN vary widely, and specific guidelines for these instruments are lacking. The incidence of CIPN varies depending on the drugs, dosage, and treatment schedules used.[3-11] The incidence of severe CIPN has been estimated at about 3% to 7% in individuals treated with single agents and upward of 38% in those treated with multiple chemotherapeutic agents.[3-11]

Risk factors

Risk factors associated with worsening CIPN symptoms include prior use of chemotherapies (particularly platinum-based therapies), older age, and female gender. Comorbid conditions that appear to place patients at greater risk for CIPN include diabetes, human immunodeficiency virus infection, alcoholism, preexisting neuropathies (diabetic neuropathy, small fiber neuropathies), and vitamin B deficiencies.[3,6,11,13-15] The symptoms associated with CIPNs also vary widely (Table 1), and little is known about other risk factors. Moreover, even when neurophysiologic methods are used to diagnose CIPNs, there is still wide variation in the resultant symptoms, which enhances the difficulty in predicting and modeling which patients are potentially at the greatest risk.[4-11]

Mechanisms

The sensory and motor symptoms and signs of CIPNs are potentially disabling and can have a significant impact on QOL.[1-11] Yet, the mechanisms and risk factors associated with the development of CIPNs have not been fully elucidated. Several interesting mechanisms have been proposed. For instance, in patients with cancer, the immune response to tumor cells contributes to an already adverse proinflammatory state. One potential consequence is that tumoral invasion at central or peripheral sites can lead to mechanical damage, proteolysis, and the release of inflammatory pain mediators, including proinflammatory cytokines (ie, interleukin-1, interleukin-6, and tumor necrosis factor-α). These may result in damage to surrounding tissues and may also play a prominent role in the initiation, development, and maintenance of chronic pain states, including neuropathic pain.[16-26]

Other research has examined the impact of platinum-based cancer chemotherapies on mitochondrial function.[27] Alterations in mitochondrial function has been noted in cancer cell resistance to chemotherapeutic agents. Cisplatin's toxic side effects appear to be associated with mitochondrial injury in vivo and in vitro, highlighting the plausible role of mitochondria, including the role of production of mitochondrial electron transport chain reactive oxygen species in models of other forms of painful peripheral neuropathy.[27-30]

Variation in symptoms: presentation, progression, and resolution

The primary effects of CIPN are sensory, occurring in a stocking-and-glove distribution in the toes and fingers. The lack of gold-standard measures for CIPN and the wide variation in symptoms contribute to limitations in symptom management in patients. CIPN can vary in its onset, severity, and length, and its resolution cannot be predicted, as the symptomology can last from a few days to a lifetime.[3-11] The symptoms are described briefly below.

- The majority of patients report a gradual onset of neuropathic symptoms, although some develop symptoms more rapidly.[3-11]
- The primary effects are sensory, occurring in a stocking-and-glove distribution in the toes and fingers.[3-11]
- Terms such as "burning," "tingling," "electric shock sensation," and "painful numbness" have all been used to describe the sensations.[4,8]
- Patients may also report increased pain during walking, with descriptions of sensations such as "walking on shards of glass" or "stepping on razorblades."[4,8]
- Physical examination may reveal tactile allodynia, cold allodynia, hypersensitivity, and loss of deep tendon reflexes.[4,8]
- Motor symptoms such as declines in muscle strength can lead to muscle weakness and atrophy, precipitating functional impairment.
- Patients may also experience a loss of proprioception, the unconscious perception of movement and spatial orientation within the body.

Table 1. Symptoms of CIPN

Sensory symptoms
• Paresthesia
• Hyperesthesia or hypoesthesia
• Dysesthesia
• Pain
• Allodynia
• Numbness and tingling
• Electrical sensation (L'Hermitte's sign)
• Hyporeflexia or areflexia
• Diminished or absent proprioception
• Diminished or absent vibratory sensation
• Diminished or absent cutaneous sensation
• Diminished or absent sense of sharp/dull discrimination
Motor symptoms
• Weakness
• Gait disturbance
• Balance disturbance
• Difficulty with fine motor skills (buttoning clothing, writing)
Autonomic symptoms
• Constipation
• Urinary retention
• Sexual dysfunction
• Blood pressure alterations

CIPN indicates chemotherapy-induced peripheral neuropathy.

In addition, loss of proprioception can lead to significant safety issues.[8,9,13] Patients without proprioception are at a great risk for falls because they also tend to lose all sense of the position of their feet. This raises concerns about their ability to drive safely, particularly when they are unable to feel the brakes or lack the strength to press a pedal adequately.[7,9,15]

Heterogeneity in CIPN-related symptoms can range from an almost exclusively sensory to a sensory-motor neuropathy, with or without clinical evidence of autonomic impairment.[3,11,13-15,24-26] Recent insight from animal and human studies suggests that the great heterogeneity in the underlying mechanism(s) of nerve injury caused by individual agents may partly explain the wide variation in the resultant symptoms.[3,11,24,26,31-34] Chemotherapeutic toxicity is also influenced by multiple genetic factors and nongenetic factors, including age, gender, and drug-drug interactions.[26,31-38] The manifestations of adverse drug reactions also differ between men and women. Women tend to experience greater toxicity from chemotherapeutic drugs than men.[34] Recent studies suggest that the mechanisms underlying the various forms of peripheral neuropathy

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Table 2. Pharmacologic Prevention and Treatment of CIPN

Agent	Studies	Conclusions
Acetyl L-carnitine	Bianchi G, et al. 2005[35] Maestri A, et al. 2005[64]	• Tested for the treatment of preexisting paclitaxel- or cisplatin-induced peripheral neuropathy • Nonrandomized design and small sample sizes are limitations • Randomized clinical trials are necessary before recommendation as a potential treatment for CIPN
Amifostine	Hilpert F, et al. 2005[42] Leong SS, et al. 2003[74] Moore D, et al. 2003[43] Openshaw H, et al. 2004[44]	• Due to negligible toxicity, low cost, and lack of interference with chemotherapy, may be a viable preventive treatment for oxaliplatin-based therapy
Calcium/magnesium infusions	Gamelin L, et al. 2004[48] Hochster HS, et al. 2007[75] Hochster HS, et al. 2008[76] Nikcevich DA, et al. 2008[77]	• Because of negligible toxicity, low cost, and lack of interference with chemotherapy, may be a viable preventive treatment for patients receiving oxaliplatin-based therapy
Carbamazepine	Eckel F, et al. 2002[51] von Delius S, et al. 2007[52]	• No grade 2 to 4 neuropathy in patients treated with carbamazepine vs 30% in historical controls • In patients with colorectal cancer, no differences in neurotoxicity with carbamazepine • Randomized, placebo-controlled trials are necessary to determine use for prevention or treatment of CIPN
Gabapentin	Rao RD, et al. 2007[62]	• No benefit with gabapentin to treat CIPN symptoms found in phase 3 trial
Glutamine	Stubblefield MD, et al. 2005[53] Vahdat L, et al. 2001[54] Wang WS, et al. 2007[55]	• Patients developed less grade 1 to 2 CIPN as compared with controls • Larger, randomized, placebo-controlled trials are necessary to assess efficacy for the prevention of CIPN
Glutathione	Cascinu S, et al. 1995[59] Cascinu S, et al. 2002[57] Smyth JF, et al. 1997[58]	• Significantly less CIPN experienced by patients • Randomized clinical trials are needed to test the effectiveness as an intervention for CIPN
Nortriptyline	Hammack JE, et al. 2002[63]	• Based on one small pilot study and lack of objective measurements of neuropathy, effectiveness in reducing neuropathy-associated paresthesia is not established
Vitamin E	Argyriou AA, et al. 2005[47] Argyriou AA, et al. 2006[78] Bove L, et al. 2001[45] Pace A, et al. 2003[46] Pace A, et al. 2007[79]	• Reduced the incidence and severity of cisplatin-related CIPN • Randomized clinical trials with larger sample sizes are still needed to further evaluate role in prevention and treatment of CIPN

CIPN indicates chemotherapy-induced peripheral neuropathy.

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may actually be different, and therapies have to be tailored in light of these different neurotoxic effects.[27] These issues further contribute to the difficulties in predicting which patients from which populations will exhibit long-term damage from chemotherapeutic treatments.[39-41]

Some chemotherapeutic agents are known to induce neurotoxicity that extends beyond the discontinuation of therapy, a phenomenon known as coasting.[3] It is still quite difficult to predict whether otherwise neurologically normal patients will exhibit susceptibility to the neurotoxic effects of chemotherapy.[3-11] The diagnosis, assessment, and management of CIPNs are also complicated by the lack of a reliable and standardized means to diagnose and monitor patients at risk of or who become symptomatic from this complication of treatment.[26,31,32] Finally, no well-established guidelines exist for dose reduction.[8-11] This wide variation in symptoms remains a significant barrier that further contributes to the inadequate pain assessment and management of CIPNs.

Prevention of CIPN

Chemoprotectants

Chemoprotectants such as amifostine have been tested as a means of detoxifying chemotherapy and facilitating DNA repair while not interfering with the efficacy of chemotherapy (Table 2). In the studies testing the effect of amifostine on peripheral neuropathy associated with taxane-based chemotherapy regimens, no differences were found in sensory or motor neurotoxic symptoms in patients treated with amifostine. Amifostine was also found to be ineffective in preventing or reducing the neurotoxic effects of high-dose paclitaxel.[42-44]

Vitamin E

Vitamin E has been thought to protect against cellular oxidative damage and side effects, such as numbness, tin-

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COMMENTARY

Chemotherapy-induced Peripheral Neuropathy: Prevention and Treatment: A Nurse's Perspective

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Knowledge of current treatment and supportive care strategies for common cancer-related toxicities is critical to the provision of quality nursing care. Visovsky and Moore provide a comprehensive overview of the epidemiology, prevalence, characteristics, and management of chemotherapy-induced peripheral neuropathy (CIPN). The article will not only serve as an excellent resource for clinical oncology nurses, but also allow them to provide comprehensive education for cancer patients about what to expect with CIPN.

The assessment and management of CIPN continues to be a clinical challenge for healthcare professionals for several reasons that are addressed by the authors and others. First, there is great variability in the characteristics of symptoms related to CIPN. This may, in part, be related to the specific class of chemotherapeutic agents that causes CIPN, but currently there is no conclusive evidence that explains this variability. The variability in symptom characteristics also poses a clinical challenge for developing effective assessment and follow-up protocols for CIPN. Second, although research is ongoing, CIPN is still overall a poorly understood phenomenon. Current evidence related to the underlying neurobiology, actual prevalence rates, and a lack of definitive animal models are factors that affect our overall understanding of CIPN.[1] Finally, despite the growing number of clinical trials testing various therapeutic options for CIPN, currently there is no standard, evidence-based treatment for the prevention or treatment of CIPN.[2]

Understanding the relationship between CIPN and quality of life (QOL) is important not only for patients but also for nurses caring for individuals with cancer. To thoroughly understand how CIPN affects the QOL of our patients, there is a need to capture the overall experience of living with CIPN from the patient's perspective. Few qualitative studies conducted in recent years have attempted to understand CIPN from the subjective perspective. Bakitas conducted an excellent qualitative study that described the CIPN symptom experience and the effect of symptoms on everyday life.[3] Patients described CIPN as "background noise" that can be overshadowed by other treatment- and disease-related issues, but CIPN's unpleasantness can interfere with daily activities and socialization. The awareness of CIPN was often inaccurate and surprising because most patients did not recall being educated or advised to anticipate the symptoms. When monitoring CIPN, clinicians primarily focused on how the symptoms affected motor functionality (dexterity, gait) but rarely asked about CIPN's effect on daily living. CIPN caused disruptions with daily living, leisure, work, and family roles. Patients who reported a pain component to their CIPN often experienced functional difficulties, fatigue, sleep disturbance, and mood disturbances. Patients also described the use of multiple processes in learning to live with CIPN.

Similar results have been described in another qualitative study conducted by Closs and colleagues[4] as well as in our work at the City of Hope. Our descriptive, mixed methods study explored the impact of peripheral neuropathy on QOL in 53 patients with colorectal cancer. Our qualitative data suggest that although patients did not find the dysesthesias and cold-related allodynia distressing, the acute sensations were surprising when first experienced, and patients made adjustments in life (eating and drinking habits related to cold foods and beverages) to cope with these neuropathic symptoms.[5]

There are several ways that nurses can contribute clinically and scientifically to the sparse evidence in CIPN prevention and management. By keeping abreast with the most current information on CIPN management, nurses are better equipped to provide quality care and support to cancer patients living with CIPN. The prompt assessment of symptoms related to CIPN is essential for determining appropriate and effective management strategies. The assessment of CIPN should continue throughout treatment and beyond, because chronic CIPN can occur months and even years beyond treatment.[6] Most important, nurses must be vigilant in educating patients on what to expect with CIPN. It is evident from some of the current evidence that clinicians are not doing an optimal job of providing patients with timely information on CIPN. Beyond pharmacologic treatments, it may also be helpful for nurses to discuss nonpharmacologic supportive care strategies to cope with CIPN, such as personal safety measures to prevent burns, falls, or other problems that may be related to sensory motor deficits.[7] Finally, for nurses who are committed to advancing the science of CIPN management, there is a need for more studies and evidence that focuses on outcomes beyond the efficacy of therapeutic agents.[8] Studies that characterize the time of onset, duration, and resolution or persistence of CIPN are needed to develop a more comprehensive and subjective understanding of CIPN.[1] ●

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gling, burning, and/or pain in peripheral extremities produced by cisplatin and other cytotoxic drugs. Three studies examined the cytoprotective effect of vitamin E supplementation on the development of CIPN following the administration of cisplatin, paclitaxel, or a combination regimen.[45-47] The findings, based on subjective, clinical, and electrophysiologic assessments, showed that the incidence of neurotoxicity was lower in the group that received vitamin E as compared with the control group. Further randomized clinical trials are needed, however, to evaluate the role of vitamin E in the prevention and treatment of CIPN.

Calcium and magnesium

Infusions of calcium and magnesium have been used as a means of preventing oxaliplatin-associated CIPN. Oxalate, an oxaliplatin metabolite, seeks out and binds to calcium and magnesium.[48] In one study, 140 patients were randomly assigned to receive calcium gluconate and magnesium sulfate or placebo before and after oxaliplatin to reduce neurotoxicity. Improvements in the clinical manifestations of acute neurotoxicity were reported after infusion of calcium and magnesium, and at the end of oxaliplatin therapy, 65% of the patients in the calcium/magnesium infusion group had no symptoms of neuropathy compared with only 37% in the control group.[48] There was concern that tumor response rates may be lower in patients who received calcium and magnesium infusions. A subsequent review of computed tomography scans from the trial, however, showed that the antitumor response rates were actually numerically higher in the group that received the calcium and magnesium infusions compared with those who received placebo. Thus, calcium and magnesium infusions appear to offer a safe, cost-effective means of preventing oxaliplatin-related peripheral neuropathy.[49,50]

Carbamazepine

Carbamazepine, an anticonvulsant drug, appears to protect against oxaliplatin-induced neurotoxicity by slowing the rate of recovery of voltage-activated sodium channels. Carbamazepine was tested in the prevention of CIPN in a single nonrandomized pilot study consisting of 10 previously treated patients with advanced colorectal cancer receiving oxaliplatin, leucovorin, and 5-fluorouracil. Results indicated the absence of World Health Organization grade 2 to 4 neuropathy development in the patients treated with carbamazepine compared with 30% who experienced grade 2 to 4 neuropathy in a historical control group.[51] In a randomized controlled trial, von Delius and colleagues tested the efficacy and safety of carbamazepine for neuropathy in 36 patients with

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Chemotherapy-induced Peripheral Neuropathy: Prevention and Treatment: A Pharmacist's Perspective

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Chemotherapy-induced peripheral neuropathy (CIPN) is a relatively common and poorly treated adverse effect of several anticancer drug classes, including the taxanes, vinca alkaloids, platinum analogs, and the antimyeloma drugs, thalidomide, lenalidomide, and bortezomib.

Because there are no proven therapies to treat CIPN, methods to prevent CIPN are particularly important. The ability of any given agent to prevent CIPN needs to be weighed against any real or theoretical concern of diminished antitumor effect. Because the mechanisms of CIPN are thought to be at least in part an extension of the drug's mechanism of antitumor effect (eg, tubulin inhibition, DNA adduct formation), the proposed protective agents (amifostine, calcium/magnesium, vitamin E, glutamine, N-acetylcysteine, glutathione, acetyl L-carnitine, and erythropoietin) need to be used thoughtfully. This is particularly true given that there is no strong evidence that many of these agents lower rates of CIPN.

The ability of any given agent to prevent CIPN needs to be weighed against any real or theoretical concern of diminished antitumor effect.

One method of reducing the rates of CIPN is related to advances in drug development and formulation of anticancer drugs. For example, carboplatin was developed by the addition of a more complex and bulky-leaving group to the cisplatin molecule, leading to the production of less reactive platinum species and lower rates of several of the toxicities associated with cisplatin, including CIPN. Oxaliplatin is much more like cisplatin despite its more complex chemical structure, and substantial reduction in CIPN compared with cisplatin has not been realized. Cisplatin may be more likely to produce permanent neurologic damage, consistent with the science showing three times more platinum-DNA adduct formation in the dorsal root ganglia with cisplatin compared with oxaliplatin.[1] The CIPN associated with docetaxel is less severe than that with paclitaxel. Variation is also seen among the vinca alkaloids, vinblastine and vinorelbine, which are associated with lower rates of CIPN compared with vincristine. The differences between these antimitotic drugs are based on differences in their affinity for axonal microtubules.

In addition to drug selection that can minimize CIPN, a number of new formulations of neurotoxic chemotherapy may improve tolerability. For instance, although nanoparticle albumin-bound paclitaxel is not less likely to produce CIPN than solvent-based paclitaxel, the CIPN that develops may be more reversible.[2]

The inhibitors of tumor progression commonly used to treat multiple myeloma (thalidomide, lenalidomide, and bortezomib) have differing liability for CIPN. Thalidomide is a common cause of CIPN, which is only slowly or incompletely reversible and related to cumulative dose. In comparison, CIPN is uncommon with lenalidomide and, when present, is usually mild. Bortezomib is associated with neuropathy in approximately one third of patients.[3] Bortezomib-induced CIPN, however, is generally more rapidly reversible than that with thalidomide, and resolves in most patients after dose reduction or discontinuation.[3,4] Unfortunately, determining the clinical nature of the CIPN associated with these agents is difficult given that patients with multiple myeloma may have a history of receiving neurotoxic therapy, and the underlying disease itself may be associated with neurologic deficit.[4]

It is not always possible to switch between drugs of the same class because of either nonequivalence in a given tumor or lack of data demonstrating clinical equipose. In addition, lower rates of CIPN are often at the cost of higher rates of myelosuppression or other toxicities that may create equal or greater clinical issues.

In conclusion, although prevention of CIPN is preferred given the lack of agents to effectively treat CIPN and the potential irreversibility of the damage, there are limited data on the value of preventive agents. In addition, antagonism of antitumor activity with preventive therapies is not a settled issue. The appropriate selection of both analog and formulation may be an effective method of minimizing this important complication of chemotherapy. ●

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advanced colorectal cancer.[52] No differences were found between the groups on assessments of neurotoxicity. Further randomized, placebo-controlled trials are necessary to determine if carbamazepine can be used to prevent or treat CIPN.

Glutamine

Glutamine, a neutral gluconeogenic nonessential amino acid, is thought to have neuroprotective effects for patients receiving paclitaxel.[53] In one study, 12 women with advanced breast cancer were given glutamine 10 g daily for 4 days starting 24 hours after completion of paclitaxel and 33 women did not receive glutamine. Only 8% of women treated reported dysesthesias in the fingers and toes compared with 40% of the women who did not receive glutamine.[54] In another study, Stubblefield and colleagues examined the neuroprotective effect of glutamine on 46 patients scheduled to receive high-dose paclitaxel before stem cell transplant.[53] Seventeen patients received glutamine, and 29 patients made up the control group. Responses to questions about neurologic symptoms and results of electrodiagnostic testing indicate that those who received glutamine developed less weakness, loss of vibratory sensation, and toe numbness compared with those in the control group. In a nonrandomized pilot study, Wang and colleagues tested the efficacy of glutamine for reducing the incidence and severity of peripheral neuropathy in patients receiving oxaliplatin in 86 patients with colorectal cancer.[55] Glutamine supplementation significantly reduced the incidence and severity of oxaliplatin-induced neuropathy. The percentage of grade 3 to 4 sensory neuropathy was lower in the glutamine group after four cycles of treatment and remained that way for six cycles. The results suggest that glutamine is a potential neuroprotective agent but must be studied in larger populations in a randomized, placebo-controlled trial. Concerns still exist about glutamine supplements protecting tumor cells from the cytotoxic effects of chemotherapy.[55]

Glutathione

Some evidence shows that glutathione, a naturally occurring thiol tripeptide, may also prevent neurotoxicity induced by platinum compounds by preventing the initial accumulation of platinum adducts in the dorsal root ganglia.[56] Three studies testing the potential neuroprotective effects of glutathione have been published.[57-59] Following all cycles of chemotherapy, the incidence of neuropathy was greater in the placebo-treated arms compared with those who received glutathione. Further randomized clinical trials are needed to test the effectiveness of this agent in CIPN.

Treatment of CIPN

Historically, treatments for CIPNs have been supportive.[60] Neuropathic pain management is aimed at the reduction of symptoms, generally by suppressing neuronal activity not glial cell activation, which has also recently been associated with the development and maintenance of chronic pain states.[13,61] At this time, no medications exist that can fully relieve the sensory and motor loss associated with advanced CIPNs. The needs of patients with CIPNs are largely unmet because of the absence of adequate assessment and evidence-based treatments that could be widely applied across clinical CIPN patient populations and could potentially prevent or mitigate this increasingly common clinical problem.[11]

Patients who received acetyl L-carnitine showed improvement in neuropathy symptoms and in objective measures of sensory and motor neuropathy.

Gabapentin

Gabapentin is an antiepileptic medication that has demonstrated efficacy for the treatment of neuropathic pain, possibly in patients with CIPNs. Gabapentin was initially synthesized to mimic the chemical structure of the neurotransmitter gamma-aminobutyric acid, but it is not believed to act on the same brain receptors. Although the exact mechanism of action is unknown, the therapeutic action of gabapentin on neuropathic pain is thought to involve voltage-gated calcium channels. In a phase 3, randomized, double-blind, placebo-controlled, crossover trial, 115 patients with symptomatic CIPN were randomized to receive either gabapentin or placebo over the course of two 6-week phases separated by a 2-week "washout" period. No significant differences were reported between the groups on scores of symptom distress or mood states. The only significant difference between the groups was in the McGill Pain Rating Index, which showed lower pain in the gabapentin group at the end of the first 6-week treatment period. The study failed to demonstrate the benefit of gabapentin to treat CIPN symptoms.[62]

Nortriptyline

Nortriptyline, a tricyclic antidepressant, works by blocking the reuptake of serotonin and norepinephrine in the pain-modulating system within the CNS.[63] In a randomized, double-blind, placebo-controlled, crossover study, 51 patients treated with cisplatin received escalating doses of nortriptyline up to 100 mg/day over a 4-week period. Responses to questionnaires concerning pain, sleep, QOL, and neuropathic symptoms also indicate a relatively modest benefit in cisplatin-induced paresthesia over the placebo group. Objective measures of neuropathy were not used in this small pilot study, and thus the effectiveness of nortriptyline in reducing paresthesias related to CIPN cannot be established.

Acetyl L-carnitine

Acetyl L-carnitine is an acetylated form of L-carnitine that has shown neuroprotective effects and may be useful in treating peripheral nerve injury. Two small studies examined the use of acetyl L-carnitine in the treatment of preexisting paclitaxel- or cisplatin-induced peripheral neuropathy.[64] Patients who received acetyl L-carnitine showed improvement in neuropathy symptoms and in objective measures of sensory and motor neuropathy; however, small sample sizes and nonrandomized one-group designs limit these studies. Further randomized clinical trials are necessary before acetyl L-carnitine can be recommended as a potential treatment for CIPN.

Alternative treatments

Acupuncture

In one case series study testing the use of acupuncture in five patients with CIPN, this modality was found to improve sensation and gait, resulting in decreased analgesic use. Control of symptoms persisted for 6 months for four of the five patients treated.[65]

Physical activity/exercise

Three relatively small studies examined progressive resistance exercise, aerobic exercise, and stretching exercises in the treatment of diabetic peripheral neuropathy and myotonic dystrophy. All three studies found significant improvement in stance, functional reach, and peroneal and sural motor nerve conduction velocity. The findings of these studies should be interpreted with caution, as they have not been replicated in patients who have or are at risk for CIPN.[66-68]

Pulsed infrared light therapy (PILT)

PILT, also called anodyne therapy, consists of delivering infrared light to the feet of patients with diabetes, but it has not been tested as a treatment for CIPN. Following a series of treatments, significant improvement in sensation, neuropathic symptoms, and pain was evident in most patients.[69] Prendergast and colleagues found anodyne therapy improved sensory impairments as measured by peroneal nerve function and current perception thresholds in 26 participants after 10 treatments delivered over 2 weeks, each lasting 40 minutes.[70] In another study, significant improvements in sensation were found when PILT treatments were given for 30 minutes three times a week over an 8-week period.[71]

Transcutaneous electrical nerve stimulation (TENS)

TENS has been tested in patients with diabetic neuropathy, but not in patient populations with cancer. In a randomized clinical trial of 19 patients with diabetic neuropathy, Forst and colleagues compared TENS with pseudostimulation by an electrically inactive device.[72] Significant subjective improvements in neuropathy symptoms, including numbness, pain, and allodynia, were demonstrated in 70% of treatment group participants compared with 29% in the control group.

Capsaicin ointment

Capsaicin has been studied for the treatment of peripheral neuropathy in the diabetic population, with inconclusive results that prevent recommendation at this time. Although 10 patients who received capsaicin completed a study with a significant decrease in hypoesthesia, two patients discontinued treatment due to erythema or generalized allergic skin reaction at the application site.[73]

Conclusions

Evidence supports the need for careful and ongoing assessment of CIPNs in patients receiving chemotherapy. Specifically, clinical practice procedures need to be developed that address the need for standardized assessments of CIPN, the frequency of CIPN evaluations while undergoing chemotherapy, and the length of assessments once treatment is completed. In addition, there is a need to determine the clinically significant amount of sensory and motor changes noted in either sensory or motor nerves that may warrant a dose reduction in the treatment drug and/or the need for a

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rehabilitation evaluation by a physical or occupational therapist. In the absence of evidence-based prevention or treatment modalities for CIPNs, clinicians must educate their patients about the functional changes they may expect to occur as a result of neurotoxic chemotherapy and assist patients in developing strategies to manage limitations resulting from CIPNs. ●

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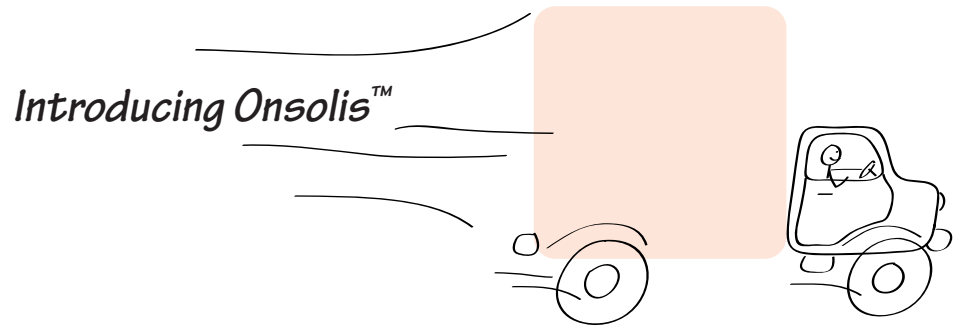


Unique Delivery System

A fentanyl buccal delivery system now approved for the management of breakthrough pain in opioid-tolerant adult patients with cancer.[1]

- All patients MUST begin treatment using one 200-mcg film
- Do not switch patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to Onsolis

Thin (0.26 mm) soluble film shown actual size

New

Onsolis™

fentanyl buccal soluble film

www.onsolis.com

Indication

ONSOLIS is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

ONSOLIS contains fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics. This should be considered when prescribing or dispensing ONSOLIS in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances, which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

ONSOLIS is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ONSOLIS is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis.

ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS. Patients beginning treatment with ONSOLIS must begin with titration from the 200 mcg dose [see *Dosage and Administration* (2)].

When dispensing, do not substitute an ONSOLIS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of ONSOLIS compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ONSOLIS. If the breakthrough pain episode is not relieved, patients should wait at least 2 hours before taking another dose [see *Dosage and Administration* (2)].

ONSOLIS is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that ONSOLIS contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All ONSOLIS films must be kept out of the reach of children [see *Patient Counseling Information* (17)].

The concomitant use of ONSOLIS with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations and may cause potentially fatal respiratory depression [see *Drug Interactions* (7)].

Because of the risk for misuse, abuse, and overdose, ONSOLIS is available only through a restricted distribution program, called the FOCUS Program. Under the FOCUS Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS. To enroll in the FOCUS Program, call 1-877-466-7654 (1-877-4ONSOLIS) or visit www.OnsolisFocus.com [see *Warnings and Precautions* (5.3.1)].

Important Safety Information

- The most serious adverse reactions associated with all opioids including ONSOLIS™ are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression
- In ONSOLIS™ trials, the most common adverse events (frequency ≥10%) were nausea, vomiting, dizziness, anemia, dehydration, peripheral edema, dyspnea, and somnolence

Please see Boxed Warning and brief summary of Prescribing Information on adjacent pages.

1. Onsolis™ [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc.; 2009.

MEDA PHARMACEUTICALS

ONSOLIS™ (fentanyl buccal soluble film), CII

Brief Summary: Please see full prescribing information.

PHYSICIANS AND OTHER HEALTHCARE PROVIDERS MUST BECOME FAMILIAR WITH THE IMPORTANT WARNINGS IN THIS LABEL.

WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE

ONSOLIS contains fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics. This should be considered when prescribing or dispensing ONSOLIS in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances, which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

ONSOLIS is indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg of oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ONSOLIS is contraindicated for use in opioid non-tolerant patients including those using opioids intermittently, on an as needed basis.

ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products.

When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS. Patients beginning treatment with ONSOLIS must begin with titration from the 200 mcg dose [see *Dosage and Administration* (2)].

When dispensing, do not substitute an ONSOLIS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of ONSOLIS compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of ONSOLIS for any other fentanyl product may result in fatal overdose.

Special care must be used when dosing ONSOLIS. If the breakthrough pain episode is not relieved, patients should wait at least 2 hours before taking another dose [see *Dosage and Administration* (2)].

ONSOLIS is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that ONSOLIS contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. All ONSOLIS films must be kept out of the reach of children [see *Patient Counseling Information* (17)].

The concomitant use of ONSOLIS with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations and may cause potentially fatal respiratory depression [see *Drug Interactions* (7)].

Because of the risk for misuse, abuse, and overdose, ONSOLIS is available only through a restricted distribution program, called the FOCUS Program. Under the FOCUS Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS. To enroll in the FOCUS Program, call 1-877-466-7654 (1-877-40NSOLIS) or visit www.OnsolisFocus.com [see *Warnings and Precautions* (5.3.1)].

INDICATIONS AND USAGE

ONSOLIS (fentanyl buccal soluble film) is an opioid analgesic indicated only for the management of breakthrough pain in patients with cancer, 18 years of age and older, **who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain.** Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression could occur in patients not taking chronic opiates. For this reason, ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

ONSOLIS is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

CONTRAINDICATIONS

Because life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients, ONSOLIS is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. This product **must not** be used in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

ONSOLIS is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

DOSAGE AND ADMINISTRATION

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

Only prescribers enrolled in the FOCUS Program may prescribe ONSOLIS [see *Warnings and Precautions* (5.3.1)].

Dose Titration

The goal of dose titration is to find the individual patient's effective and tolerable dose. The dose of ONSOLIS is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by dose titration.

Starting Dose: Individually titrate ONSOLIS to a dose that provides adequate analgesia with tolerable side effects. All patients MUST begin treatment using **one** 200 mcg ONSOLIS film. Due to differences in pharmacokinetic properties and individual variability, **patients switching from another oral transmucosal fentanyl product must be started on no greater than 200 mcg of ONSOLIS. When prescribing, do not switch patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to ONSOLIS** as ONSOLIS is not equivalent on a mcg per mcg basis with any other fentanyl product. ONSOLIS is NOT a generic version of any other oral transmucosal fentanyl product.

From the initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia.

If adequate pain relief is *not achieved* after **one** 200 mcg ONSOLIS film, titrate using multiples of the 200 mcg ONSOLIS film (for doses of 400, 600, or 800 mcg). Increase the dose by 200 mcg in each subsequent episode until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Do not use more than four of the 200 mcg ONSOLIS films simultaneously. When multiple 200 mcg ONSOLIS films are used, they **should not be placed on top of each other** and may be placed on both sides of the mouth.

If adequate pain relief *is not achieved* after 800 mcg ONSOLIS (i.e., **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film. Doses above 1200 mcg ONSOLIS should not be used.

Once adequate pain relief is *achieved* with a dose between 200 and 800 mcg ONSOLIS, the patient should use or safely dispose of all remaining 200 mcg ONSOLIS films [see *Disposal of ONSOLIS* (16.2)]. Patients who require 1200 mcg ONSOLIS, should dispose of all remaining unused 200 mcg ONSOLIS films [see *Disposal of ONSOLIS* (16.2)]. The patient should then get a prescription for ONSOLIS films of the dose determined by titration (i.e., 200, 400, 600, 800, or 1200 mcg) to treat subsequent episodes.

Single doses should be separated by at least 2 hours. ONSOLIS should only be used once per breakthrough cancer pain episode, i.e., ONSOLIS should not be redosed within an episode.

During any episode of breakthrough cancer pain, if adequate pain relief *is not achieved* after ONSOLIS, the patient may use a rescue medication (after 30 minutes) as directed by their healthcare provider.

Dose Titration					
ONSOLIS is available in five dosage strengths: **200, 400, 600, 800,** and **1200 mcg**					
The initial dose is 200 mcg ONSOLIS					
▼ Titrate by incrementally increasing the dose once per episode					
Fentanyl dose	**200 mcg**	**400 mcg**	**600 mcg**	**800 mcg**	**1200 mcg**
Using	200 mcg ONSOLIS film(s)				1200 mcg ONSOLIS film
Using	1	2	3	4	1
▼					
If adequate pain relief *is achieved*, treat subsequent breakthrough cancer pain episodes using the determined dose.					
ONSOLIS should only be used once per episode. **ONSOLIS dosing should be separated by at least 2 hours.** During any episode, if adequate pain relief *is not achieved* within 30 minutes, the patient may use a rescue medication as directed.					

Dosage Adjustment

During maintenance treatment, if the prescribed dose no longer adequately manages the breakthrough cancer pain episode for several consecutive episodes, increase the dose of ONSOLIS as described in Dose Titration (2.1). Once a successful dose has been found, each episode is treated with a single film. ONSOLIS should be limited to four or fewer doses per day. Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than four breakthrough cancer pain episodes daily.

Administration of ONSOLIS

Use the tongue to wet the inside of the cheek or rinse the mouth with water to wet the area for placement of ONSOLIS. Open the ONSOLIS package immediately prior to product use. Place the entire ONSOLIS film near the tip of a dry finger with the pink side facing up and hold in place. Place the pink side of the ONSOLIS film against the inside of the cheek. Press and hold the ONSOLIS film in place for 5 seconds. The ONSOLIS film should stay in place on its own after this period. Liquids may be consumed after 5 minutes.

An ONSOLIS film, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when used as directed [see *Clinical Pharmacology – Pharmacokinetics* (12.3)].

The ONSOLIS film should not be cut or torn prior to use.

The ONSOLIS film will dissolve within 15 to 30 minutes after application. The film should not be manipulated with the tongue or finger(s) and eating food should be avoided until the film has dissolved.

WARNINGS AND PRECAUTIONS

***See Boxed Warning* - WARNINGS: IMPORTANCE OF PROPER PATIENT SELECTION and POTENTIAL FOR ABUSE**

Respiratory Depression (Hypoventilation)

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in ONSOLIS. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

Patient/Caregiver Instructions

Patients and their caregivers must be instructed that ONSOLIS contains a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. Patients and their caregivers must be instructed to keep ONSOLIS out of the reach of children. [see *How Supplied* (16.3), *Storage and Handling* (16.1), and *Patient Counseling Information* (17)]. Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

ONSOLIS Dispensing

When dispensing, do not substitute an ONSOLIS prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetic profile of ONSOLIS compared to other fentanyl products (e.g., see Figure 1) that result in clinically important differences in the extent of absorption of fentanyl. **As a result of these differences, the substitution of ONSOLIS for any other fentanyl product may result in fatal overdose. ONSOLIS is NOT a generic version of any other transmucosal fentanyl product.**

ONSOLIS Distribution Program

ONSOLIS is available only through a restricted distribution program called the FOCUS Program. Under the FOCUS Program, only prescribers, pharmacies, and patients registered with the program are able to prescribe, dispense, and receive ONSOLIS. This program provides educational materials, patient counseling and facilitated distribution of the drug. To enroll in the FOCUS Program, call 1-877-466-7654 (1-877-40NSOLIS) or visit www.OnsolisFocus.com. Prescribers and patients are required to understand the risks of therapy with ONSOLIS. Prescribers are required to understand the information in the prescribing information and to:

- **Ensure proper patient selection, including that the patient is opioid tolerant**
- **Educate patients about the benefits and risks of treatment with ONSOLIS and ensure that the patient receives the Medication Guide**
- **Complete the FOCUS Program prescriber enrollment form; sign and fax the form to the FOCUS Program**
- **Obtain the patient's signature on the patient enrollment form; sign and fax the form to the FOCUS Program**
- **Follow FOCUS Program-specific procedures for prescribing ONSOLIS using a courier**

Additive CNS Depressant Effects

The concomitant use of ONSOLIS with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation). Concomitant use with inhibitors of the cytochrome P450 3A4 (CYP3A4) isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [see *Drug Interactions* (7)].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of ONSOLIS if warranted.

Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking ONSOLIS of these dangers and counsel them accordingly.

Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate ONSOLIS with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to hypoventilation. In such patients, even normal therapeutic doses of ONSOLIS may further decrease respiratory drive to the point of respiratory failure.

Head Injuries and Increased Intracranial Pressure

Administer ONSOLIS with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use ONSOLIS with caution in patients with bradyarrhythmias.

MAO Inhibitors

ONSOLIS is not recommended for use in patients who have received MAO inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

ADVERSE REACTIONS

Clinical Studies Experience

The safety of ONSOLIS has been evaluated in 306 opioid tolerant patients with breakthrough cancer pain in the efficacy study and an open-label safety study. The mean duration of therapy was 115 days, with 32 patients treated for more than 1 year.

The adverse reactions seen with ONSOLIS are typical opioid side effects in a population with cancer. Frequently, opioid-associated adverse reactions will cease or decrease in intensity with continued use of ONSOLIS. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including ONSOLIS are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

Because the clinical trials of ONSOLIS were designed to evaluate safety and efficacy in treating patients with breakthrough pain associated with cancer, all patients were also taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse event among patients who received ONSOLIS for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of ONSOLIS therapy, or cancer-related symptoms. Adverse reactions are included regardless of severity.

Because clinical trials are conducted under widely varying conditions, adverse event 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.

Table 1 lists, by maximum dose received, adverse reactions with an overall frequency of 5% or greater that occurred during titration. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schedules used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1
Adverse Reactions Which Occurred During Titration at a Frequency of ≥5%

System Organ Class, Preferred Term, n (%)	ONSOLIS Dose (mcg)						
	200 (N=303)	400 (N=257)	600 (N=207)	800 (N=138)	1200 (N=79)	>1200 (N=9)	Total (N=306)
Gastrointestinal Disorders							
Nausea	16 (5)	12 (5)	6 (3)	5 (4)	4 (5)	0	42 (14)
Vomiting	7 (2)	9 (4)	8 (4)	2 (1)	0	0	26 (8)
Nervous System Disorders							
Dizziness	5 (2)	5 (2)	6 (3)	2 (1)	4 (5)	0	22 (7)
Somnolence	6 (2)	2 (1)	4 (2)	2 (1)	4 (5)	1 (11)	17 (6)

Table 2 lists, by successful dose, adverse reactions with an overall frequency of ≥5% that occurred during long-term treatment (i.e., the double-blind or open-label maintenance periods).

Table 2

Adverse Reactions Which Occurred During Long-Term Treatment at a Frequency of ≥5%

System Organ Class, Preferred Term, n (%)	ONSOLIS Dose (mcg)						
	200 (N=23)	400 (N=59)	600 (N=79)	800 (N=91)	1200 (N=81)	>1200 (N=28)	Total (N=213)
Gastrointestinal							
Nausea	2 (9)	6 (10)	8 (10)	12 (13)	26 (32)	4 (14)	56 (26)
Vomiting	1 (4)	5 (8)	9 (11)	8 (9)	23 (28)	3 (11)	45 (21)
Constipation	2 (9)	4 (7)	4 (5)	4 (4)	6 (7)	4 (14)	23 (11)
Diarrhea	1 (4)	1 (2)	4 (5)	4 (4)	10 (12)	0	19 (9)
Dry mouth	1 (4)	4 (7)	3 (4)	2 (2)	3 (4)	1 (4)	14 (7)
Abdominal pain	0	0	3 (4)	1 (1)	7 (9)	1 (4)	11 (5)
General/administration site							
Asthenia	0	6 (10)	3 (4)	8 (9)	7 (9)	4 (14)	28 (13)
Fatigue	2 (9)	6 (10)	1 (1)	7 (8)	7 (9)	3 (11)	25 (12)
Investigations							
Weight decreased	3 (13)	0	2 (3)	5 (5)	5 (6)	1 (4)	15 (7)
Metabolism/nutrition							
Dehydration	1 (4)	4 (7)	6 (8)	5 (5)	10 (12)	3 (11)	28 (13)
Decreased appetite	0	4 (7)	4 (5)	6 (7)	2 (2)	2 (7)	18 (8)
Anorexia	2 (9)	1 (2)	3 (4)	4 (4)	6 (7)	1 (4)	17 (8)
Nervous system							
Dizziness	2 (9)	4 (7)	2 (3)	3 (3)	10 (12)	2 (7)	23 (11)
Headache	2 (9)	1 (2)	3 (4)	9 (10)	7 (9)	0	20 (9)
Somnolence	2 (9)	0	4 (5)	2 (2)	3 (4)	3 (11)	14 (7)
Psychiatric							
Confusional state	1 (4)	0	4 (5)	4 (4)	6 (7)	4 (14)	18 (8)
Depression	0	3 (5)	1 (1)	4 (4)	7 (9)	3 (11)	18 (8)
Insomnia	0	2 (3)	2 (3)	3 (3)	4 (5)	2 (7)	12 (6)
Anxiety	1 (4)	1 (2)	2 (3)	3 (3)	3 (4)	1 (4)	11 (5)
Respiratory							
Dyspnea	3 (13)	4 (7)	3 (4)	8 (9)	6 (7)	3 (11)	26 (12)
Cough	1 (4)	0	3 (4)	5 (5)	6 (7)	1 (4)	15 (7)
Vascular							
Hypotension	0	3 (5)	3 (4)	1 (1)	3 (4)	1 (4)	11 (5)

In a mucositis study, a group of patients (n=7) with Grade 1 oral mucositis and a matched group of control patients (n=7) without oral mucositis were included in a clinical trial designed to support the safety of ONSOLIS. The adverse event profile was similar in both subsets of patients. There was no evidence that ONSOLIS caused or worsened oral mucosal irritation or pain in either study group.

The duration of exposure to ONSOLIS varied greatly, and included open-label and double-blind studies. The adverse reactions listed below represent those that were reported by ≥1% of patients from two clinical trials (the titration and post-titration periods) while receiving ONSOLIS. Events are classified by system organ class.

Cardiac disorders: tachycardia
Eye disorders: vision blurred, diplopia
Gastrointestinal disorders: nausea, vomiting, constipation, diarrhea, dry mouth, abdominal pain, dyspepsia, dysphagia, abdominal distension, intestinal obstruction, flatulence
General disorders and administration site conditions: asthenia, fatigue, malaise
Injury, poisoning and procedural complications: fall, contusion
Investigations: weight decreased, blood pressure increased
Metabolism and nutrition disorders: dehydration, decreased appetite, anorexia
Nervous system disorders: dizziness, somnolence, headache, lethargy, amnesia, sedation
Psychiatric disorders: confusional state, depression, insomnia, anxiety, hallucination, agitation, mental status changes
Renal and urinary disorders: urinary retention
Respiratory, thoracic and mediastinal disorders: dyspnea, cough
Skin and subcutaneous tissue disorders: pruritus, rash
Vascular disorders: hypotension, hot flush, deep vein thrombosis, hypertension

DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when ONSOLIS is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of ONSOLIS with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving ONSOLIS who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done conservatively [see *Warnings and Precautions* (5.4)].

The concomitant use of ONSOLIS with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of ONSOLIS. Patients receiving ONSOLIS who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of decreased ONSOLIS activity and the dose of ONSOLIS should be adjusted accordingly.

USE IN SPECIFIC POPULATIONS

Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women.

ONSOLIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for ONSOLIS.

Fentanyl citrate was not teratogenic when administered to pregnant animals. In published studies, pregnant rats were treated with fentanyl (10, 100, or 500 mcg/kg/day) via implanted microosmotic minipumps from Day 7 to 21 of their 21 day gestation period. Fentanyl was not teratogenic at doses up to 500 mcg/kg/day [approximately 3-times the maximum recommended human dose (MRHD) of 1200 mcg for ONSOLIS per breakthrough cancer pain episode]. Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation Day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic

Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, use of ONSOLIS during labor and delivery is not recommended.

Nursing Mothers

Fentanyl is excreted in human milk; therefore, ONSOLIS should not be used in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using ONSOLIS.

Pediatric Use

Safety and efficacy in pediatric patients below the age of 18 years have not been established.

Geriatric Use

Of the 306 opioid tolerant patients with breakthrough cancer pain in clinical studies of ONSOLIS, 98 (32.0%) were 65 years of age and older. There was no difference in the median titrated dose in patients aged 65 years and older compared to those <65 years. No clinically meaningful difference was noted in the safety profile of the group 65 years of age and older as compared to younger patients in ONSOLIS clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously compared with the younger population. Therefore, exercise caution when individually titrating ONSOLIS in elderly patients to provide adequate efficacy while minimizing risk.

Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of ONSOLIS in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP3A4 isoenzyme system and the inactive metabolite is mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

It is recommended that ONSOLIS be titrated to clinical effect for all patients with special care taken in patients with severe renal or hepatic disease.

Gender

Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. ONSOLIS may be subject to misuse, abuse and addiction.

Abuse and Addiction

Manage the handling of ONSOLIS to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [see *How Supplied* (16.3) and *Storage and Handling* (16.1)].

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since ONSOLIS may be abused for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse of this product.

Dependence

Guide the administration of ONSOLIS by the response of the patient.

Physical dependence is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug.

Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

OVERDOSAGE

Clinical Presentation

The manifestations of ONSOLIS overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being hypoventilation [see *Clinical Pharmacology – Pharmacodynamics* (12.2)].

Immediate Management

Immediate management of opioid overdose includes removal of the ONSOLIS film, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

Treatment of Overdose in Opioid Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

General Considerations for Overdose

Management of severe ONSOLIS overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

Although muscle rigidity interfering with respiration has not been seen following the use of ONSOLIS, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by the administration of an opioid antagonist, and, as a final alternative, by the administration of a neuromuscular blocking agent.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium or E. coli* or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for ONSOLIS.

PATIENT COUNSELING INFORMATION

See *Medication Guide* (17.3) for specific patient instructions.

Patient/Caregiver Instructions

Patients will need to be enrolled in the FOCUS Program to receive ONSOLIS. The patient will receive their prescription via a traceable courier (with proof of delivery and adult signature required). The patient will receive a counseling call at the time of the first prescription to verify that they are opioid tolerant and discuss how to use the drug.

Provide patients and their caregivers with a Medication Guide for ONSOLIS (17.3).

Patients and their caregivers must be instructed that ONSOLIS contains medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. Patients and their caregivers must be instructed to keep ONSOLIS out of the reach of children. Patients and members of their household must be instructed to dispose of any unneeded films remaining from a prescription as soon as possible [see *How Supplied* (16.3) and *Storage and Handling* (16.1)].

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Disposal of Unneeded ONSOLIS Films

Patients and members of their household must be instructed on the safe disposal of any unneeded films remaining from a prescription as soon as they are no longer needed.

To dispose of the unneeded ONSOLIS films:

1. Remove the ONSOLIS film from its foil package.
2. Drop the ONSOLIS film into the toilet.
3. Repeat steps 1 and 2 for each ONSOLIS film. Flush the toilet after all unneeded films have been put into the toilet.

Do not flush the ONSOLIS foil packages or cartons down the toilet [see How Supplied (16.3) and Storage and Handling (16.1)].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of ONSOLIS are provided in the Medication Guide (17.3). Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unneeded films that remain in the home after a patient has expired, instruct them to call Meda Pharmaceuticals Inc. at 1-800-526-3840 or seek assistance from their local Drug Enforcement Agency (DEA) office.

MEDA Pharmaceuticals
MEDA Pharmaceuticals Inc.
Somerset, NJ 08873

Cancer Center Profile

University of Pittsburgh Medical Center Cancer Centers and Cancer Institute

The University of Pittsburgh Medical Center (UPMC) Cancer Centers work in tandem with the University of Pittsburgh Cancer Institute (UPCI) to offer advances in cancer prevention, early detection, diagnosis, and treatment throughout a three-state region (western Pennsylvania, Ohio, West Virginia). UPCI has been designated as a Comprehensive Cancer Center by the National Cancer Institute (NCI).

UPCI ranked 11th in funding from the NCI in 2007, and 12th among *U.S. News & World Report*'s "Best of the Best" cancer programs in the nation.

UPMC's network of 2300 physicians, scientists, staff, and other healthcare professionals provides clinical care to 30,000 patients annually at its facilities while engaging in cutting-edge cancer research. Medical, radiation, and surgical oncologists and disease-specific specialists collaborate closely in a model of multidisciplinary care. Ancillary service providers in behavioral medicine, rehabilitation, social work, palliative care, nutrition, and genetic counseling are incorporated into the multidisciplinary team to ensure that all aspects of care are addressed.

The hub and satellite network of UPMC Cancer Centers consists of more than 45 community-based locations in western Pennsylvania and two centers in Ireland.

The hub-and-spoke model ensures extensive distribution of radiation therapy and medical oncology facilities throughout the tri-state region, said Barry Lembersky, MD, a medical oncologist. "Our pathways of standard of care are uniform throughout this area, and the full array of clinical trials is available to patients at all satellite facilities," he said.

Thirteen areas of expertise

The range of knowledge covers virtually all types of adult cancer, with 13 areas of expertise being recognized, including a world-renowned melanoma program. Other programs are devoted to brain cancers, breast cancer, colon and gastrointestinal cancers, head and neck cancers, leukemias and lymphomas, liver cancer, lung cancer, gynecologic cancers, prostate and urologic cancers, and stem-cell transplantation.

The Melanoma and Skin Cancer Program consists of both basic and clinical research and has patients coming from all over the world to participate in clinical trials for melanoma under the direction of John Kirkwood, MD. Major areas of research range from the development of a melanoma vaccine to the search for biomarkers to aid in the development of personalized treatments. UPMC was one of the first centers to use a digital mole mapping system to assess high-risk patients for skin cancer.

In addition, UPMC has "a well-organized pancreatic cancer program whereby patients with all forms of pancreatic cancer and all stages are seen in a multidisciplinary clinic with innovative clinical trials in the preoperative setting and the adjuvant and metastatic setting," Lembersky said.

For instance, a preoperative clinical trial of gemcitabine with radiation therapy and bevacizumab is in progress, with the goal of evaluating the downstaging and histologic changes that occur with such treatment. "That's a pretty novel approach that holds promise not only for better outcome but for the paradigm of evaluating new drugs and new drug combinations; give the drugs prior to pancreatic resection to look for surrogate markers of response (ie, tumor necrosis), and correlate it with long-term outcome," he said. "The treatment has been very well tolerated and resection rates are high. In most patients, there is evidence of significant necrosis and chemotherapy or radiation effect, and what that means for survivorship is uncertain at this time."

Other research involves the testing of a vaccine for colon cancer prevention in persons at high risk for developing the disease. In a novel approach, the vaccine is directed against an abnormal variant of the gene *MUC1*, which is altered and produced in excess in advanced adenomas and cancer. Stimulating an immune response against the protein encoded by *MUC1* in precancerous growths may not only trigger the immune system to destroy the abnormal cells to prevent progression to cancer but may also prevent polyp recurrence. *MUC1* vaccines have been tested for safety and immunogenicity in patients with late-stage colon cancer and pancreatic cancer.

Integrated drug discovery program allows for range of studies

A vertically integrated drug development program at UPCI, called Molecular Therapeutics Drug Discovery, employs 69 members with interests in one of four areas: chemical diversity, molecular targets, pharmacokinetics/pharmacodynamics, and phase 1 clinical trials. "The goal is to have seamless movement from chemistry into patients, and if we make observations in patients, to be able to take them back and look at them on a mechanistic/molecular level," said Merrill Egorin, MD, professor of medicine at UPCI.

"We are one of the six NCI animal pharmacology contractors, so that puts us in the pipeline of any drug that the NCI is considering putting into patients," he said. "We've got an early signal on what's coming through the NCI. If we have in-place methods to measure the drug—we've defined its metabolism, we know its molecular targets, and we have assays to measure those molecular targets in animal models of tumors—it's a huge strength when we put in a request to do a first-in-human study or phase 2 study," Egorin said.

Researchers at UPCI are also involved in a number of ongoing studies with the target poly (ADP-ribose) polymerase (PARP), an enzyme involved in the recognition of DNA damage and repair. By inhibiting PARP, the hope is that the activity of anticancer drugs can be potentiated, presumably by decreasing the resistance or increasing the sensitivity of tumor cells to standard chemotherapy.

BRCA1- and *BRCA2*-mutated tumors should be specifically sensitive to inhibition of PARP, according to Egorin. This synthetic lethal approach has already been validated in vitro and in preclinical models. "There has already been a clinical study with a different PARP inhibitor that has demonstrated the case that *BRCA* tumors will respond to this, and the toxicities are essentially none," he said. ●

—Wayne Kuznar

Sue Frank, BSN, MSN, Director of Operations

The rapid growth of Hillman Cancer Center at the University of Pittsburgh Medical Center (UPMC) Cancer Centers presented a challenge to Sue Frank, BSN, MSN, the director of operations at Hillman.


Sue Frank, BSN, MSN

Hillman represents the hub of UPMC's hub-and-spoke model, the 22 outlying facilities being the spokes.

Ms. Frank was recruited to UPMC as a nurse assistant while attending the University of Pittsburgh School of Nursing. She rose through the ranks, eventually becoming director of cardiovascular services at UPMC Presbyterian, until the director of operations was created at Hillman about 2 years ago.

Prior to her arrival, Hillman experienced a surge in volume of 475% over 5 years. "My position evolved, because with the growth, we didn't have the right structure to deal with all of the issues that had come with volume surges," Frank explained. "The challenge is that Hillman does one-stop shopping for multiple patient needs. Patients come through for 8 hours, but they have multiple stops, from radiology, to a physician visit, to getting their labs drawn, to a treatment room visit, and can also end up going for a radiation oncology visit.

"The minute one domino falls or there's a delay in one area, there's a chain reaction with the rest of the patients, and we have to compensate for that."

Under her direction, specialty care centers were created to move patients through the system seamlessly from the first visit, through a series of coordinated stops. To this end, a nurse coordinator is assigned to each patient before navigating the system. Patient navigators and liaisons help along the way.

"We're working on new automated systems from electronic resources so we know where patients are coming through the Hillman system," she said.

"The biggest complaint I had when I started was that patients were going from a surgeon to someone in GI a week or 2 later, or a medical oncology consult, so they felt as if they have a cancer growing during this time before they get a plan of care," said Frank. "With the specialty care centers, we've focused on that plan of care. Sometimes we can do it in 1 day, sometimes it's over a week or 2, but we have focused on trying to give them some information as they're going through the process. We're trying to make that pathway very succinct, even though it's not always as productive for physicians. It's better for patients and quality of care to see multiple doctors in one stop."

This model of care was started for patients with pancreatic cancer, and surveys showed a high level of satisfaction with the process, Frank noted.

She looks at her more than 20 years at UPMC as both a nurse and an administrator as an advantage. "I see it as a positive because within UPMC we have the opportunity to do multiple things in nursing. I've had cardiac experience, thoracic experience, and experience in a clinical cancer care model," she said. ●

Fertility Preservation

Continued from page 18

Oncologists expressing favorable attitudes toward fertility preservation were 4.9 times more likely to discuss the impact of cancer treatment on future fertility than those with unfavorable attitudes. Oncologists who are knowledgeable about fertility preservation were 2.6 times more likely to discuss the impact of cancer treatment than those less knowledgeable and were 1.9 times more likely to report feeling comfortable discussing fertility preservation, Quinn reported.

In addition, physicians who said their patients always or often asked about fertility preservation were twice as likely to refer patients to specialists as those who said their patients sometimes, rarely, or never asked. Female oncologists were 2.12 times more likely to refer patients to reproductive endocrinologists than were their male colleagues.

Timing is critical

The primary barrier to discussion was the imperative to initiate treatment immediately, as soon as 24 hours after diagnosis in some cases, which leaves no time to pursue fertility preservation options, the respondents said. Other concerns were time constraints and affordability of treatment (Table 2).

But Kutluk Oktay, MD, professor and director of the Division of Reproductive Medicine at New York Medical College and director of the Institute for Fertility Preservation, New York, emphasized that fertility preservation must be considered as early as possible to maintain the full range of treatment options.

"Most approaches revolve around the menstrual period. If patients are not referred early enough, they may miss this opportunity," he pointed out. "Our biggest ally is time. We need 2 weeks from the start of the menstrual period in order to stimulate egg production and perform embryo or egg freezing. Oncologists should not be having this discussion at the end of the treatment plan."

Table 1. Risk Associated with Common Breast Cancer Regimens

Degree of risk for amenorrhea	Treatment protocol and age
High risk (>80%)	• CAF x 6 in women ≥40 years • CEF x 6 in women ≥40 years • CMF x 6 in women ≥40 years
Intermediate risk (30%-70%)	• CMF x 6 in women 30-39 years • CEF x 6 in women 30-39 years • CAF x 6 in women ≥40 years • AC x 4 in women ≥40 years
Low risk (<20%)	• AC x 4 in women 30-39 years • CAF x 6 in women <30 years • CEF x 6 in women <30 years • CMF x 6 in women <30 years

CAF indicates cyclophosphamide, doxorubicin, 5-fluorouracil; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; AC, doxorubicin, cyclophosphamide.

One possible solution: more involvement of nurses

"Another significant barrier is time limitation—time to discuss the cancer diagnosis and treatment plan, as well as to deal with the psychosocial issues of the new diagnosis," Quinn noted.

She maintained that this barrier can be lessened with the aid of training curricula and the involvement of nurses. "While physicians will want to present the information initially, nurses may be the more appropriate providers for having lengthy conversations and doing follow-up and referrals," she suggested.

Oktay agreed on the need to utilize nonphysician staff for these discussions. "We should train registered nurses or nurse practitioners, appoint consultants in fertility preservation within cancer centers, and develop focused fertility preservation programs," he said.

Table 2. Key Results from National Survey of Oncologists (n = 613)

Issue	Always/often	Sometimes	Rarely/never
Barriers to discussion			
• Inability to delay treatment because patient is too ill	35%	44%	21%
• Patient cannot afford FP	29%	41%	29%
• Patient does not want to discuss FP	14%	50%	37%
• There is no place or person to refer to for FP	9%	13%	79%
• Time constraints affect ability to discuss FP	12%	23%	66%
Practice patterns			
• I consult an infertility specialist or reproductive endocrinologist with questions	24%	29%	47%
• I refer patients with questions to an infertility specialist or reproductive endocrinologist	47%	29%	24%
• I discuss the impact of cancer treatment on fertility	77%	16%	7%
• I provide patients with educational materials about FP	14%	26%	60%
• I consult ASCO recommendations about FP	18%	22%	37%

Note: Percentages were rounded to the nearest whole number and may not equal 100%.
ASCO indicates American Society of Clinical Oncology; FP, fertility preservation.

Options for preserving fertility

Typically completed before cancer treatment, the established options for women are embryo cryopreservation in the case of systemic chemotherapy, and ovarian transposition (relocation of ovaries in an abdominal site outside of the treatment field) when therapy is limited to the pelvic area, although ovarian transposition is protective only about 50% of the time because of scatter radiation.

In women with breast cancer, embryo freezing is a common approach but concerns have been raised about the use of fertility drugs that can increase estrogen levels. The addition of aromatase inhibitors to suppress the estrogenic response that accompanies ovarian stimulation is being investigated.

Embryo cryopreservation, however, requires in vitro fertilization and a participating male partner, an option that may not be acceptable to prepubertal, adolescent girls. Cryopreservation of oocytes (with or without gonadotropin stimulation) is an alternative; however, it is more problematic than cryopreservation of embryos or sperm and is still considered experimental by some protocols. To date, there have been more than 1000 live births resulting from this approach. In vitro fertilization with vitrification (rapid freezing) results in a live birth per transfer rate of 34%, which approaches the rate of 43% achieved with fresh eggs, Oktay reported. "The gap is closing," he observed, "and many think we should take oocyte freezing out of the experimental category."

Cryopreservation of ovarian tissue has also recently emerged as a new option that is relatively fast and simple, and one that offers female children a chance for fertility preservation. A recent meta-analysis found a 37% rate of conception after ovarian transplant, although not all involved frozen tissue (Bedaiwy MA, et al. *Hum Reprod*. 2008;23:2709-2717).

For men, sperm cryopreservation is well established. Intracytoplasmic sperm injection requires only a single sperm to fertilize the egg "so that one sperm collection can last a lifetime when used with assisted reproduction techniques," he noted.

In younger boys who have problems with ejaculation, advanced techniques for sperm retrieval can be used. In prepubertal boys, the sole option is testicular tissue freezing, which is still highly experimental. ●

—Caroline Helwick

Oncology Drug Codes

Medications Used for the Treatment of Leukemias

The following sections include:

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

204 Lymphoid leukemia
- 204.00 Acute—without mention of having achieved remission
- 204.01 Acute—in remission
- 204.02 Acute—in relapse
- 204.10 Chronic—without mention of having achieved remission
- 204.11 Chronic—in remission
- 204.12 Chronic—in relapse

205 Myeloid leukemia
- 205.00 Acute—without mention of having achieved remission
- 205.01 Acute—in remission
- 205.02 Acute—in relapse
- 205.10 Chronic—without mention of having achieved remission
- 205.11 Chronic—in remission
- 205.12 Chronic—in relapse

206 Monocytic leukemia
- 206.00 Acute—without mention of having achieved remission
- 206.01 Acute—in remission
- 206.02 Acute—in relapse
- 206.10 Chronic—without mention of having achieved remission
- 206.11 Chronic—in remission
- 206.12 Chronic—in relapse

Generic (brand) name	HCPCS code: code description	FDA-approved for leukemias	*NCCN Drugs & Biologics Compendium* off-label use for leukemias	Current code price (AWP-based pricing), effective 11/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
alemtuzumab (Campath)	J9010: injection, alemtuzumab, 10 mg			$660.90	$570.22	96413, 96415
arsenic trioxide (Trisenox)	J9017: injection, arsenic trioxide, 1 mg			$43.58	$37.44	96413, 96415
asparaginase (Elspar)	J9020: injection, asparaginase, 10,000 units			$70.42	$58.01	96401, 96413
azacitidine (Vidaza)	J9025: injection, azacitidine, 1 mg			$5.74	$4.87	96401, 96409, 96413
bendamustine (Treanda)	J9033: injection, bendamustine HCl, 1 mg			$21.60	$18.53	96413
betamethasone (Celestone Soluspan)	J0702: injection, betamethasone acetate, 3 mg and betamethasone sodium phosphate, 3 mg			$6.85	$6.56	11900, 11901, 20600, 20605, 20610, 96372
busulfan (Myleran)	J8510: busulfan, oral, 2 mg			$4.46	$3.22	N/A
chlorambucil (Leukeran)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
chlorambucil (Leukeran)	S0172: chlorambucil, oral, 2 mg			$3.86	S0172: not payable by Medicare	N/A

NHL Mantle Cell Trial
Now Recruiting Investigators and Enrolling Study Participants

Celgene CC-5013-MCL-001

emerge™

A Phase 2 Study for Patients With Relapsed/Refractory Mantle Cell Non-Hodgkin's Lymphoma

Primary Investigator

André Goy, MD

Primary Objective

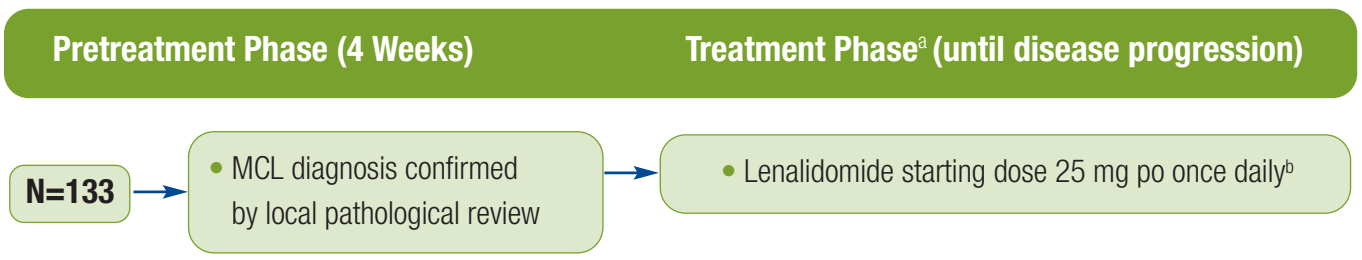
To determine the tumor response and duration of response of lenalidomide monotherapy in subjects with mantle cell lymphoma (MCL) who have relapsed or progressed after treatment with bortezomib or are refractory to bortezomib

Key Eligibility Criteria*

- Individuals with MCL previously treated with all of the following (alone or in combination):
  - Bortezomib† – An anthracycline or mitoxantrone
  - Rituximab – Cyclophosphamide
- Individuals must have documented relapse after bortezomib treatment or be refractory to bortezomib
- Excluding individuals who are candidates for high-dose chemotherapy/allogeneic stem cell transplant

*Additional criteria apply.
†Note: When the agent bortezomib is mentioned this also includes ANY BORTEZOMIB-CONTAINING REGIMEN.

Study Design



[a]Lenalidomide will be dosed po once daily on days 1-21 of each 28-day cycle.
[b]Subjects with creatinine clearance ≥30 mL/min but <60 mL/min will receive a lower starting dose of lenalidomide 10 mg po once daily. Dose may be escalated to 15 mg po once daily if no dose-limiting toxicities occur during the first 2 cycles.

Investigational use of lenalidomide.

For more information contact
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dingenito@celgene.com
(908) 673-9581
www.clinicaltrials.gov (NCT00737529)

Celgene

Generic (brand) name	HCPCS code: code description	FDA-approved for leukemias	*NCCN Drugs & Biologics Compendium* off-label use for leukemias	Current code price (AWP-based pricing), effective 11/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
cladribine (Leustatin)	J9065: injection, cladribine, per 1 mg			$58.20	$25.64	96413, 96415
clofarabine (Clolar)	J9027: injection, clofarabine, 1 mg			$135.00	$116.40	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 gram			$54.62	$43.03	96409, 96413, 96415
cyclophosphamide injection (Cytoxan)	J9092: cyclophosphamide, 2.0 grams			$98.30	$86.06	96409, 96413, 96415
cytarabine (Cytosar-U)	J9100: injection, cytarabine, 100 mg			$3.60	$1.72	96409, 96413, 96415, 96450
cytarabine (Cytosar-U)	J9110: injection, cytarabine, 500 mg			$10.20	$3.92	96409, 96413, 96415, 96450
dasatinib (Sprycel)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
daunorubicin (Cerubidine)	J9150: injection, daunorubicin, 10 mg			$25.20	$15.24	96409, 96413
dexamethasone (Decadron)	J1100: injection, dexamethasone sodium phosphate, 1 mg			$0.15	$0.08	11900, 11901,20600, 20605, 20610, 96372, 96374
dexamethasone (Decadron)	J8540: dexamethasone, oral, 0.25 mg			$0.09	$0.38	N/A
doxorubicin HCl (Adriamycin)	J9000: injection, doxorubicin hydrochloride, 10 mg			$13.20	$3.69	96409
fludarabine (Fludara)	J9185: injection, fludarabine phosphate, 50 mg			$330.32	$154.27	96413
gemtuzumab ozogamicin (Mylotarg)	J9300: injection, gemtuzumab ozogamicin, 5 mg			$3,104.82	$2,622.30	96413, 96415
hydrocortisone (Solu-Cortef)	J1720: injection, hydrocortisone sodium succinate, up to 100 mg			$2.46	$2.92	96365, 96366, 96372, 96374
hydroxyurea (Hydrea)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
hydroxyurea (Hydrea)	S0176: hydroxyurea, oral, 500 mg			$1.28	S0176: not payable by Medicare	N/A
idarubicin (Idamycin)	J9211: injection, idarubicin hydrochloride, 5 mg			$381.56	$98.56	96409
imatinib (Gleevec)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
imatinib (Gleevec)	S0088: imatinib, 100 mg			$42.12	S0088: not payable by Medicare	N/A
interferon alfa-2b (Intron-A)	J9214: injection, interferon, alfa-2b, recombinant, 1 million units			$21.90	$15.84	96372, 96401
mechlorethamine (Mustargen)	J9230: injection, mechlorethamine hydrochlorid (nitrogen mustard), 10 mg			$178.71	$147.34	96409
mercaptopurine (Purinethol)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A

Generic (brand) name	HCPCS code: code description	FDA-approved for leukemias	*NCCN Drugs & Biologics Compendium* off-label use for leukemias	Current code price (AWP-based pricing), effective 11/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
mercaptopurine (Purinethol)	S0108: mercaptopurine, oral, 50 mg			$4.09	S0108: 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			$2.68	$2.12	96372, 96374, 96401, 96409, 96450
methylprednisolone (Depo-Medrol)	J1030: injection, methylprednisolone acetate, 40 mg			$5.84	$3.79	11900, 11901, 20600, 20605, 20610, 96372
methylprednisolone (Depo-Medrol)	J1040: injection, methylprednisolone acetate, 80 mg			$11.46	$7.27	11900, 11901, 20600, 20605, 20610, 96372
methylprednisolone (Solu-Medrol)	J2920: injection, methylprednisolone sodium succinate, up to 40 mg			$2.36	$2.56	96365, 96366, 96372, 96374
methylprednisolone (Solu-Medrol)	J2930: injection, methylprednisolone sodium succinate, up to 125 mg			$4.15	$3.45	96365, 96366, 96372, 96374
methylprednisolone (Medrol)	J7509: methylprednisolone, oral, per 4 mg			$0.54	$0.06	N/A
mitoxantrone (Novantrone)	J9293: injection, mitoxantrone hydrochloride, per 5 mg			$116.50	$66.77	96409, 96413
nilotinib (Tasigna)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
pegaspargase (Oncaspar)	J9266: injection, pegaspargase, per single dose vial			$3,280.00	$2,747.51	96401, 96413, 96415
peginterferon alfa-2a (Pegasys)	J3490[a]: unclassified drugs			NDC level pricing	NDC level pricing	96372
peginterferon alfa-2a (Pegasys)	S0145: injection, pegylated interferon alfa-2a, 180 mcg per mL			$589.12	S0145: not payable by Medicare	96372
peginterferon alfa-2b (Peg-Intron)	J3490[a]: unclassified drugs			NDC level pricing	NDC level pricing	96372
peginterferon alfa-2b (Peg-Intron)	S0146: injection, pegylated interferon alfa-2b, 10 mcg per 0.5 mL			$106.42	S0146: not payable by Medicare	96372
pentostatin (Nipent)	J9268: injection, pentostatin, per 10 mg			$2,182.80	$1,426.47	96409, 96413
prednisolone (Millipred, Orapred, Veripred)	J7510: prednisolone, oral, per 5 mg			$0.56	$0.02	N/A
prednisone	J7506: prednisone, oral, per 5 mg			$0.05	$0.05	N/A
rituximab (Rituxan)	J9310: injection, rituximab, 100 mg			$664.32	$563.33	96413, 96415
teniposide (Vumon)	Q2017: injection, teniposide, 50 mg			$376.55	$325.57	96413, 96415
thioguanine (Tabloid)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A
tretinoin (Vesanoid)	J8999[a]: prescription drug, oral, chemotherapeutic, not otherwise specified			NDC level pricing	NDC level pricing	N/A

Generic (brand) name	HCPCS code: code description	FDA-approved for leukemias	*NCCN Drugs & Biologics Compendium* off-label use for leukemias	Current code price (AWP-based pricing), effective 11/1/09	Medicare allowable (ASP + 6%), effective 10/1/09-12/31/09	CPT administration codes
vinCRIStine (Vincasar PFS)	J9370: vincristine sulfate, 1 mg			$8.12	$5.72	96409
vinCRIStine (Vincasar PFS)	J9375: vincristine sulfate, 2 mg			$16.24	$11.44	96409
vinCRIStine (Vincasar PFS)	J9380: vincristine sulfate, 5 mg			$40.60	$28.59	96409

[a]When billing a nonclassified medication using a CMS 1500 claim form you must include both the HCPCS code (ie, J8999 for Tasigna) 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 Drugs & Biologics Compendium*; 2009; 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 November 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.

Recent FDA Approvals

Folotyn for Relapsed or Refractory Peripheral T-cell Lymphoma

The first single-agent therapy for relapsed or refractory peripheral T-cell lymphoma, pralatrexate injection (Folotyn, Allos Therapeutics), has been approved by the US Food and Drug Administration (FDA). The approval for this indication was based on overall response rate. At current, improvement in progression-free survival and overall survival has not been demonstrated. Additional clinical studies are ongoing to verify and describe the agent's clinical benefits.

Cervarix Cervical Cancer Vaccine

The FDA has approved a new human papillomavirus (HPV) bivalent (types 16 and 18) vaccine, recombinant (Cervarix, GlaxoSmithKline) for the prevention of cervical precancers and cervical cancer associated with oncogenic HPV types 16 and 18 for use in girls and young women aged 10 to 15 years. The approval was based on a study that showed the vaccine to be 93% efficacious in the prevention of cervical precancers associated with HPV 16 and 18 in women without evidence of current infection or prior exposure to these types of HPV at time of vaccination.

Votrient for Advanced Renal Cell Carcinoma

The FDA has approved the oral agent pazopanib (Votrient, GlaxoSmithKline) for treatment of advanced renal cell carcinoma. The agent, which interferes with angiogenesis, was approved based on a 435-patient study that examined progression-free survival (PFS). PFS averaged 9.2 months for patients who received the drug compared with 4.2 months for those who did not.

Elitek for Management of Plasma Uric Acid Levels

The FDA has approved rasburicase (Elitek, sanofi-aventis US) for use in the initial management of plasma uric acid (PUA) levels in adults with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy expected to result in tumor lysis syndrome and subsequent elevations of PUA. Approval was based on a phase 3 trial that demonstrated that rasburicase significantly reduced PUA levels compared with oral allopurinol (the current standard therapy).

Arzerra for Chronic Lymphocytic Leukemia

The FDA has granted accelerated approval of ofatumumab (Arzerra, GlaxoSmithKline/Genmab) for use in patients with chronic lymphocytic leukemia (CLL) that is refractory to fludarabine and alemtuzumab. Approval was based on a study in which 42% of patients with treatment-refractory CLL responded to treatment with ofatumumab, a monoclonal antibody drug targeting the CD20 protein on B cells. These patients had a median duration of response of 6.5 months. Common adverse events included neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

Istodax for Cutaneous T-cell Lymphoma

The FDA has approved romidepsin (Istodax, Gloucester Pharmaceuticals) for the treatment of cutaneous T-cell lymphoma in patients who have received at least one prior systemic therapy. Approval of the histone deacetylase inhibitor was based on efficacy data from two studies totaling 167 patients. The overall response rates, defined as the proportion of patients with confirmed complete response or partial response, were 34% and 35%. The complete response rate was 6% in both studies. ●

STRONG. FROM THE START.

HELP ESTABLISH A SUCCESSFUL CINV PREVENTION STRATEGY FROM THE FIRST CYCLE

When your patients experience acute chemotherapy-induced nausea and vomiting (CINV) during their first cycle of chemotherapy, they may have an increased risk of CINV on subsequent days and in subsequent cycles.[1-3]

ALOXI®:

- Starts strong to prevent CINV[4]
- A single IV dose lasts up to 5 days after MEC[4,5*]
- Can be used with multiple-day chemotherapy regimens[6†]

* Moderately emetogenic chemotherapy.

† Based on sNDA approval in August 2007, the restriction on repeated dosing of ALOXI (palonosetron HCl) injection within a 7-day interval was removed.

Indication

ALOXI® (palonosetron HCl) injection 0.25 mg is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy, and acute nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy.

Important Safety Information

- ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components
- Most commonly reported adverse reactions in chemotherapy-induced nausea and vomiting include headache (9%) and constipation (5%)

Please see the following brief summary of prescribing information.

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

Eisai HELSINN

Aloxi®
palonosetron HCl injection
STARTS STRONG
LASTS LONG

www.ALOXI.com

International Oncology News

Reports from International Meetings and Researchers

Hospital Is Good Starting Point for Smoking Cessation

VIENNA, AUSTRIA—The hospital setting provides a good opportunity for promoting smoking cessation, Australian investigators reported at the 2009 European Respiratory Society (ERS) annual meeting.

"Hospitals are an ideal setting for starting patients on a smoking cessation program given that they see a high number of tobacco-related admissions and given that smokers are forced to abstain during admission," said Jerneen Williams, BSc, who is a study coordinator in oncology at the Queen Elizabeth Hospital in Adelaide.

Williams presented data showing that hospitalized smokers who used nicotine replacement therapy (NRT) for craving control during their hospitalization and continued to participate in a smoking cessation program after they had been discharged had higher long-term continuous abstinence rates than smokers who did not use NRT. The study included 123 patients who had smoked at least five cigarettes a day at the start of their hospitalization.

The study also demonstrated that the hospital-based intervention produces comparable quit rates to those in outpatient settings.

"Hospitalization potentially provides a teachable moment, and studies have shown that smokers who believe that their illness is related to smoking are more likely to attempt cessation following an admission," Williams commented.

"Smoking is banned in hospital buildings and restricted on most hospital grounds in Australia; however, smoking cessation interventions are not initiated as part of routine care as it is often perceived to be a community rather than a hospital issue," she added.

Increased Public Awareness of Head and Neck Cancer Needed

AMSTERDAM, THE NETHERLANDS—New data demonstrate a lack of knowledge among Europeans about the risk factors and symptoms of head and neck cancer.

The findings were reported by researchers who analyzed responses to online questionnaires completed by about 7500 people in France, Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom.

The "About Face" survey revealed that only 23% of participants were aware of the term "head and neck cancer," and less than half were able to correctly identify symptoms of head and neck cancer. Sixty percent of respondents thought that brain tumors are a type of head and neck cancer.

Most participants knew that there is a link between head and neck cancer and smoking or high alcohol intake, but few patients knew of the role of the human papilloma virus infection or excessive sun exposure.

"Efforts need to address the gaps in knowledge among the general public in head and neck cancer," according to C. Rene Leemans, MD, co-director of the VUMC Cancer Centre in Amsterdam, the Netherlands. This is particularly important since knowledge gaps can lead to a delay in seeing a physician, which translates into a delay in diagnosis, he added. ●

—Jill Stein

■ Hormonal Therapy Use for Prostate Cancer and Comorbid Conditions

Background: Hormonal therapy (HT), when combined with external beam radiation therapy (RT), improves cancer-specific and overall survival versus RT alone. A recent posttrandomization hypothesis-generating analysis suggested that men with moderate to severe comorbidity did not receive this survival benefit. Which condition(s) eliminates this benefit was not determined.

Design: Risk of all-cause mortality was measured by Cox regression in 5077 men (median age, 69.5 years) with localized or locally advanced prostate cancer. The patients were treated with or without a median of 4 months of neoadjuvant HT followed by RT.

Summary: Neoadjuvant HT use was not associated with an increased risk of all-cause mortality in men with no comorbidity (9.6% vs 6.7%, adjusted HR, 0.97; 95% CI, 0.72-1.32; *P* = .86) or a single coronary artery disease (CAD) risk factor (10.7% vs 7.0%, adjusted HR, 1.04; 95% CI, 0.75-1.43; *P* = .82) after median follow-ups of 5.0 and 4.4 years, respectively. However, for men with CAD-induced congestive heart failure (CHF) or myocardial infarction (MI), after a median follow-up of 5.1 years, neoadjuvant HT use was significantly associated with an increased risk of all-cause mortality (26.3% vs 11.2%, adjusted HR, 1.96; 95% CI, 1.04-3.71; *P* = .04).

Takeaway: Neoadjuvant HT use is significantly associated with all-cause mortality among men with a history of CAD-induced CHF or MI. No association was found among men with no comorbidity or a single CAD risk factor.

Nanda A, et al. JAMA. *2009;302: 866-873.*

■ Improved Event-free Survival in Children and Adolescents with Ph+ ALL

Background: Imatinib monotherapy has been shown to produce high response rates in Philadelphia chromosome–positive (Ph+) acute lymphoblastic leukemia (ALL), but with recurrence in months. It has been used in combination with intensive hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone therapy followed by blood and marrow transplantation (BMT) in adults with Ph+ ALL. Efficacy and tolerability with multiagent chemotherapy in children is not known.

Design: Patients with Ph+ ALL aged 1 to 21 years (N = 92) received imatinib 340 mg/m^2/day introduced stepwise into their chemotherapy regimen. Exposure to imatinib was increased progressively in five patient cohorts that received the agent from 42 to 280 days before maintenance therapy. Ph- ALL patients (N = 65) who received the same chemotherapy without imatinib were used as comparators. Patients with compatible sibling donors underwent BMT with imatinib given for 6 months following.

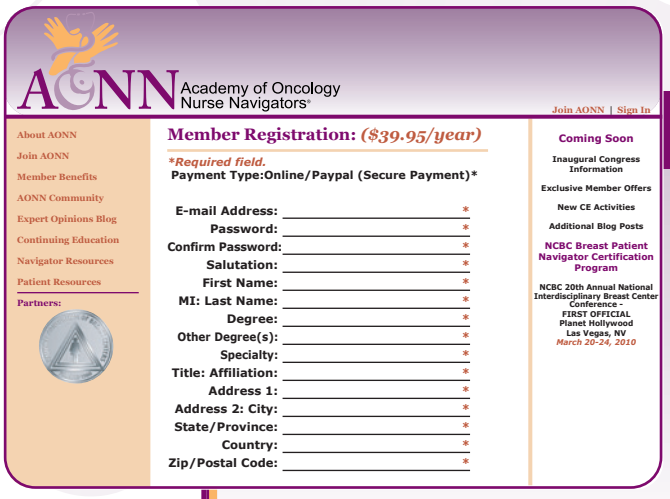
Summary: Continuous imatinib exposure improved outcome in patients in the fifth cohort with a 3-year event-free survival (EFS) of 80% ± 11% (95% CI, 64%-90%). Three-year EFS was similar for patients in the fifth cohort treated with chemotherapy plus imatinib (88% ± 11%; 95% CI, 66%-96%) or sibling-donor BMT (57% ± 22%; 95% CI, 30.4%-76.1%). No appreciable increase in toxicities was associated with adding imatinib to intensive chemotherapy.

Takeaway: Imatinib added to intensive chemotherapy improved 3-year EFS in children and adolescents with Ph+ ALL. Outcomes were not superior when imatinib plus chemotherapy was added to BMT.

Nanda A, et al. JAMA. *2009;302: 866-873.* ●

CALLING ALL NURSE

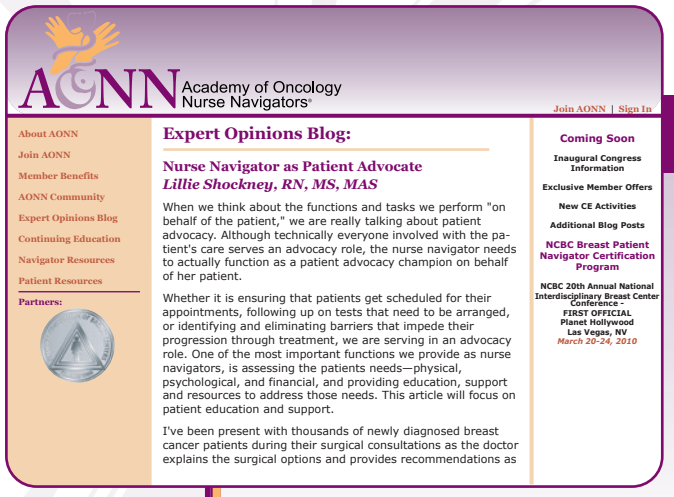
AONN Academy of Oncology Nurse Navigators®



JOIN

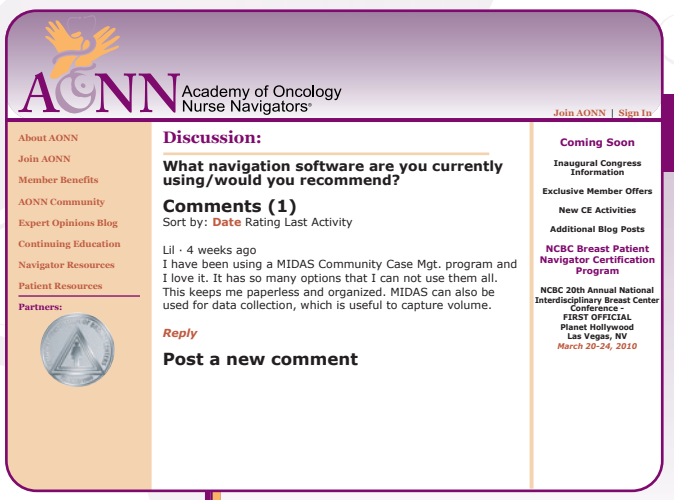
AONN membership provides you with free subscriptions to *The Oncology Nurse* and the bimonthly *Journal of Multi-disciplinary Cancer Care*, as well as discounts on all educational programs, including registration for future annual meetings.

JOIN TODAY



BLOG

Experts from various disciplines will be featured in blog segments over the course of the year, allowing members to interact with their colleagues on multiple subject areas.



DISCUSS

Interact with your colleagues on the subjects impacting your daily practice to receive feedback and answers to your questions as well as to share your personal stories.

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News & Announcements

October 22, 2009
Part 3 of the new blog series by Lillie Shockney, RN, BS, MAS on the history of navigation available

October 15, 2009
Part 2 of the new blog series by Lillie Shockney, RN, BS, MAS on the history of navigation available

September 28, 2009
Part 1 of the new blog series by Lillie Shockney, RN, BS, MAS on the history of navigation available

The Academy of Oncology Nurse Navigators

NAVIGATORS

$39.95 First Year Membership

Join AONN | Sign In

September 14, 2009
Carol Lewis, RN, BSN, OCN, CRNI and Pamela Matten, RN, BSN, OCN join the AONN leadership council

August 28, 2009
Susan M. Gardner, RN, CBEC, CBCN joins the AONN leadership council New blog post by Lillie Shockney, RN, BS, MAS

August 21, 2009
AONN partners with the National Consortium of Breast Centers (NCBC)

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NCBC 20th Annual National Interdisciplinary Breast Center Conference -
FIRST OFFICIAL
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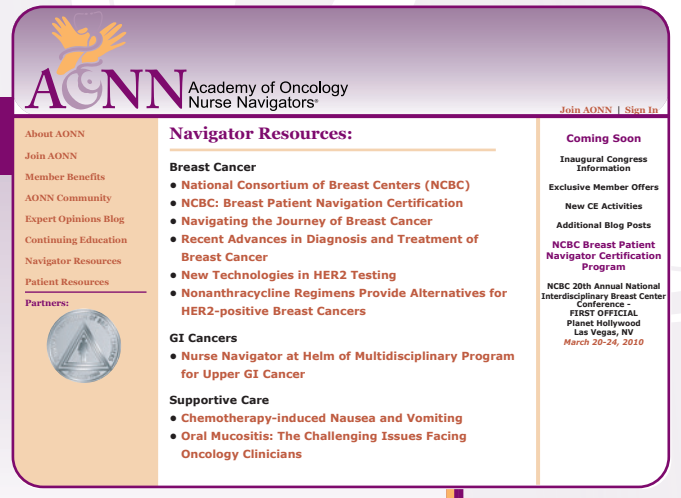
is devoted to educating Nurse Navigators, Practice Managers, Patient Care Coordinators, and Nursing Administrators on the complexities of the cancer care treatment continuum, to improve patient outcomes and quality of life.

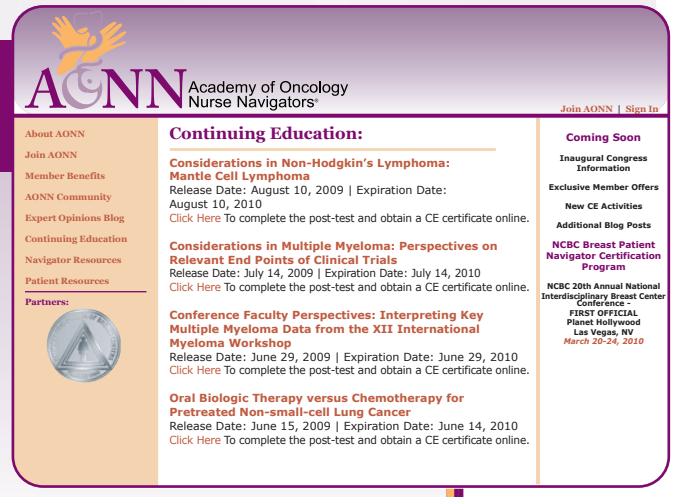
RESOURCES

Informational/educational resources to help you and your patients navigate their cancer treatment and improve their quality of life.



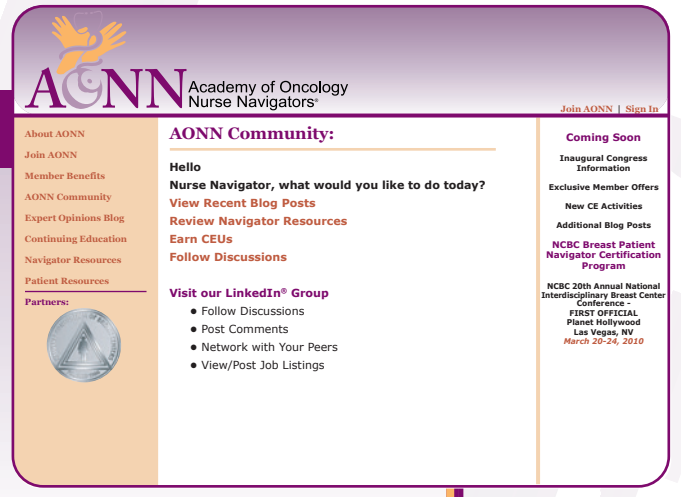
CONTINUING EDUCATION

Access to free continuing education activities focused on improving patient outcomes by elevating the knowledge, competency, and performance of oncology nurse navigators.



COMMUNITY

Connect with your peers across the country to gain valuable insight into different navigation practices, as well as help to organize local and regional AONN chapters.



JOURNAL SUBSCRIPTIONS

Members receive subscriptions to the journal *The Oncology Nurse* (a $150 value) and the bimonthly *Journal of Multidisciplinary Cancer Care*.

*Membership is required for access to blogs, forums and other resources.

www.AONNonline.org

Nursing Life


©iStockphoto.com/Joe Biafore

Crunchy Pumpkin Pie

With only a small amount of oil in the crust and skim milk in the filling, this delicious pie is a heart healthy treat.

Ingredients

For the crust:

1 cup quick cooking oats
¼ cup whole wheat flour
¼ cup ground almonds
2 tablespoons brown sugar
¼ teaspoon salt
3 tablespoons vegetable oil
1 tablespoon water

For the filling:

¼ cup brown sugar, packed
½ teaspoon ground cinnamon
¼ teaspoon ground nutmeg
¼ teaspoon salt
1 egg, beaten
4 teaspoons vanilla
1 cup canned pumpkin
⅔ cup evaporated skim milk

To prepare crust:

- Preheat oven to 425 degrees
- Mix oats, flour, almonds, sugar, and salt in small bowl
- Blend oil and water in measuring cup with fork or small wire whisk
- Add oil mixture to dry ingredients and mix well. If needed, add small amount of water to hold mixture together
- Press into 9-inch pie pan and bake for 8 to 10 minutes, or until light brown
- Turn oven down to 350 degrees

To prepare filling:

- Mix sugar, cinnamon, nutmeg, and salt in bowl
- Add egg and vanilla, and mix to blend ingredients
- Add pumpkin and milk and stir to combine

Putting it together:

- Pour filling into prepared pie shell
- Bake for 45 minutes at 350 degrees or until knife inserted near center comes out clean

Nutritional Information
Yield: 9 servings
Serving size: 1/9 of 9-inch pie

Each serving provides:
Calories: 169; Total fat: 7 g; Saturated fat: 1 g; Cholesterol: 24 mg; Sodium: 207 mg; Total fiber: 3 g; Protein: 5 g; Carbohydrates: 22 g; Potassium: 223 mg

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.

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Oncology Nutrition
Soy and Breast Cancer

BY **AMANDA SALDIVAR, MS, RD, LD**
TAUSSIG CANCER INSTITUTE, CLEVELAND, OHIO

Soy foods are made from the soybean plant, which is a legume (other plants categorized as legumes include peas, beans, lentils, and peanuts). In recent years, the soybean and its derived foods have been noted for their high nutritional value. It is an excellent source of protein (one of the only plant sources of "complete" protein, containing all the essential amino acids needed for normal growth), making it a staple in many vegetarian diets. It is also high in fiber, contains no cholesterol, and is rich in vitamins. Foods that use soy as a primary ingredient include tofu, miso, tempeh, soy oil, soy sauce, soy milk, soy flour, soy protein isolates, and concentrates.[1]

Because of the significantly lower incidence of chronic disease (especially premenopausal breast cancer) among the Asian population, soy has been studied for its potential health benefits.[1] Soy has been found to contain high levels of polyphenolic compounds. Most noted are isoflavones, also known as phytoestrogens, named so because of their similar chemical structure to human estrogen.

Because of this similar structure, soy has been studied to determine whether it mimics the effect of estrogen. Some studies have shown that soy has a 1000 times weaker mimicking effect. Other studies have shown that soy slows the multiplication of cancer cells[2] and reduces mammographic density.[3] A group of studies showing a negative effect, however, has raised much controversy among healthcare providers. Because some studies have shown that phytoestrogens can mimic real estrogen by binding to estrogen receptors on the outer surfaces of cells and promote cancer growth,[4,5] this poses a concern when it comes to estrogen receptor–positive breast cancer, which grows in the presence of estrogen in the body.[6] However, this research has been confined to in vitro and animal studies, and it is difficult to duplicate these results in studies focusing on isoflavones' action in the human body[7] or to determine the specified amount of soy a woman would have to ingest to produce the same effects.[8] Furthermore, other stud-


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On the Lighter Side of Life

Amanda Saldivar, MS, RD, LD

ies have suggested that the effect that soy isoflavones have on the body is dependent on the activity of bacteria that colonize the human intestinal tract, which can vary from person to person.[9] So it is difficult to provide a concrete answer as to whether women should avoid or add soy to their diets.

The American Cancer Society[10] issued consensus recommendations on soy consumption for women who have a history of breast cancer based on the intake of women in Asian countries.[11] This includes up to three servings of soy foods that are less processed (eg, tofu, soy milk, tempeh, and miso). Consumption of highly processed soy foods (eg, frozen convenience soy foods) is not as encouraged because of their fat and sodium contents. Soy isolates and supplements also are not recommended because of the higher concentrations of isoflavones as well as the lack of other beneficial properties found in natural soy protein. If a patient is taking a general multivitamin that contains soy lecithin and/or soybean oil, there is no need for concern because these two ingredients do not contain isoflavones.

Consumption of highly processed soy foods is not as encouraged because of their fat and sodium contents.

It is up to each patient whether to include soy into her diet. It is important to note, however, that a growing number of foods contain soy as an ingredient. I always try to stress to my patients to keep focused on other guidelines that they should be following (managing their weight, incorporating physical activity daily, consuming seven to nine servings of fruits and vegetables, choosing whole grains, and lowering their fat intake) rather than becoming overwhelmed with looking at every ingredient and eliminating a food because it contains a small amount of soy.

These recommendations could be of concern to vegetarian or vegan patients, whose primary protein source is soy. They (as well as other cancer survivors) can include several other foods that can provide adequate protein without concern. These include wheat gluten (also known as wheat meat or seitan), dried beans, peas, nuts, seeds, and lentils. Instead of soy milk, patients can use fortified rice or almond milk. Protein also can be found in most of the other food groups: grains, vegetables, and some fats contain protein in smaller amounts. It is important that vegetarian patients work with a registered dietitian if they are not well-versed in vegetarianism to ensure that their diet contains all the essential nutrients. ●

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Medical Minutes

BY **JOHN SCHIESZER**

Combating Drug Side Effects in Breast Cancer Patients

Aromatase inhibitors (AIs), the same drugs that have buoyed long-term survival rates among breast cancer patients, also carry side effects that are so severe that many patients discontinue these lifesaving medicines. Now, new research has uncovered patterns that may help clinicians identify women at risk of these symptoms sooner to increase their chances of sticking with their treatment regimen.

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In a study published in the journal *Cancer*, researchers at the University of Pennsylvania School of Medicine found that estrogen withdrawal may play a role in the onset of arthralgia during treatment. The investigators found that women who stopped getting their menstrual periods less than 5 years before starting breast cancer treatment were three times more likely to experience arthralgia than those who reached menopause more than a decade earlier (2009;115:3631-3639).

In a separate study published in *Integrative Cancer Therapies*, the Pennsylvania researchers found that among women experiencing arthralgia during treatment with AIs, those who received electroacupuncture (a technique that combines traditional acupuncture with electric stimulation) reported a reduction in joint pain severity and stiffness. The women who received electroacupuncture also reported less fatigue and anxiety (2009;8:123-129).

"We are fortunate today to have many effective treatments for breast cancer. Unfortunately, many of these treatments have troublesome and debilitating side effects that can last for months or years after treatment, and really harm the quality of life and productivity of women who receive them," said study investigator Jun Mao, MD, an assistant professor of family medicine and community health at the University of Pennsylvania, Hershey. "These findings are just a first step in our comprehensive research program aimed at understanding the nature of treatment-related symptoms, who is likely to get them, the mechanisms by which they occur, and how best to treat them."

Patients in the new study were taking three different types of AIs: anastrozole, letrozole, or exemestane. Of the 300 patients enrolled in the study, 139 reported AI-related pain, with 75% of those reporting symptoms that began within the first 3 months of the therapy. The researchers said their findings suggest that women who entered menopause more recently may have higher levels of residual circulating estrogen in their bodies, which combined with exposure to AIs, may cause a steeper, quicker drop in estrogen levels, leading to worse symptoms.

A New Way to Classify Gastric Cancers

An international team of scientists has discovered a new way to classify stomach cancers, and it may be an important step toward designing more effective treatments and improving long-term survival.

Stomach (gastric) cancer is particularly prevalent in Asia, and it represents the second leading cause of cancer deaths worldwide. The new research is based on clinical findings from patients in Singapore, Australia, and the United Kingdom and represents the largest genomic analysis of gastric cancers to date. The new system classified gastric cancers by the signaling pathways the tumors use to grow and spread, as opposed to the more traditional approach that describes them by cell type or structure.

Stomach cancer is notoriously resistant to chemotherapy and newer biologic-based therapies have not proven very effective. With current treatments, fewer than a quarter of patients live longer than 5 years after surgery.

"These new findings may give us the first way to truly offer our gastric cancer patients personalized medicine," said senior study author Patrick Tan, MD, PhD, a member of the Duke-NUS Graduate Medical School and the Genome Institute of Singapore.

Investigators obtained 301 gastric tumors from three independent patient groups. They used computational methods to map the activation levels of 11 different cell-signaling pathways already known to be active in the development of gastric cancer. They found that three pathways, the primary drivers of cell growth and death (NF-kappa B, Wnt/beta-catenin, and proliferation/stem cell) were deregulated in most of the tumors. Stratifying patients by single pathways did not predict outcomes, but stratifying them by combinations of pathways did.

"We feel that the ability to perform 'high-throughput pathway profiling' opens up a number of interesting possibilities," Tan said. "It suggests that pathway combinations, rather than single pathways alone, may play a more critical role in influencing tumor behavior. We feel our findings about the NF-kappa B pathway may be especially important, because this pathway has been understudied in gastric cancer. Finally, our methods could certainly be used to study pathway profiles in other cancers, which could lead to new insight into tumor behavior and outcomes."

Obesity Hinders Chemotherapy in Children with Leukemia

Obesity is an important factor contributing to chemotherapy resistance and increasing relapse rates among children with leukemia, according to California researchers. Obesity is associated with increased incidence and mortality of many types of cancer. However, it now appears that fat cells have biological effects that impair chemotherapy. In addition, relapsing leukemia cells can be found in fat tissue, and this may provide a possible explanation for the high rate of cancer relapse among obese patients.

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These new findings involve leukemia patients; however, given the increasing prevalence of obesity worldwide, they could have important implications for cancer treatment overall. "Obesity could increase cancer incidence and mortality through a variety of ways. It may impair the immune system's ability to stop cancer or predispose cells to become cancerous," said Steven Mittelman, MD, PhD, an assistant professor of pediatrics, physiology, and biophysics at the Keck School of Medicine at the University of Southern California, Los Angeles. "Once you have cancer, and if you are obese, the fat cells themselves may impair the ability of chemotherapy to fight cancerous cells."

He said the current study was prompted by a previous study that showed that obese children diagnosed with leukemia have a 50% higher risk of relapsing compared with lean children. Using preclinical models, Mittelman and his colleagues developed a mouse model of obesity and leukemia, cultured fat and leukemia cells together, and treated the leukemia cells with traditional chemotherapy drugs used in children (vincristine, nilotinib, daunorubicin, and dexamethasone).

The researchers found that obese mice with leukemia had higher relapse rates than lean mice after treatment with the first-line chemotherapeutic agent vincristine. All the chemotherapy treatments worked less effectively in culture when fat cells were nearby. When the mice relapsed from the leukemia, the researchers discovered leukemia "hiding out" in the fat tissue during chemotherapy.

"These four drugs attack leukemia cells by different routes, so when we saw fat cells blocking them, we realized there could be an important mechanism promoting their ability to live and divide," said Mittelman. "We were surprised to find leukemia cells in the fat tissue."

Based on the finding that adipocytes accumulate chemotherapy drugs, the researchers say careful attention should be paid to dose adjustments based on pharmacokinetic measurements.

John Schieszer is an award-winning national journalist and radio broadcaster of The Medical Minute. He can be reached at medminutes@aol.com.

Meetings

JANUARY 2010

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22-24 ORLANDO, FL
2010 Gastrointestinal Cancers Symposium
www.asco.org

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30 MINNEAPOLIS, MN
7th Annual Mayo Clinic Hematology Review
www.mayo.edu

FEBRUARY 2010

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13-16 SAN DIEGO, CA
Scripps Cancer Center's 30th Annual Conference: Clinical Hematology and Oncology
www.scripps.org

25 CHANDLER, AZ
Multidisciplinary Head and Neck Cancer Symposium
www.headandnecksymposium.org

MARCH 2010

7-11 ATLANTA, GA
16th International Conference on Cancer Nursing
www.isncc.org

MARCH 2010

3-6 MIAMI, FL
27th Annual Miami Breast Cancer Conference
www.cancerlearning.com

5-7 SAN FRANCISCO, CA
Genitourinary Cancers Symposium
www.asco.org

5-7 SAN DIEGO, CA
7th Annual Oncology Nursing Advanced Practice: Innovation through Practice
www.scripps.org

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Indications

RITUXAN® (Rituximab) is indicated for the treatment of patients with:

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  - Weekly ×8
  - Bulky disease
  - Retreatment
- 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

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.

For additional safety information, please see following page for brief summary of prescribing information, including **BOXED WARNINGS** and Medication Guide.

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

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