**PRACTICAL APPLICATIONS**
Clinical advances in the treatment of myelodysplastic syndromes

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Nursing career specialist increases recruitment, retention

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DECEMBER 2008 • VOL. 1, NO. 6 www.theoncologynurse.com

# The Oncology Nurse™

The Official Newspaper of Record for the Hem/Onc Nurse

## NURSE NAVIGATORS

# Navigating the Journey of Breast Cancer

An interview with Sharon S. Gentry, RN, MSN, AOCN

Sharon S. Gentry, RN, MSN, AOCN, is a nurse who has braved unchartered waters herself by organizing her center's first "nurse navigation" program after devoting 20 years to nursing on the inpatient oncology unit. She now helps breast cancer patients navigate their own journey as a breast nurse navigator at the Derrick L. Davis Forsyth Regional Cancer Center in Winston-Salem, NC. Gentry is one of a growing number of nurses who guide cancer patients through and around barriers in the complex cancer care system, including lack of information, gaps in care, and need for financial help, social support, or transportation. Nurse navigators not only help to ensure timely treatment, but provide their support in a manner that is compassionate, respectful, and culturally sensitive.

At the Derrick L. Davis Forsyth Regional Cancer Center, in 2001 Gentry started the seamless thread that ties together the center's community-based breast cancer care,

*Continued on page 9*

## NURSING LIFE

# Study Suggests Devastating Consequences of Smoking on the Nursing Profession

SEATTLE—For the first time, researchers have looked at smoking and the nursing profession and the findings are rather surprising. The study shows a dichotomy between what nurses advise their patients and what they do themselves. It also emphasizes the importance of supporting smoking cessation programs for nurses.

"Nurses witness firsthand how smoking devastates the health of their patients with cancer and respiratory and cardiovascular diseases," said principal investigator Linda Sarna, DNSc, a professor at the University of

*Continued on page 10*

## NURSING PRACTICE

# Integrating the Humanistic and Scientific Aspects of Patient Care

At the 2008 Annual Meeting of the American Society of Clinical Oncology, chair Teresa Gilewski, MD, medical oncologist, Breast Cancer Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center (MSKCC), New York, introduced an educational session entitled "Integrating

*Continued on page 5*

## CANCER CONCEPTS

# Cancer Self-seeding: New Concept May Explain Why What Goes Around Comes Around

A new concept of "self-seeding" of cancer by circulating cells returning to the original tumors may help to inform some long-standing problems in cancer biology and treatment, including why chemotherapy may often be only partially effective.

*Continued on page 17*

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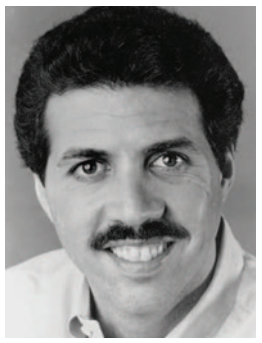
# Medical Minutes

BY **JOHN SCHIESZER**



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

## Improving the Management of Cancer-related Fatigue

Nurses can play an important role in improving the management of cancer-related fatigue by addressing the problem early in the course of treatment, according to researchers at the Cancer Institute of New Jersey (CINJ). The investigators also have found that a self-care fatigue diary may be beneficial.

"Empowering the patient with information and education related to symptoms of fatigue is important," said Beth Knox, MSN, RN, APN-C, AOCN, an adult oncology–certified nurse practitioner at the CINJ, New Brunswick, NJ. "We need more education and the patients need to be educated before their chemotherapy begins, and this often does not happen. The patients are not empowered with enough information to manage their fatigue symptoms throughout the course of their treatment."

Knox and her colleagues are conducting a supportive care trial focused on the use of a self-care fatigue diary. The study addresses use of the diary to help manage chemotherapy-induced side effects, such as fatigue, and associated symptoms. One of the primary aims of the study is to measure patient/provider satisfaction in the management of cancer-related fatigue. Knox contends that many patients are inadequately treated for cancer-related fatigue because of the significant communication barriers that currently exist. She said this is a problem at institutions all across the United States.

"I think that there are barriers because patients feel the doctors are not interested or don't have specific recommendations that they give patients. Patients have fear of discussing fatigue because they fear that the disease has progressed and that is indicated by the fatigue. Also, there is a fear about it jeopardizing their ability to stay on their cancer treatment," said Knox. "Another issue is that many patients want to limit their medications, and so they don't want to get more medications. They may worry that can happen if they bring up their problems with fatigue."

Knox said the use of a self-care fatigue diary can help address some of these issues by improving communication between patients and providers. She said it is important that nurses bring up these issues as early as possible. Knox said oncology nurses should try to help patients address the physical, emotional, spiritual, practical, social, and financial effects of cancer. By doing this, she said it may be possible to improve a patient's comfort and reduce symptoms that may cause pain and diminish quality of life.

## Dietary Supplement Genistein May Undermine Breast Cancer Treatment

Oncology nurses may want to warn their breast cancer patients who are taking aromatase inhibitors to think twice before taking a soy-based dietary supplement. Researchers at the University of Illinois have found that genistein, a soy isoflavone that mimics the effects of estrogen in the body, can negate the effectiveness of aromatase inhibitors, which are designed to reduce the levels of estrogens that can promote tumor growth.

Aromatase inhibitors work by interfering with the enzyme aromatase, which catalyzes a crucial step in converting precursor molecules to estradiol. About two thirds of all cases of breast cancer diagnosed in the United States are estrogen dependent or estrogen sensitive, which means that the tumors grow more rapidly in the presence of estrogen.

The researchers conducted several trials in animal models using the widely prescribed aromatase inhibitor letrozole (Femara). They found that when genistein (a plant estrogen or phytoestrogen present in many dietary supplements) was given with letrozole, there was a dose-dependent reduction in the effectiveness of the breast cancer drug. Specifically, the tumors began to grow again and they grew the fastest at the highest dietary doses of genistein.

"To think that a dietary supplement could actually reverse the effects of a very effective drug is contrary to much of the perceived benefits of soy isoflavones, and unsettling," said principal study investigator William Helferich, who is a professor of food science and human nutrition at the University of Illinois, Champaign. "You have women who are taking these supplements to ameliorate postmenopausal symptoms and assuming that they are as safe as consuming a calcium pill or a B vitamin."

Many women currently take genistein supplements to control hot flashes and other symptoms of menopause. The Illinois researchers found that the doses commonly available in dietary supplements were potent enough to negate the effectiveness of aromatase inhibitors.

"These compounds have complex biological activities that are not fully understood. Dietary supplements containing soy-based phytoestrogens provide high enough dosages that it could be a significant issue to breast cancer patients and survivors," said Helferich. "We are just starting to understand the complex effects of the dietary supplements that contain phytoestrogens….These findings raise serious concerns about the potential interaction of the estrogenic dietary supplements with current breast cancer therapies." [See related story on page 17.]

## Cancer Breath: Detecting Cancer Earlier Through Exhaled Air

Early cancer detection can significantly improve survival rates. Current diagnostic tests, however, often fail to detect cancer in the earliest stages and at the same time expose a patient to the harmful effects of radiation. Now, researchers in Oklahoma are hoping to use mid-infrared lasers to detect biomarker gases exhaled in the breath of a person with cancer to pick up their cancer earlier.

Proof-of-concept detection of a suspected lung cancer biomarker in exhaled breath has already been established by the Oklahoma researchers. Their research was inspired by studies showing that dogs can detect cancer by sniffing the exhaled breath of cancer patients. In a study reported in the March 2006 issue of *Integrative Cancer Therapies*, researchers found that by sniffing the exhaled breath of patients with cancer, dogs could identify breast cancer and lung cancer patients with accuracies of 88% and 97%, respectively.

"A device that measures cancer-specific gases in exhaled breath would change medical research as we know it," said Patrick McCann, a professor in the College of Engineering at the University of Oklahoma, Norman.

He said it appears that it is possible to develop easy-to-use detection devices for cancer, particularly for hard-to-detect cancers like lung cancer. In the future, oncology nurses may be able to use these devices at the bedside to help diagnose and guide the management of patients with cancer.

"Improved methods to detect molecules have been demonstrated, and more people need to be using these methods to detect molecules given off from cancer. We have developed laser-based methods to detect molecules. Mid-infrared lasers can measure suspected cancer biomarkers: ethane, formaldehyde, and acetaldehyde," said McCann. "However, more capital and research infrastructure are needed for this device to become a reality."

He is currently using nanotechnology to improve laser performance and shrink the laser systems, which would allow battery-powered operation of a handheld sensor device. McCann said, however, it would be at least 5 years before a low-cost device like this could be available in the clinic.



MEDICAL MINUTES

Vol. 1, No. 6 December 2008

## Feature Articles



## Departments



**Practical Applications**
*Clinical advances in the treatment of myelodysplastic syndromes*

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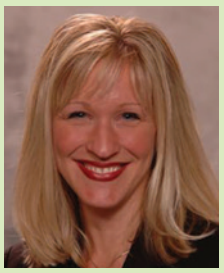

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# A Letter from the Editor

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

*EDITOR-IN-CHIEF*

The latest cancer statistics are encouraging—for the first time, both rates of new cancer diagnoses and deaths from cancer have declined in the US population as a whole. The declines are attributed in part to healthier lifestyles as well as advances in diagnosis and treatment. Of concern, however, is the increase in lung cancer in women. As recent results from the Nurses' Health Study show, smoking is a concern for ourselves as well as our patients. With our busy, often stressful lives, it is easy to fall back into old habits like smoking or lack of exercise, but, in order to set a good example for our colleagues, our patients, and the community in which we live, we must practice what we preach. Nurses are in an excellent position to lead efforts to curb smoking and promote healthy lifestyles in general.

Much positive news about advances in cancer diagnosis and treatment was reported at recent meetings of the American Society of Hematology, The Oncology Nursing Society, the European Society of Medical Oncology and will be reviewed in this and coming issues. One notable example is myelodysplastic syndrome, as the article by Sandra Kurtin eloquently explains. For the first time, data are now available showing prolonged survival with newer therapies, offering new hope for patients, their families, and their caregivers. Another good example is progress in the treatment of metastatic renal cell carcinoma, with new therapies that are not only more effective than previous agents but also offer patients an improved quality of life.

Despite all this good news, a diagnosis of cancer can be devastating for the patient and the variety of treatment choices bewildering. Patients often need someone to guide them in making decisions about treatment and coping with the emotional, financial, insurance, employment, and other issues that arise at the time of diagnosis and throughout the course of the disease and survivorship. To meet this need, a new specialty in nursing is emerging—the nurse navigator. The interview with Sharon Gentry, one of the leaders in this movement, is the first in a series in *The Oncology Nurse* that will follow developments in this field, including formation of a national organization of oncology nurse navigators and the role of nurse navigators in treatment of various types of cancer. If you would like to share your own experience as a nurse navigator with our readers, please write to **Karen@greenhillhc.com.**



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# Integrating Aspects of Patient Care

*Continued from cover*

the Humanistic and Scientific Aspects of Patient Care: The Perspective of Seasoned Surgical, Medical, Pediatric, and Radiation Oncologists." She followed the presentation with a 30-minute video she produced containing interviews with 11 physicians, a medical resident, and a pre-med student.

### A challenging issue

Gilewski sees both science and humanism as integral components of medicine, but feels that because the humanistic aspects are difficult to quantify, they receive less attention and will require innovative approaches like her video, which she hopes will eventually be available for viewing by a wider audience. The interviewees all seemed to feel that the process of integrating science and humanism in practice was difficult, although the reasons for this were not entirely clear. Kathleen Foley, MD, an interviewee who is a neurologist at MSKCC, believes that humanistic behavior can be learned, but if practitioners cannot learn the behavior, then they can certainly learn to model humanistic behavior. This puts some responsibility on those who train healthcare providers, in either classroom or clinical settings, to teach by example.

### The physician's perspective

Hyman Bernard Muss, MD, professor of medicine, University of Vermont and Vermont Cancer Center, Burlington, presented the perspective of a medical oncologist. He observed that although the oncologist often becomes the patient's primary care physician, the team concept, which includes constructive interaction with nurses and other healthcare providers, is foreign to many oncologists. One obstacle to a humanistic approach to patient care, he said, is the continuing computerization of medical care, which will require a conscious effort on the part of physicians to continue to provide compassion, empathy, guidance, reassurance, and comfort. Another obstacle he believes is the lifestyle gap between today's doctors and patients. What he has found helpful is to make a conscious effort to sit down and listen, to start patient encounters saying, "Now tell me about yourself."

Melissa M. Hudson, MD, St. Jude Children's Research Hospital, provided a pediatric perspective. "At St. Jude's," she observes, "[we] are not driven by the bottom line and can spend whatever time is needed with patients." She seeks to understand the patients, the family perspective, their community and culture, and to be sensitive to their perspective, even if it is not her own. "You don't know what the patients and family are going through. You need to acknowledge their unique fears and uncertainty, be open-minded and patient to questions, then be patient with more questions, anticipate what they do not hear, and collaborate to find answers and solutions," Hudson says. "The oncologist may think a treatment is well-tolerated, but the patient may not." She sees humanism in practice as focusing care on the patient, not the disease. This requires evaluation of all aspects: physical, emotional, social, and financial, something she thinks pediatricians excel at.

Hudson noted issues that irritate her in medical situations, including unexplained delays, provider inaccessibility, rushed interactions, lack of or poor communication, lack of respect for privacy or dignity (eg, having a prolonged discussion with a patient in a gown), and which should be avoided. She also emphasized that healthcare providers should acknowledge the limits of their knowledge, time, and energy, and tell patients when they do not know something and that they will get back to them. The benefits of this approach are enhanced communication, a collaborative relationship with the patient, respect for provider time and effort, care satisfaction, and a willingness to forgive shortcomings. These benefits, however, come at the expense of extra time spent, as well as emotional and physical demands on practitioners.

Jay R. Harris, MD, a radiation oncologist at the Dana-Farber Cancer Center, Boston, sees humanism in medicine as a demonstration to patients that there is a commitment to understand their psychosocial as well as medical issues, and to convince patients he cares about them. He thinks patients need this because they are often more fearful of the short- and long-term effects of radiation therapy than they are of surgery and medical treatment. He notes that the practice of radiation oncology depends on teamwork and positive interactions between physicians and nurses. He observes that at Harvard Medical School, radiation oncology is a popular field because of the quality and quantity of time students get to spend with patients.

The perspective of the surgical oncologist was presented by Murray F. Brennan, MD, a surgeon at MSKCC, who said that humanism should not be taught as a course, but by example in patient care, where it begins with the first consultation and never ends. He said, "Do not promise what you can't deliver when communicating with a patient, particularly when the patient expects a miracle and you can't deliver it. This extends to not promising what colleagues, like medical or radiation oncologists, also can't deliver. Anyone can tell a patient the surgery went well. The surgeon needs to be there to tell the patient the cancer was inoperable or he couldn't get it all." This sort of situation requires both the patient and healthcare provider to organize their thoughts to balance optimism with reality.

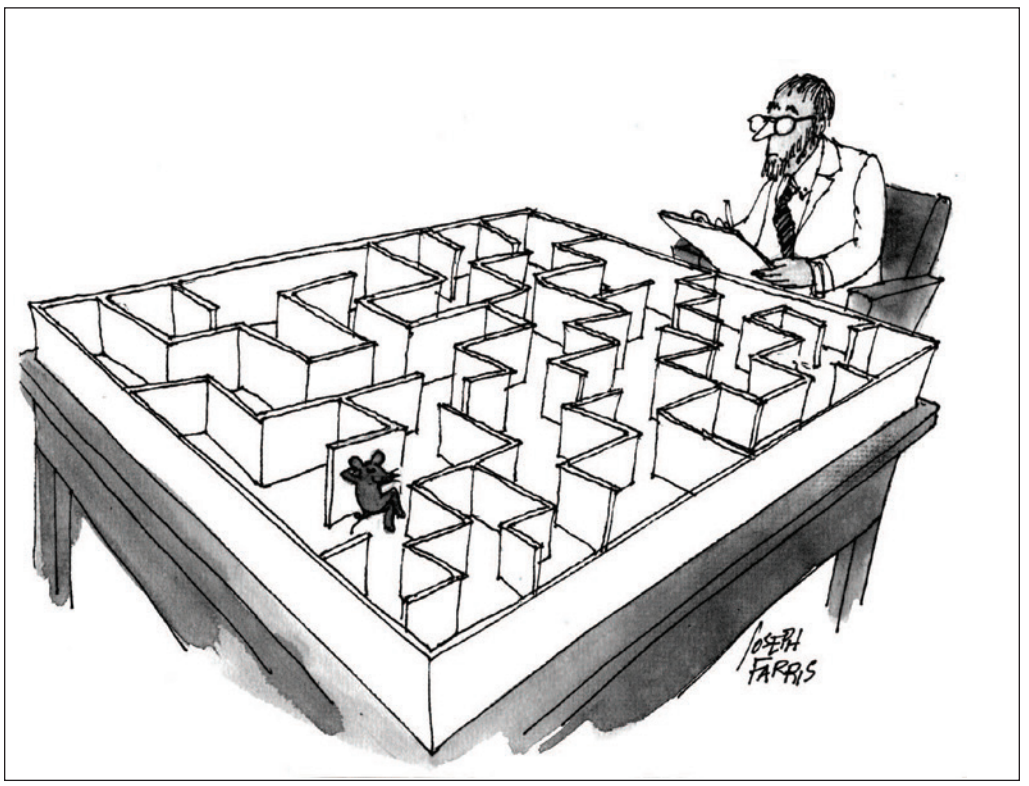
**She sees humanism in practice as focusing care on the patient, not the disease.**


### The nurse's perspective

Ruth McCorkle, PhD, FAAN, professor of nursing, Yale School of Nursing, and program leader for cancer control at the Yale Comprehensive Cancer Center, thinks "it's ironic we have to talk about being humanistic. It should be part of what we are." When asked how to help people be more humanistic, McCorkle responds, "A lot is just basic kindness." McCorkle teaches a course in living and dying. "The unfortunate part is that it's an elective. It's still quite amazing to me that it's not required," she says. She noted that at the Yale School of Nursing this fall there will be an end-of-life workshop. "This is absolutely a topic for continuing nursing education," she emphasizes.

McCorkle cited the Institute of Medicine (IOM) study report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, published in 2007, which established that care that does not address patients' mental and emotional well-being is not quality care. The IOM Committee on Psychosocial Services to Cancer Patients/Families in a Community Setting included Drs McCorkle and Hudson, as well as psychiatrists, physicians, social workers, policy experts, oncologists, and nursing school faculty. The report describes the lack of attention to patients' psychosocial health in cancer care, and the feeling among patients that their healthcare providers do not understand their psychosocial needs, do not consider support as integral to their care, are unaware of available resources, and do not either recognize and treat patients' psychosocial problems or refer them to appropriate treatment. The IOM Committee has identified six domains of patient psychosocial problems as well as the services needed to address them and has described a standard of care based on effective communication, identification of patient needs, and implementation of a plan to address those needs. The report is available at http://www.iom.edu/CMS/3809/34252/47228.aspx.

*—Lynne Lederman*








NURSING PRACTICE

# News Notes

## Cancer Rates Fall in United States

For the first time since reporting began in 1998, both overall cancer incidence and mortality have decreased significantly in men and women and in most racial and ethnic groups in the United States. According to a report issued by the American Cancer Society, the Centers for Disease Control and Prevention, the National Cancer Institute, and the North American Association of Central Cancer Registries, the incidence and mortality of the three most common cancers among men (lung, colorectal, and prostate) and two of the most common among women (breast and colorectal) decreased. Lung cancer incidence and death rates, however, rose in women in 18 states, mostly in states in the South or Midwest that have not passed antismoking laws. In contrast, California, where smoking is banned in workplaces and other public places, is the only state in which lung cancer rates declined. The findings, the authors say, "underscore the need to maintain and strengthen many state tobacco control programs." (*J Natl Cancer Inst*. 2008;100:1672-1694.)

## Suboptimal Radiotherapy Linked to Higher Risk of Recurrence, Death

Women who postpone radiotherapy (RT) or do not complete the full radiation regimen after breast-conserving surgery are at significantly increased risk of recurrence or death, researchers at Weill Cornell Medical College in New York report. They reviewed the medical records of 7791 women 66 years or older with stage I breast cancer or ductal carcinoma in situ; 16% postponed RT and 3% did not complete the full regimen. The risk of a subsequent breast cancer event was 1.4 times higher in patients with stage I breast cancer who waited 8 weeks before starting RT, and four times higher in women who delayed 12 weeks or longer. Patients who had a truncated course of RT (defined as less than 3 weeks instead of the usual 5 to 7 weeks) had a 32% greater overall mortality rate, the researchers found. (*Cancer*. 2008;113:3108-3115.)

## Free CE Credits Available at COEXM Web Site

The Center of Excellence Media (COEXM) web site offers a variety of complimentary CE programs for oncology nurses and other members of the cancer care team. To view all available CE programs and current and past issues of *The Oncology Nurse*, please log on to www.coexm.com and click on *The Oncology Nurse* at the top of the page. You can also register to receive your free subscription to *The Oncology Nurse* and related publications and obtain guidelines for authors.

## Home-based Diet and Exercise Program Improves Elderly Cancer Survivors' Physical Function

Elderly cancer survivors who participated in a home-based diet and exercise program showed improvements in their diet and exercise habits and improved physical function scores. Preliminary results of the Reach-out to Enhance Wellness (RENEW) trial were presented by Wendy Demark-Wahnefried, PhD, of M.D. Anderson Cancer Center at the seventh annual American Association for Cancer Research Frontiers in Cancer Prevention conference. Of 641 participants who were 65 years of age or older and had been diagnosed with cancer at least 5 years previously, 319 received the intervention and 322 were waitlisted. At the end of the year-long program, which included 15 telephone counseling sessions with a personal trainer, those in the intervention group had increased their physical activity to 44.9 minutes per week compared with 29.7 minutes in the control group and showed improvements in strength of their legs and other measures of physical function. In addition, the intervention group had a 3% decrease in body weight compared with a 1% drop in the control group. (www.mdanderson.org.)

## But Cancer Burden Growing Worldwide

Despite declines in cancer rates in

# News Notes

the United States, the global burden of cancer is increasing and could nearly triple by 2030, a new report by the International Agency for Research on Cancer (IARC) shows. At a press conference, leaders of the American Cancer Society (ACS), Susan G. Komen for the Cure, and the Lance Armstrong Foundation announced they will join forces with the IARC and the National Cancer Institute of Mexico to focus attention on this growing worldwide problem. The ACS, Susan G. Komen for the Cure, and the Lance Armstrong Foundation also issued a six-point call to action outlining steps the new US administration can take to ease the global cancer burden. (www.cancer.org.)

## Online Guide to e-Prescribing Available

Beginning in 2009, the Centers for Medicare & Medicaid Services (CMS) will offer financial incentives for physicians who successfully use e-prescribing systems. Only about 6% of US physicians are currently using e-prescribing systems, according to eHealth Initiative. The group in collaboration with the American Medical Association and other healthcare organizations has prepared *A Clinician's Guide to Electronic Prescribing*, which is available online (http:www.ehealthinitiative.org/assets/Documents/e-Prescribing_Clinicians_Guide_Final.pdf). The guide includes a section designed to familiarize physicians with e-prescribing and its benefits as well as possible challenges in making the transition. Another section is designed to guide readers through the implementation process. Information on the CMS e-Prescribing Incentive Program can be found at http://www.cms.hhs.gov/ PQRI/03_EPrescribingIncentiveProgram.asp.





NEWS NOTES

BRIEF SUMMARY OF PROCRIT® PRESCRIBING INFORMATION FOR THE TREATMENT OF ANEMIA IN CANCER PATIENTS ON CHEMOTHERAPY

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- **To decrease these risks, as well as the risk of serious cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusion.**
- **Use ESAs only for treatment of anemia due to concomitant myelosuppressive chemotherapy.**
- **ESAs are not indicated for patients receiving myelosuppressive therapy when the anticipated outcome is cure.**
- **Discontinue following the completion of a chemotherapy course.**

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**(See WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events, WARNINGS: Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION in full Prescribing Information.)**

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- PROCRIT ® is not indicated for the treatment of anemia in cancer patients due to other factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding (see PRECAUTIONS: Lack or Loss of Response).
- PROCRIT ® use has not been demonstrated in controlled clinical trials to improve symptoms of anemia, quality of life, fatigue, or patient well-being.

## CONTRAINDICATIONS

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## WARNINGS

### Pediatrics

**Risk in Premature Infants**

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### Adults

**Increased Mortality, Serious Cardiovascular and Thromboembolic Events**

Patients with chronic renal failure experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies. Patients with chronic renal failure and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular events and mortality than other patients. PROCRIT® and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction, stroke, congestive heart failure, and hemodialysis vascular access thrombosis. A rate of hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks.

In a randomized prospective trial, 1432 anemic chronic renal failure patients who were not undergoing dialysis were assigned to Epoetin alfa (rHuEPO) treatment targeting a maintenance hemoglobin concentration of 13.5 g/dL or 11.3 g/dL. A major cardiovascular event (death, myocardial infarction, stroke, or hospitalization for congestive heart failure) occurred among 125 (18%) of the 715 patients in the higher hemoglobin group compared to 97 (14%) among the 717 patients in the lower hemoglobin group (HR 1.3, 95% CI: 1.0, 1.7, p = 0.03).

Increased risk for serious cardiovascular events was also reported from a randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure). In this trial, patients were assigned to PROCRIT® treatment targeted to a maintenance hematocrit of either 42 ± 3% or 30 ± 3%. Increased mortality was observed in 634 patients randomized to a target hematocrit of 42% [221 deaths (35% mortality)] compared to 631 patients targeted to remain at a hematocrit of 30% [185 deaths (29% mortality)]. The reason for the increased mortality observed in this study is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs. 2.3%), vascular access thromboses (39% vs. 29%), and all other thrombotic events (22% vs. 18%) were also higher in the group randomized to achieve a hematocrit of 42%. An increased incidence of thrombotic events has also been observed in patients with cancer treated with erythropoietic agents.

In a randomized controlled study (referred to as Cancer Study 1 - the 'BEST' study) with another ESA in 939 women with metastatic breast cancer receiving chemotherapy, patients received either weekly Epoetin alfa or placebo for up to a year. This study was designed to show that survival was superior when an ESA was administered to prevent anemia (maintain hemoglobin levels between 12 and 14 g/dL or hematocrit between 36% and 42%). The study was terminated prematurely when interim results demonstrated that a higher mortality at 4 months (8.7% vs. 3.4%) and a higher rate of fatal thrombotic events (1.1% vs. 0.2%) in the first 4 months of the study were observed among patients treated with Epoetin alfa. Based on Kaplan-Meier estimates, at the time of study termination, the 12-month survival was lower in the Epoetin alfa group than in the placebo group (70% vs. 76%; HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

A systematic review of 57 randomized controlled trials (including Cancer Studies 1 and 5 - the 'BEST' and 'ENHANCE' studies) evaluating 9353 patients with cancer compared ESAs plus red blood cell transfusion with red blood cell transfusion alone for prophylaxis or treatment of anemia in cancer patients with or without concurrent antineoplastic therapy. An increased relative risk of thromboembolic events (RR 1.67, 95% CI: 1.35, 2.06; 35 trials and 6769 patients) was observed in ESA-treated patients. An overall survival hazard ratio of 1.08 (95% CI: 0.99, 1.18; 42 trials and 8167 patients) was observed in ESA-treated patients.

An increased incidence of deep vein thrombosis (DVT) in patients receiving Epoetin alfa undergoing surgical orthopedic procedures has been observed (see ADVERSE REACTIONS, Surgery Patients: Thrombotic/Vascular Events in full Prescribing Information). In a randomized controlled study (referred to as the 'SPINE' study), 681 adult patients, not receiving prophylactic anticoagulation and undergoing spinal surgery, received either 4 doses of 600 U/kg Epoetin alfa (7, 14, and 21 days before surgery, and the day of surgery) and standard of care (SOC) treatment, or SOC treatment alone. Preliminary analysis showed a higher incidence of DVT, determined by either Color Flow Duplex Imaging or by clinical symptoms, in the Epoetin alfa group [16 patients (4.7%)] compared to the SOC group [7 patients (2.1%)]. In addition, 12 patients in the Epoetin alfa group and 7 patients in the SOC group had other thrombotic vascular events. Deep venous thrombosis prophylaxis should be strongly considered when ESAs are used for the reduction of allogeneic RBC transfusions in surgical patients (see BOXED WARNINGS and DOSAGE AND ADMINISTRATION in full Prescribing Information).

Increased mortality was also observed in a randomized placebo-controlled study of PROCRIT® in adult patients who were undergoing coronary artery bypass surgery (7 deaths in 126 patients randomized to PROCRIT® versus no deaths among 56 patients receiving placebo). Four of these deaths occurred during the period of study drug administration and all four deaths were associated with thrombotic events. ESAs are not approved for reduction of allogeneic red blood cell transfusions in patients scheduled for cardiac surgery.

**Increased Mortality and/or Increased Risk of Tumor Progression or Recurrence**

Erythropoiesis-stimulating agents resulted in decreased locoregional control/progression-free survival and/or overall survival (see Table 1). These findings were observed in studies of patients with advanced head and neck cancer receiving radiation therapy (Cancer Studies 5 and 6), in patients receiving chemotherapy for metastatic breast cancer (Cancer Study 1) or lymphoid malignancy (Cancer Study 2), and in patients with non-small cell lung cancer or various malignancies who were not receiving chemotherapy or radiotherapy (Cancer Studies 7 and 8).

**Table 1: Randomized, Controlled Trials with Decreased Survival and/or Decreased Locoregional Control**

| Study / Tumor / (n) | Hemoglobin Target | Achieved Hemoglobin (Median Q1,Q3) | Primary Endpoint | Adverse Outcome for ESA-containing Arm |
|---|---|---|---|---|
| **Chemotherapy** | | | | |
| **Cancer Study 1** Metastatic breast cancer (n=939) | 12-14 g/dL | 12.9 g/dL 12.2, 13.3 g/dL | 12-month overall survival | Decreased 12-month survival |
| **Cancer Study 2** Lymphoid malignancy (n=344) | 13-15 g/dL (M) 13-14 g/dL (F) | 11.0 g/dL 9.8, 12.1 g/dL | Proportion of patients achieving a hemoglobin response | Decreased overall survival |
| **Cancer Study 3** Early breast cancer (n=733) | 12.5-13 g/dL | 13.1 g/dL 12.5, 13.7 g/dL | Relapse-free and overall survival | Decreased 3 yr. relapse-free and overall survival |
| **Cancer Study 4** Cervical Cancer (n=114) | 12-14 g/dL | 12.7 g/dL 12.1, 13.3 g/dL | Progression-free and overall survival and locoregional control | Decreased 3 yr. progression-free and overall survival and locoregional control |
| **Radiotherapy Alone** | | | | |
| **Cancer Study 5** Head and neck cancer (n=351) | ≥15 g/dL (M) ≥14 g/dL (F) | Not available | Locoregional progression-free survival | Decreased 5-year locoregional progression-free survival Decreased overall survival |
| **Cancer Study 6** Head and neck cancer (n=522) | 14-15.5 g/dL | Not available | Locoregional disease control | Decreased locoregional disease control |
| **No Chemotherapy or Radiotherapy** | | | | |
| **Cancer Study 7** Non-small cell lung cancer (n=70) | 12-14 g/dL | Not available | Quality of life | Decreased overall survival |
| **Cancer Study 8** Non-myeloid malignancy (n=989) | 12-13 g/dL | 10.6 g/dL 9.4, 11.8 g/dL | RBC transfusions | Decreased overall survival |

*Decreased overall survival:*

Cancer Study 1 (the 'BEST' study) was previously described (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events). Mortality at 4 months (8.7% vs. 3.4%) was significantly higher in the Epoetin alfa arm. The most common investigator-attributed cause of death within the first 4 months was disease progression; 28 of 41 deaths in the Epoetin alfa arm and 13 of 16 deaths in the placebo arm were attributed to disease progression. Investigator assessed time to tumor progression was not different between the two groups. Survival at 12 months was significantly lower in the Epoetin alfa arm (70% vs. 76%, HR 1.37, 95% CI: 1.07, 1.75; p = 0.012).

Cancer Study 2 was a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo) study conducted in 344 anemic patients with lymphoid malignancy receiving chemotherapy. With a median follow-up of 29 months, overall mortality rates were significantly higher among patients randomized to darbepoetin alfa as compared to placebo (HR 1.36, 95% CI: 1.02, 1.82).

Cancer Study 7 was a Phase 3, multicenter, randomized (Epoetin alfa vs. placebo), double-blind study, in which patients with advanced non-small cell lung cancer receiving only palliative radiotherapy or no active therapy were treated with Epoetin alfa to achieve and maintain hemoglobin levels between 12 and 14 g/dL. Following an interim analysis of 70 of 300 patients planned, a significant difference in survival in favor of the patients on the placebo arm of the trial was observed (median survival 63 vs. 129 days; HR 1.84; p = 0.04).

Cancer Study 8 was a Phase 3, double-blind, randomized (darbepoetin alfa vs. placebo), 16-week study in 989 anemic patients with active malignant disease, neither receiving nor planning to receive chemotherapy or radiation therapy. There was no evidence of a statistically significant reduction in proportion of patients receiving RBC transfusions. The median survival was shorter in the darbepoetin alfa treatment group (8 months) compared with the placebo group (10.8 months); HR 1.30, 95% CI: 1.07, 1.57.

*Decreased progression-free survival and overall survival:*

Cancer Study 3 (the 'PREPARE' study) was a randomized controlled study in which darbepoetin alfa was administered to prevent anemia conducted in 733 women receiving neo-adjuvant breast cancer treatment. After a median follow-up of approximately 3 years, the survival rate (86% vs. 90%, HR 1.42, 95% CI: 0.93, 2.18) and relapse-free survival rate (72% vs. 78%, HR 1.33, 95% CI: 0.99, 1.79) were lower in the darbepoetin alfa-treated arm compared to the control arm.

Cancer Study 4 (protocol GOG 191) was a randomized controlled study that enrolled 114 of a planned 460 cervical cancer patients receiving chemotherapy and radiotherapy. Patients were randomized to receive Epoetin alfa to maintain hemoglobin between 12 and 14 g/dL or to transfusion support as needed. The study was terminated prematurely due to an increase in thromboembolic events in Epoetin alfa-treated patients compared to control (19% vs. 9%). Both local recurrence (21% vs. 20%) and distant recurrence (12% vs. 7%) were more frequent in Epoetin alfa-treated patients compared to control. Progression-free survival at 3 years was lower in the Epoetin alfa-treated group compared to control (59% vs. 62%, HR 1.06, 95% CI: 0.58, 1.91). Overall survival at 3 years was lower in the Epoetin alfa-treated group compared to control (61% vs. 71%, HR 1.28, 95% CI: 0.68, 2.42).

Cancer Study 5 (the 'ENHANCE' study) was a randomized controlled study in 351 head and neck cancer patients where Epoetin beta or placebo was administered to achieve target hemoglobin of 14 and 15 g/dL for women and men, respectively. Locoregional progression-free survival was significantly shorter in patients receiving Epoetin beta (HR 1.62, 95% CI: 1.22, 2.14; p = 0.0008) with a median of 406 days Epoetin beta vs. 745 days placebo. Overall survival was significantly shorter in patients receiving Epoetin beta (HR 1.39, 95% CI: 1.05, 1.84; p = 0.02).

*Decreased locoregional control:*

Cancer Study 6 (DAHANCA 10) was conducted in 522 patients with primary squamous cell carcinoma of the head and neck receiving radiation therapy randomized to darbepoetin alfa with radiotherapy or radiotherapy alone. An interim analysis on 484 patients demonstrated that locoregional control at 5 years was significantly shorter in patients receiving darbepoetin alfa (RR 1.44, 95% CI: 1.06, 1.96; p = 0.02). Overall survival was shorter in patients receiving darbepoetin alfa (RR 1.28, 95% CI: 0.98, 1.68; p = 0.08).

**Pure Red Cell Aplasia**

Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with PROCRIT®. This has been reported predominantly in patients with chronic renal failure (CRF) receiving PROCRIT® by subcutaneous administration. Any patient who develops a sudden loss of response to PROCRIT®, accompanied by severe anemia and low reticulocyte count, should be evaluated for the etiology of loss of effect, including the presence of neutralizing antibodies to erythropoietin (see PRECAUTIONS: Lack or Loss of Response). If anti-erythropoietin antibody-associated anemia is suspected, withhold PROCRIT® and other erythropoietic proteins. Contact ORTHO BIOTECH at 1 888 2ASK OBI (1-888-227-5624) to perform assays for binding and neutralizing antibodies. PROCRIT® should be permanently discontinued in patients with antibody-mediated anemia. Patients should not be switched to other erythropoietic proteins as antibodies may cross-react (see ADVERSE REACTIONS: Immunogenicity).

**Albumin (Human)**

PROCRIT® contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

## PRECAUTIONS

The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur (see CONTRAINDICATIONS). In clinical trials, while transient rashes were occasionally observed concurrently with PROCRIT® therapy, no serious allergic or anaphylactic reactions were reported (see ADVERSE REACTIONS in full Prescribing Information for more information regarding allergic reactions).

The safety and efficacy of PROCRIT® therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagulable disorders).

In some female patients, menses have resumed following PROCRIT® therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated.

**Hematology:** Exacerbation of porphyria has been observed rarely in patients with CRF treated with PROCRIT®. However, PROCRIT® has not caused increased urinary excretion of porphyrin metabolites in normal volunteers, even in the presence of a rapid erythropoietic response. Nevertheless, PROCRIT® should be used with caution in patients with known porphyria.

In preclinical studies in dogs and rats, but not in monkeys, PROCRIT® therapy was associated with subclinical bone marrow fibrosis. Bone marrow fibrosis is a known complication of CRF in humans and may be related to secondary hyperparathyroidism or unknown factors. The incidence of bone marrow fibrosis was not increased in a study of adult patients on dialysis who were treated with PROCRIT® for 12 to 19 months, compared to the incidence of bone marrow fibrosis in a matched group of patients who had not been treated with PROCRIT®.

Cancer patients should have hemoglobin measured once a week until hemoglobin has been stabilized, and measured periodically thereafter.

**Lack or Loss of Response:** If the patient fails to respond or to maintain a response to doses within the recommended dosing range, the following etiologies should be considered and evaluated: 1. Iron deficiency: Virtually all patients will eventually require supplemental iron therapy (see IRON EVALUATION); 2. Underlying infectious, inflammatory, or malignant processes; 3. Occult blood loss; 4. Underlying hematologic diseases (ie, thalassemia, refractory anemia, or other myelodysplastic disorders); 5. Vitamin deficiencies: Folic acid or vitamin B12; 6. Hemolysis; 7. Aluminum intoxication; 8. Osteitis fibrosa cystica; 9. Pure Red Cell Aplasia (PRCA) or anti-erythropoietin antibody-associated anemia: In the absence of another etiology, the patient should be evaluated for evidence of PRCA and sera should be tested for the presence of antibodies to erythropoietin (see WARNINGS: Pure Red Cell Aplasia).

**Iron Evaluation:** During PROCRIT® therapy, absolute or functional iron deficiency may develop. Functional iron deficiency, with normal ferritin levels but low transferrin saturation, is presumably due to the inability to mobilize iron stores rapidly enough to support increased erythropoiesis. Transferrin saturation should be at least 20% and ferritin should be at least 100 ng/mL.

Prior to and during PROCRIT® therapy, the patient's iron status, including transferrin saturation (serum iron divided by iron binding capacity) and serum ferritin, should be evaluated. Virtually all patients will eventually require supplemental iron to increase or maintain transferrin saturation to levels which will adequately support erythropoiesis stimulated by PROCRIT®.

**Drug Interaction:** No evidence of interaction of PROCRIT® with other drugs was observed in the course of clinical trials.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Carcinogenic potential of PROCRIT® has not been evaluated. PROCRIT® does not induce bacterial gene mutation (Ames Test), chromosomal aberrations in mammalian cells, micronuclei in mice, or gene mutation at the HGPRT locus. In female rats treated IV with PROCRIT®, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg.

**Pregnancy Category C:** PROCRIT® has been shown to have adverse effects in rats when given in doses 5 times the human dose. There are no adequate and well-controlled studies in pregnant women. PROCRIT® should be used during pregnancy only if potential benefit justifies the potential risk to the fetus.

In studies in female rats, there were decreases in body weight gain, delays in appearance of abdominal hair, delayed eyelid opening, delayed ossification, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. In female rats treated IV, there was a trend for slightly increased fetal wastage at doses of 100 and 500 Units/kg. PROCRIT® has not shown any adverse effect at doses as high as 500 Units/kg in pregnant rabbits (from day 6 to 18 of gestation).

**Nursing Mothers:** Postnatal observations of the live offspring (F1 generation) of female rats treated with PROCRIT® during gestation and lactation revealed no effect of PROCRIT® at doses of up to 500 Units/kg. There were, however, decreases in body weight gain, delays in appearance of abdominal hair, eyelid opening, and decreases in the number of caudal vertebrae in the F1 fetuses of the 500 Units/kg group. There were no PROCRIT®-related effects on the F2 generation fetuses.

It is not known whether PROCRIT® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PROCRIT® is administered to a nursing woman.

**Pediatric Use:** See WARNINGS: Pediatrics

*Pediatric Cancer Patients on Chemotherapy:* The safety and effectiveness of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study (see CLINICAL EXPERIENCE, Weekly (QW) Dosing, Pediatric Patients in full Prescribing Information).

**Geriatric Use:** Insufficient numbers of patients age 65 or older were enrolled in clinical studies of PROCRIT® for the treatment of anemia associated with pre-dialysis chronic renal failure, cancer chemotherapy, and Zidovudine-treatment of HIV infection to determine whether they respond differently from younger subjects.

**Information for Patients**

Patients should be informed of the increased risks of mortality, serious cardiovascular events, thromboembolic events, and increased risk of tumor progression or recurrence (see WARNINGS). In those situations in which the physician determines that a patient or their caregiver can safely and effectively administer PROCRIT® at home, instruction as to the proper dosage and administration should be provided. Patients should be instructed to read the PROCRIT® Medication Guide and Patient Instructions for Use and should be informed that the Medication Guide is not a disclosure of all possible side effects. Patients should be informed of the possible side effects of PROCRIT® and of the signs and symptoms of allergic drug reaction and advised of appropriate actions. If home use is prescribed for a patient, the patient should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container should be available for the disposal of used syringes and needles, and guidance provided on disposal of the full container.

**Hypertension:** Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with PROCRIT®. Nevertheless, blood pressure in patients treated with PROCRIT® should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease.

**Seizures:** In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with PROCRIT® TIW and 2.9% (n = 2/68) of placebo-treated patients had seizures. Seizures in 1.6% (n = 1/63) of patients treated with PROCRIT® TIW occurred in the context of a significant increase in blood pressure and hematocrit from baseline values. However, both patients treated with PROCRIT® also had underlying CNS pathology which may have been related to seizure activity.

In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 1.2% (n = 2/168) of safety-evaluable patients treated with PROCRIT® and 1% (n = 1/165) of placebo-treated patients had seizures. Seizures in the patients treated with weekly PROCRIT® occurred in the context of a significant increase in hemoglobin from baseline values however significant increases in blood pressure were not seen. These patients may have had other CNS pathology.

**Thrombotic Events:** In double-blind, placebo-controlled trials, 3.2% (n = 2/63) of patients treated with PROCRIT® TIW and 11.8% (n = 8/68) of placebo-treated patients had thrombotic events (eg, pulmonary embolism, cerebrovascular accident), (see WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events).

In a placebo-controlled, double-blind trial utilizing weekly dosing with PROCRIT®, 6.0% (n = 10/168) of safety-evaluable patients treated with PROCRIT® and 3.6% (n = 6/165) (p = 0.444) of placebo-treated patients had clinically significant thrombotic events (deep vein thrombosis requiring anticoagulant therapy, embolic event including pulmonary embolism, myocardial infarction, cerebral ischemia, left ventricular failure and thrombotic microangiopathy). A definitive relationship between the rate of hemoglobin increase and the occurrence of clinically significant thrombotic events could not be evaluated due to the limited schedule of hemoglobin measurements in this study.

The safety and efficacy of PROCRIT® were evaluated in a randomized, double-blind, placebo-controlled, multicenter study that enrolled 222 anemic patients ages 5 to 18 receiving treatment for a variety of childhood malignancies. Due to the study design (small sample size and the heterogeneity of the underlying malignancies and of anti-neoplastic treatments employed), a determination of the effect of PROCRIT® on the incidence of thrombotic events could not be performed. In the PROCRIT® arm, the overall incidence of thrombotic events was 10.8% and the incidence of serious or life-threatening events was 7.2%.

## ADVERSE REACTIONS

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. Neutralizing antibodies to erythropoietin, in association with PRCA or severe anemia (with or without other cytopenias), have been reported in patients receiving PROCRIT® (see WARNINGS: Pure Red Cell Aplasia) during post-marketing experience.

There has been no systematic assessment of immune responses, i.e., the incidence of either binding or neutralizing antibodies to PROCRIT®, in controlled clinical trials.

Where reported, the incidence of antibody formation is highly dependent on the sensitivity and 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 across products within this class (erythropoietic proteins) may be misleading.

**Adverse Experiences Reported in Clinical Trials**

In double-blind, placebo-controlled studies of up to 3 months duration involving 131 cancer patients, adverse events with an incidence > 10% in either patients treated with PROCRIT® or placebo-treated patients were as indicated below:

| | Percent of Patients Reporting Event | |
|---|---|---|
| | Patients Treated With PROCRIT® | Placebo-treated Patients |
| **Event** | **(n = 63)** | **(n = 68)** |
| Pyrexia | 29% | 19% |
| Diarrhea | 21%* | 7% |
| Nausea | 17%* | 32% |
| Vomiting | 17% | 15% |
| Edema | 17%* | 1% |
| Asthenia | 13% | 16% |
| Fatigue | 13% | 15% |
| Shortness of Breath | 13% | 9% |
| Parasthesia | 11% | 6% |
| Upper Respiratory Infection | 11% | 4% |
| Dizziness | 5% | 12% |
| Trunk Pain | 3%* | 16% |

* Statistically significant

Although some statistically significant differences between patients being treated with PROCRIT® and placebo-treated patients were noted, the overall safety profile of PROCRIT® appeared to be consistent with the disease process of advanced cancer. During double-blind and subsequent open-label therapy in which patients (n = 72 for total exposure to PROCRIT®) were treated for up to 32 weeks with doses as high as 927 Units/kg, the adverse experience profile of PROCRIT® was consistent with the progression of advanced cancer.

Three hundred thirty-three (333) cancer patients enrolled in a placebo-controlled double-blind trial utilizing Weekly dosing with PROCRIT® for up to 4 months were evaluable for adverse events. The incidence of adverse events was similar in both the treatment and placebo arms.

## OVERDOSAGE

The expected manifestations of PROCRIT® overdosage include signs and symptoms associated with an excessive and/or rapid increase in hemoglobin concentration, including any of the cardiovascular events described in WARNINGS and listed in ADVERSE REACTIONS in full Prescribing Information. Patients receiving an overdosage of PROCRIT® should be monitored closely for cardiovascular events and hematologic abnormalities. Polycythemia should be managed acutely with phlebotomy, as clinically indicated. Following resolution of the effects due to PROCRIT® overdosage, reintroduction of PROCRIT® therapy should be accompanied by close monitoring for evidence of rapid increases in hemoglobin concentration (>1 gm/dL per 14 days). In patients with an excessive hematopoietic response, reduce the PROCRIT® dose in accordance with the recommendations described in DOSAGE AND ADMINISTRATION in full Prescribing Information.

## DOSAGE AND ADMINISTRATION

**IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic Events.**

Prior to initiating treatment with PROCRIT® a hemoglobin should be obtained to establish that it is >10 to ≤13 g/dL. The recommended dose of PROCRIT® is 300 Units/kg/day subcutaneously for 10 days before surgery, on the day of surgery, and for 4 days after surgery.

An alternate dose schedule is 600 Units/kg PROCRIT® subcutaneously in once weekly doses (21, 14, and 7 days before surgery) plus a fourth dose on the day of surgery.

All patients should receive adequate iron supplementation. Iron supplementation should be initiated no later than the beginning of treatment with PROCRIT® and should continue throughout the course of therapy. Deep venous thrombosis prophylaxis should be strongly considered (see BOXED WARNINGS).

**PREPARATION AND ADMINISTRATION OF PROCRIT®**

1. Do not shake. It is not necessary to shake PROCRIT®. Prolonged vigorous shaking may denature any glycoprotein, rendering it biologically inactive.
2. Protect the solution from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
3. Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the vial containing PROCRIT®, and wipe the septum with a disinfectant. Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution.
4. **Single-dose**: 1 mL vial contains no preservative. Use one dose per vial; do not re-enter the vial. Discard unused portions.

   **Multidose**: 1 mL and 2 mL vials contain preservative. Store at 2° to 8°C after initial entry and between doses. Discard 21 days after initial entry.
5. Do not dilute or administer in conjunction with other drug solutions. However, at the time of SC administration, preservative-free PROCRIT® from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) at a 1:1 ratio using aseptic technique. The benzyl alcohol in the bacteriostatic saline acts as a local anesthetic which may ameliorate SC injection site discomfort. Admixing is not necessary when using the multidose vials of PROCRIT® containing benzyl alcohol.

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ORTHO BIOTECH

# Navigating the Journey

*Continued from cover*

which includes two hospitals, one mammography clinic, a regional cancer center, four surgical offices, and a variety of community resources. Laurie Mathis, RN, came on board to help in 2003. Gentry is at the helm of this emerging field locally and speaks nationally to other healthcare organizations on this concept.

### Where does the nurse navigator concept come from?

The concept of "patient navigation" or "nurse navigation" began in the 1990s when Dr Harold P. Freeman established the first program at Harlem [New York] Hospital Center after observing that many cancer patients did not return for follow-up care. He wanted to improve access to cancer screening and address the barriers to cancer care that residents of Harlem encountered. The pilot navigation program compared 5-year survival rates of breast cancer patients who were and were not "navigated" through the system by a social worker, and it demonstrated a survival advantage among patients with navigators.[1]

Word of his program and its successes spread, and the idea caught fire with the publication of the 2001 President's Cancer Panel report, *Voices for a Broken System*.[2] The report identified major barriers to cancer care encompassing all socioeconomic levels, and recommended patient navigation programs as part of the solution. In 2005, President Bush signed the Patient Navigator Outreach and Chronic Disease Prevention Act, which provided funds for navigation programs within US cancer centers. The concept now appears to be growing rapidly.

### Is there a regional or national network or organization for nurse navigators?

Nationally, there is a focus group that meets at the Oncology Nursing Society's annual congress (www.ons.org) and is led by Cynthia Cantril, RN, MPH, from Forest Knolls, Calif. Any Oncology Nursing Society member is eligible to join this networking group. There is another national group called the National Coalition of Oncology Nurse Navigators that has a mission to promote excellence in oncology patient care by fostering collaborative relationships and professional development among oncology nurse navigators and other healthcare disciplines. This group (www.nconn.org) is led by Tina Beerman, RN, BS, from Columbia, Md. Both of these organizations have a focus on nurses as the navigators.

In North Carolina, we have formed the North Carolina Oncology Navigator Association, which brings together navigators (nurses, social workers, lay navigators) who work with a variety of cancers to promote quality patient navigation and serves as a network for navigators in North Carolina. We work under the vision and mission of the North Carolina State Cancer Plan (www.NCCancer.com).

### How did your own program begin?

Our navigator program started in 2001 and was driven by breast cancer patients. Newly diagnosed breast cancer patients voiced concern that they were overwhelmed with information and choices. With focus groups, it was determined that there was a need for a central source of information and for improvement in the flow of breast care across the local healthcare system. The concept of patient navigation was explored, and the directors of the local breast imaging center and cancer center decided that a nurse would be the best fit for this venture. I had recently completed a master's degree program in nursing education and I had a background in oncology and genetics in the high-risk clinic. Since I was familiar with cancer care and resources in the community and was already working within the healthcare system, I was offered the challenge to navigate the breast cancer patients.

### Are certain background experiences, qualifications, degrees, or certifications required to be a nurse navigator?

At this time, there is no national standard of care or certification for navigation. In February 2009, the Oncology Nursing Society will offer a test for the Certified Breast Care Nurse (www.oncc.org), which is aimed at testing the knowledge necessary for a nurse to practice breast care competently. This certification will be a validation of an individual's knowledge of breast care. At the 19th Annual National Interdisciplinary Breast Center Conference in 2009, there will be a 1-day Breast Health Navigator Certification Course with a certification exam the next morning (www.breastcare.org). The purpose is to validate the healthcare professional's knowledge to perform as a breast health patient educator or navigator. Each healthcare system needs to evaluate what is needed to unify care in their system.

From a personal viewpoint, to become a nurse navigator, it helps to be an employee of that particular healthcare system so you will know the staff, know how to access medical information, and be willing to share with the administration consistent patient concerns about their care.

### What was your first step in implementing the nurse navigator program?

My aim was to improve the flow of breast care for all of our patients. It took me 18 months to put the program in place. I began by spending the first year at the breast clinic, observing how patients enter the system—where they come in, where they go next. Some come from the breast clinic, but others come from surgical offices and even emergency departments. You start by gaining a perspective on the whole system, understanding the process of care within it, and identifying resources you can tap into within the larger community.

### What obstacles might one face in implementing a navigation program?

Gaining support for the idea of navigation is most important. You need the cooperation of leaders who will champion your cause. This would be the director of the cancer center, director of the imaging center, hospital chief executive officer, chief operating officers, and so forth. These people need to be on board and to understand your goals and time frame. Our only opposition came from a few surgeons who said they didn't see the need for it. After it was shown that navigation did not challenge their role or the care they wanted their patients to receive, they gave their full support. Physicians notice that less time is needed for consultation when patients are educated and prepared for their visit with pertinent questions. That is a payoff for doctors as well as patients. In addition to getting full cooperation, another obstacle to starting a navigation program is lack of time. Our navigators are on call for the patients 24 hours a day. That concept works in our system but may not be feasible in other healthcare systems.

### Is the job description of nurse navigator universal or customized to different practice settings?

You have to customize the job to the healthcare system. For example, in our system, we considered using someone besides a nurse and it did not work out. We felt a nurse can look at the patient holistically, can understand the healthcare system, and can offer a clinical background. In other systems, social workers may have better connections to resources within the community.

Our program is community-based and we link together the breast imaging clinic, cancer center, hospitals, surgical offices, and community resources. In some other systems, the navigator may be confined to the breast clinic as a breast health educator or breast health imaging educator and may follow the patient only through his or her diagnostic biopsy. I follow patients through all aspects of care, beginning with diagnosis and through the treatment phase, even if it includes radiation, chemotherapy, and/or hormonal therapy.

### What services do you provide the patient with breast cancer?

As soon as I am notified that the patient has received a diagnosis of breast cancer, I pick up the phone or go to the physician's office to meet with her. I explain my role and say, "Let's talk about what the doctor just told you." Sometimes I need to redirect the patient on what she has heard or not heard. For example, one patient told me right after her diagnosis, "I am making out my will." But because I had her pathology report, I knew she had a very early form of breast cancer that

*Continued on page 10*

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# Navigating the Journey

*Continued from page 9*

was highly curable. It was very rewarding for me to be able to tell her what she could expect. Right up front, I can make a difference by clarifying a patient's condition for her. I can educate the patient, "This is what you have and these are your next steps." My aim is to empower the patient and help her feel in control.

During the first phone call or visit, I also try to learn about the patient's family situation. Does she have a spouse, children, insurance? I can help the patient tell her children about the cancer and refer her to other resources and patient assistance programs.

When a patient does not respond to treatment or has a recurrence, emphasis is placed on continued care, whether it is for more treatment or hospice care. I do not make decisions for the patient. I give information and support her in whatever decision she makes. Also, I do not want to duplicate the services of others (for example, hospice).

I listen to patients, hear their frustrations or complaints as they go through treatment, and take these concerns to the cancer center administration or breast care team. For example, patients were frustrated that on the day of their surgery, they had to make two stops before they checked in for surgery. After discussion with the cancer center committee, changes were made over time to eliminate one stop. This streamlined the flow and made patients happier. With feedback from patients, we develop a stronger breast cancer care program. We identify barriers and ask physicians and administration to recognize them and solve them as a team.

**Are you involved in decision-making regarding treatment?**

I am to some extent through the weekly tumor board, which is run by our nurse navigation team and the breast medical oncologist. When a patient is presented, the nurse navigator may add social factors. For instance, the patient may be a single mother with no short- or long-term disability insurance who must keep her insurance and therefore must remain employed. This information is shared so the doctors can see the whole picture.

**How is your program funded? Can you show a financial value for the services of a nurse navigator?**

My salary and benefits are financed through our cancer center. The center funds two full-time breast navigators, two part-time thoracic navigators, a full-time colon navigator, a full-time care coordinator, who is a nurse with a social work background, and an administrative assistant. We can show a return on investment, that is, how much we brought into the system. We do this by tracking patients who seek a second opinion elsewhere and who then return to our program. We can show how much revenue we would lose if that patient left us. Incidentally, patients often return because of the nurse navigator. They like how we are going to follow them through the course of care. We believe that nurse navigation is a way to retain patients in a financially responsible way and improve the care of patients, and even to make money. Cancer patients network, and they talk about their nurse navigators and the care they receive in a particular healthcare system. I had a patient who wanted to come from Virginia to North Carolina to be treated because she heard about our nurse navigators.

Our visibility and reputation also leads to fundraising. For instance, a group of women heard me talk and decided to have a benefit for navigators. We have a "Smash Cancer" tennis tournament that raises money for patient expenses not covered by insurance, such as transportation and groceries. We also have more cancer community volunteers because of the cancer survivors who had a nurse navigator and now want to "give something back."

*For more information on starting a nurse navigation program at your center, go to www.patientnavigation.com.*

*—Caroline Helwick*


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**Tell Us About Your Nurse Navigator Program**

*This is the first in a series of articles on oncology nurse navigators. Does your hospital or clinic have a nurse navigator program you would like to share with readers? Write to us at* ***karen@greenhillhc.com.***

## NURSING LIFE

# Consequences of Smoking

*Continued from cover*

California, Los Angeles (UCLA) School of Nursing. "Yet nurses struggle with nicotine addiction like the rest of the 45 million smokers in America. We are concerned that nurses who smoke may be less apt to support tobacco-control programs or encourage their patients to quit."

Brenda Nevidjon, RN, MSN, FAAN

Sarna led a team of researchers who analyzed data from the Nurses' Health Study. Launched at Brigham and Women's Hospital in the mid-1970s, the study relied on surveys completed every 2 years by 237,648 female registered nurses about their health, including smoking habits.

"The Nurses' Health Study is the largest study of women's health in the world," explained Sarna. "From a workforce perspective, however, the findings also hold a mirror up to the well-being of nurses, the largest group of healthcare professionals in the country."

The current UCLA research explored changes in smoking trends and death rates among female nurses enrolled in the Nurses' Health Study between 1976 and 2003. The researchers evaluated the differences in death rates among nurses who never smoked compared with former smokers and current smokers. In all age groups, roughly twice as many current smokers had died in comparison to nurses who had never smoked.

"Quitting smoking made a big difference in enhancing longevity, especially among nurses in their later 70s," said Sarna. "Death rates among former smokers that age were 1.5 times higher than those of nonsmokers, while current smokers were 2.3 times more likely to have died by that age than nurses who never smoked."

According to the most recent data, the smoking rate among registered nurses nationwide is nearly 12%. The rate of smoking among women in the Nurses' Health Study declined from 33.2% in 1976 to 8.4% in 2003. The number of cigarettes smoked per day also dropped. Nonetheless, the daily number among current smokers still averaged more than 15 cigarettes, or more than half a pack.

Sarna said nursing education programs gave limited attention to smoking's effect on health during the 1970s and 1980s, and still today the amount of time devoted to tobacco cessation in the curriculum remains inadequate. "Nurses in the study demonstrated behavioral patterns similar to women in the general population," said Sarna. "For example, the younger nurses in the study began smoking before entering the profession, a pattern reflected by American women starting smoking at younger ages in general. Being a nurse did not make these women immune to nicotine addiction."

Brenda Nevidjon, RN, MSN, FAAN, president of the Oncology Nursing Society and a clinical professor at Duke University School of Nursing, Durham, N.C., said these new findings are rather startling and should serve as a wake-up call. She said this is an issue that needs to be more aggressively addressed by oncology nurses in particular.

"I do think it is a wake-up call. This is a huge database," said Nevidjon in an interview with *The Oncology Nurse*. "We have to educate more people for the sake of public health. The key is to not start. Kids are starting to smoke young, and a 14-year-old girl, who doesn't even know she wants to be a nurse, may be starting to smoke."

She said although smoking rates among US nurses are lower than in the general population, major changes in this area are needed, with a greater emphasis on helping nurses quit smoking. "As nurses we need to understand how influential we are, and not just to patients and families but to the communities in which we live. If we don't demonstrate and exhibit healthy behaviors, how can we turn around and teach those healthy behaviors? It is a contradiction for us to talk about well-being, exercise, eating right, and not smoking, and then go out the backdoor and have a cigarette," said Nevidjon. "So I think there is a very serious message here for us as nurses. We need to hold the mirror up and look at ourselves and say 'are we practicing what we preach?' There are a proportion of the members of our nursing profession who may be preaching but not practicing."

Michelle Larkin, a senior program officer for the Robert Wood Johnson Foundation, which funded the UCLA team's research, said the study findings are a very serious concern to the nursing profession. She said more comprehensive strategies are needed to help nurses kick the habit. "The devastating effects of smoking are all too real for those nurses who still smoke. We need research to learn about the factors that lead them to smoking and more resources to help them quit," said Larkin.

The study findings have been published in the November/December edition of *Nursing Research*.

*—John Schieszer*

# Supportive Care

## Supersaturated Electrolyte Oral Rinse May Significantly Benefit Head/Neck Chemoradiation Patients

SEATTLE—A supersaturated electrolyte (calcium/phosphate) oral rinse appears to significantly improve the quality of life for head and neck cancer patients undergoing chemoradiation, according to new study data presented at the 2008 Oncology Nursing Society Advanced Practice Nursing Conference and Institutes of Learning.

The researchers conducted an open-label, observational study of 218 patients treated at 26 sites throughout the United States. They found that the rinse decreased the incidence and severity of oral mucositis (OM). In addition, the researchers found that there was a very high level of satisfaction among patients and clinicians coupled with high levels of patient compliance.

"We are not advocating this instead of the other available products. You use it in conjunction with the other products," said lead study investigator Marilyn Haas, PhD, ANP-C, who is a nurse practitioner and a consultant with Carolina Clinical Consultant, Asheville, NC. "It should be started on day 1 of their oncology treatment. It is better to be proactive instead of reactive in treating OM."

Haas, who presented the study findings at the meeting, said overall rates of OM in patients with head and neck cancer receiving chemoradiation are between 80% and 97%. In addition, she said 34% to 57% experience National Cancer Institute grade 3 or 4 OM.

In the study, patients at risk for developing OM were given the oral rinse with instructions to rinse four times per day initially (when beginning chemoradiation). The patients were instructed that they could use the product up to 10 times per day if symptoms increased. The researchers had the practitioners and patients complete surveys regarding four clusters: dysphagia, pain, and clinical and functional mucositis/stomatitis.

Of the 218 patients who were enrolled in the study between August 2007 and February 2008, 79% were "very satisfied" or "satisfied" with the relief provided by the oral rinse and would recommend its use. The total number of patients with head and neck cancer in the study was 68. The mean age of the patients was 63 years, and 74% were men.

The practitioners reported that 77% to 82% of these patients with head and neck cancer had grade 2 or less OM, and 13% to 21% of the patients had no OM at the end of the study. The practitioners' satisfaction rate was 77%, and they rated the product satisfactory to excellent. The compliance rate among patients was also high.

"You need to help decrease their pain and improve their ability to swallow, and this [product] can do both of those things," said Haas in an interview with *The Oncology Nurse*. "It is about quality of life, and depression is a big problem in this patient population. Having a sore mouth can be part of the problem, and helping the patients in this way may help with their mental health."

She said this product is rather expensive and not on Medicare/Medicaid formulary. However, she said it is approved by most insurance companies. "While we haven't put a cost analysis with this, the impact on quality of life, and use of narcotics is low (with this product) so that I would assume it to be cost-effective overall," added Haas.

*—John Schieszer*

Marilyn L. Haas, PhD, CNS, ANP-C





SUPPORTIVE CARE

# Safe Handling

## The Right Drug, Right Dose, Right Patient…

BY **ANDREW SCOTT**
IntrisiQ, LLC, Waltham, Massachusetts

Nurses have all heard the phrase "the right drug, right dose, right patient" more than once during training on safe drug administration. In the real world, it quickly becomes apparent that there is a lot more that needs to be considered.

Nowhere is this challenge more acute than in the world of oncology. Most chemotherapies consist of multiple drugs, and every drug administration involves a uniquely calculated dose using complex combinations of formulas. The majority of drug doses require a drug volume to be calculated and specific reconstitution guidelines to be followed. Timing and frequency of administration is an important part of maintaining patient safety. All of this occurs before the drugs get anywhere near the patient.

**The majority of drug doses require a drug volume to be calculated and specific reconstitution guidelines to be followed.**

Added to the mix are complex requirements of drug administration by the nurse. Whatever the nature of the error, it is the nurse who must correct it if it is not caught during the preparation process. A recent study that focused on medication errors specifically in pediatric oncology found that 85% of errors reached the patient. Of those errors, 48% originated in the administration phase of medication delivery compared with 30% during the prescribing phase. The most common error type was improper dose/quantity (22.9%) followed by errors of omission, wrong routes, or administration techniques.[1]

Oncology professionals have to deal with many more aspects of drug administration accuracy and safety. Many individuals with a range of professional skills are involved in the chemotherapy administration process. Outside the hospital environment, it is still commonplace for the chemotherapy nurse to assume the role of pharmacist or pharmacy technician and be responsible for reconstituting drug doses as well as administering them.

In the study by Rinke and colleagues,[1] performance and knowledge deficits accounted for nearly 49% of errors. Also, the rate of prescribing errors was almost double in the outpatient setting compared with inpatient units. In February 2008, *USA Today* reported an incident involving a 2-year-old girl in which the pharmacy technician mixed her chemotherapy drug with a saline solution 26 times above normal. This error went unnoticed by both the on-duty pharmacist who checked the formulated dose (despite the fact the bag was clearly labeled with the fluid concentration) and the nurse administering the drug. Prescribing errors have also occurred in which the bag was labeled correctly but the drug was prepared incorrectly and the nurse had no way of knowing that. In both such cases, the errors only become apparent after the event and manifest in problems experienced by the patient, which in the case of the 2-year-old girl was death.

### Instituting safeguards and efficiencies

What has technology done to help improve our lives as oncology professionals? We are now using software or medical devices throughout many phases of the chemotherapy delivery process, from prescribing and regimen management to drug dosing and administration.

Electronic medical records (EMRs) are designed to enhance patient safety by automating every aspect of a patient's care, from drug administration to record keeping, but they are not widely accepted in the specialty of oncology. Many oncology modules have been introduced in the past decade, often without success. Even the most sophisticated general practitioner order entry modules fail to provide oncology practitioners with the robust tools and flexibility necessary to calculate complex doses, prescribe multiple drug combinations of chemotherapy regimen, or manage the scheduling of the treatment plan. This has resulted in frustration for oncologists and their teams, who find they need to continue to do a large part of their work on paper.

Oncology practices are often reluctant to use hospital-mandated oncology EMR modules, preferring instead oncology-specific computerized physician order entry (CPOE) solutions for the management of core chemotherapy delivery. These systems automate the complete treatment cycle for each individual patient, providing detailed treatment regimens by disease, managing drug calculations and scheduling, monitoring dose levels and contraindications, as well as offering compounding tools for pharmacists.

These solutions have now progressed to offer documentation options for both the chemotherapy nurse and the physician, creating a comprehensive oncology patient record that can also deal with the complex billing process that follows every chemotherapy encounter. This need has been heightened by the dramatic reimbursement changes affecting every aspect of the oncology practice. In addition to managing the clinical aspects of chemotherapy, these specialist solutions are now leveraging the data captured within the course of treatment to provide sophisticated charge capture tools that aim to minimize "lost" billings.

Aside from removing the error-prone tasks of dose calculation, oncology CPOE tools eliminate the other main source of error, transcription, since all information emanates from a single source, the chemotherapy treatment plan. The chemotherapy order, pharmacy worksheets, drug labels, and nurse charting prescriptions are immediately available. The only human interventions in this process are the clinical reviews of the order and the detailed error checking that these systems provide, by the nurses, physicians, and pharmacists.

### CPOE integrates with oncology practice workflows

Once the electronic chemotherapy order is checked and the drugs are ready for compounding, most institutions still rely on a person to formulate the required doses. Despite the safeguards provided by CPOE systems, accuracy depends on the diligence of the individual and the strictness of the verification processes at the institution. Some of the most common "best practices" include a minimum of two people checking the order, checking the drugs during dispensing and before administration, and confirming the patient information.

Sophisticated automated compounding technologies exist, but many of these are prohibitive in cost and have limited practicality in the smaller oncology setting. According to the American Society of Clinical Oncology, more than 80% of cancer patients receive chemotherapy in private practices.[2]

The final step of drug administration once again requires human intervention, resting on the shoulders of the chemotherapy nurse. CPOE has helped nursing staff by providing detailed, legible, and accurate orders as well as charting tools to allow real-time comprehensive note taking. Although documentation tasks may prompt nurses to verify drugs before administration, similar potential risks are encountered, since accuracy is still predominantly reliant on diligent practitioners and strictly applied processes.

Bar coding of patients and medications in an effort to ensure that the correct medication is given to the correct patient has been implemented in the Veterans Affairs (VA) system, with mixed reviews. The VA hospital network has a proprietary system, Bar Code Medication Administration, which they say has led to a 74% reduction in the risk of administering the wrong medication and a greater reduction in the risk of medications being given to the wrong patient. However, nurses have commented on the inefficiency and unreliability of the process. Although supported by the US Food and Drug Administration, such solutions are likely to have little impact on the smaller private practices, where the economics of such a solution could not justify their investment. A study specifically of the VA system concluded that the bar coding system may itself create new sources of adverse drug events. One of the key issues cited was the confusion nurses experienced with the automated removal of medications from the inventory cabinets.[3]

The introduction of oncology-specific chemotherapy management systems has done much to eliminate sources of potential error. Human action is often a key element, and human error is the precipitant event in many drug-related errors. Often, however, these are just symptoms of wider systemic failures, which, if addressed, may have prevented the error from occurring.

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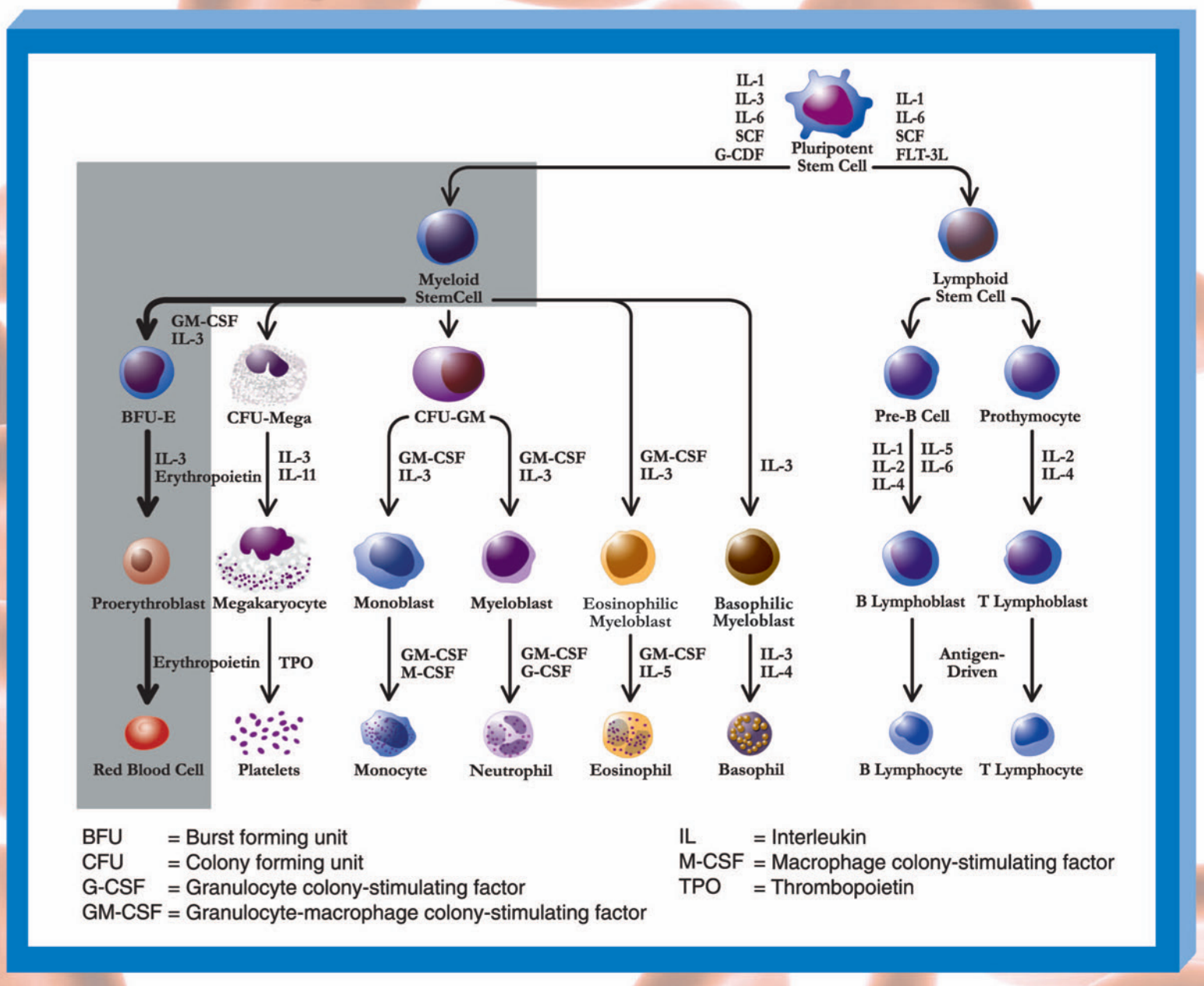


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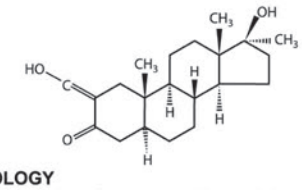
The chemical name for oxymetholone is 17ß-hydroxy-2- (hydroxymethylene)-17-methyl-5a-androstan-3-one. The structural formula is:



Inactive Ingredients - lactose
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povidone
starch

## CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Nitrogen balance is improved with anabolic agents but only when there is sufficient intake of calories and protein. Whether this positive nitrogen balance is of primary benefit in the utilization of protein-building dietary substances has not been established. Oxymetholone enhances the production and urinary excretion of erythropoietin in patients with anemias due to bone marrow failure and often stimulates erythropoiesis in anemias due to deficient red cell production.

Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. They suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

## INDICATIONS AND USAGE

ANADROL®-50 Tablets is indicated in the treatment of anemias caused by deficient red cell production. Acquired aplastic anemia, congenital aplastic anemia, myelofibrosis and the hypoplastic anemias due to the administration of myelotoxic drugs often respond. ANADROL®-50 Tablets should not replace other supportive measures such as transfusion, correction of iron, folic acid, vitamin B12 or pyridoxine deficiency, antibacterial therapy and the appropriate use of corticosteroids.

## CONTRAINDICATIONS

1. Carcinoma of the prostate or breast in male patients.
2. Carcinoma of the breast in females with hypercalcemia; androgenic anabolic steroids may stimulate osteolytic resorption of bones.
3. Oxymetholone can cause fetal harm when administered to pregnant women. It is contraindicated in women who are or may become pregnant. If the patient becomes pregnant while taking the drug, she should be apprised of the potential hazard to the fetus.
4. Nephrosis or the nephrotic phase of nephritis.
5. Hypersensitivity to the drug.
6. Severe hepatic dysfunction.

## WARNINGS

The following conditions have been reported in patients receiving androgenic anabolic steroids as a general class of drugs:

Peliosis hepatis, a condition in which liver and sometimes splenic tissue is replaced with blood-filled cysts, has been reported in patients receiving androgenic anabolic steroid therapy. These cysts are sometimes present with minimal hepatic dysfunction, but at other times they have been associated with liver failure. They are often not recognized until life-threatening liver failure or intra-abdominal hemorrhage develops. Withdrawal of drug usually results in complete disappearance of lesions.

Liver cell tumors are also reported. Most often these tumors are benign and androgen-dependent, but fatal malignant tumors have been reported. Withdrawal of drug often results in regression or cessation of progression of the tumor. However, hepatic tumors associated with androgens or anabolic steroids are much more vascular than other hepatic tumors and may be silent until life-threatening intra-abdominal hemorrhage develops.

Blood lipid changes that are known to be associated with increased risk of atherosclerosis are seen in patients treated with androgens and anabolic steroids. These changes include decreased high density lipoprotein and sometimes increased low density lipoprotein. The changes may be very marked and could have a serious impact on the risk of atherosclerosis and coronary artery disease.

Cholestatic hepatitis and jaundice occur with 17-alpha-alkylated androgens at relatively low doses. Clinical jaundice may be painless, with or without pruritus. It may also be associated with acute hepatic enlargement and right upper-quadrant pain, which has been mistaken for acute (surgical) obstruction of the bile duct. Drug-induced jaundice is usually reversible when the medication is discontinued. Continued therapy has been associated with hepatic coma and death. Because of the hepatoxicity associated with oxymetholone administration, periodic liver function tests are recommended.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. In this case, the drug should be discontinued.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease. Concomitant administration with adrenal steroids or ACTH may add to the edema. This is generally controllable with appropriate diuretic and/or digitalis therapy.

Geriatric male patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostate hypertrophy and prostatic carcinoma.

Anabolic steroids have not been shown to enhance athletic ability.

## PRECAUTIONS

**Concurrent dosing of an anabolic steroid and warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When an anabolic steroid is prescribed to a patient being treated with warfarin, doses of warfarin may need to be decreased significantly to maintain the desirable INR level and diminish the risk of potentially serious bleeding. (See PRECAUTIONS – Drug Interactions.)**

### General:

Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne and clitoromegaly). To prevent irreversible change, drug therapy must be discontinued when mild virilism is first detected. Such virilization is usual following androgenic anabolic steroid use at high doses. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities, including amenorrhea, may also occur.

The insulin or oral hypoglycemic dosage may need adjustment in diabetic patients who receive anabolic steroids.

Anabolic steroids may cause suppression of clotting factors II, V, VII and X, and an increase in prothrombin time.

### Information for the patient:

The health care provider should instruct patients to report immediately any use of warfarin and any bleeding.

The health care provider should instruction patients to report any of the following side effects of androgens.

**Adult or Adolescent Males**: Too frequent or persistent erections of the penis, appearance or aggravation of acne.

**Women**: Hoarseness, acne, changes in menstrual periods or more hair on the face.

**All Patients**: Any nausea, vomiting, changes in skin color or ankle swelling.

### Laboratory Tests:

Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of androgenic anabolic steroid therapy (see **WARNINGS**).

Because of the hepatoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of prepubertal patients to determine the rate of bone maturation and the effects of androgenic anabolic steroid therapy on the epiphyseal centers.

Anabolic steroids have been reported to lower the level of high-density lipoproteins and raise the level of low-density lipoproteins. These changes usually revert to normal on discontinuation of treatment. Increased low-density lipoproteins and decreased high-density lipoproteins are considered cardiovascular risk factors. Serum lipids and high-density lipoprotein cholesterol should be determined periodically.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolics.

Because iron deficiency anemia has been observed in some patients treated with oxymetholone, periodic determination of the serum iron and iron binding capacity is recommended. If iron deficiency is detected, it should be appropriately treated with supplementary iron.

Oxymetholone has been shown to decrease 17-ketosteroid excretion.

### Drug Interactions:

**Warfarin**: Clinically significant pharmacokinetic and pharmacodynamic interactions between anabolic steroids and warfarin have been reported in healthy volunteers. When anabolic steroid therapy is initiated in a patient already receiving treatment with warfarin, the INR (international normalized ratio) or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both ANADROL®-50 Tablets and warfarin, careful monitoring of the INR or PT and adjustment of the warfarin dosage, if indicated, are recommended when the ANADROL®-50 dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

**Anticoagulants**: Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain the desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

### Drug/Laboratory Test Interferences:

Therapy with androgenic anabolic steroids may decrease levels of thyroxine-binding globulin resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4. Free thyroid hormone levels remain unchanged and there is no clinical evidence of thyroid dysfunction. Altered tests usually persist for 2 to 3 weeks after stopping anabolic therapy.

Anabolic steroids may cause an increase in prothrombin time.

Anabolic steroids have been shown to alter fasting blood sugar and glucose tolerance tests.

### Carcinogenesis, Mutagenesis, Impairment of Fertility:

A two-year carcinogenicity study in rats given oxymetholone orally was conducted under the auspices of the US National Toxicology Program (NTP). A wide spectrum of neoplastic and non-neoplastic effects was observed. In male rats, no effects were classified as neoplastic in response to doses up to 150 mg/kg/day (5 times therapeutic exposures with 5 mg/kg based on body surface area).

Female rats given 30 mg/kg/day (1 fold the maximum recommended clinical dose of 5 mg/kg/day based on the body surface area) had increased incidences of lung alveolar/bronchiolar adenoma and adenoma or carcinoma combined. At 100 mg/kg/day (about 3 fold the maximum recommended clinical dose of 5 mg/kg/day based on BSA), female rats had increased incidences of hepatocellular adenoma and adenoma or carcinoma combined; the combined incidence of squamous cell carcinoma and carcinoma of the sweat glands also was increased.

Human data: There are rare reports of hepatocellular carcinoma in patients receiving long-term therapy with androgens in high doses. Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgens may be at an increased risk of developing prostatic hypertrophy and prostatic carcinoma although conclusive evidence to support this concept is lacking.

In studies conducted under the auspices of the US National Toxicology Program, no evidence of genotoxicity was found using standard assays for mutagenicity, chromosomal aberrations, or induction of micronuclei in erythrocytes.

Impairment of fertility was not tested directly in animal species. However, as noted below under **ADVERSE REACTIONS**, oligospermia in males and amenorrhea in females are potential adverse effects of treatment with ANADROL®-50 Tablets. Therefore, impairment of fertility is a possible outcome of treatment with ANADROL®-50 Tablets.

### Pregnancy:

Pregnancy category X. (see **CONTRAINDICATIONS**).

### Nursing Mothers:

It is not known whether anabolics are excreted in human milk. Because of the potential for serious adverse reactions in nursed infants from anabolics, women who take oxymetholone should not nurse.

### Pediatric Use:

Anabolic/androgenic steroids should be used very cautiously in children and only by specialists who are aware of their effects on bone maturation.

Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children, and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising the adult height.

### Geriatric Use:

Clinical studies of ANADROL®-50 Tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

## ADVERSE REACTIONS

**Hepatic**: Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis have been reported in association with long-term androgenic anabolic steroid therapy (see **WARNINGS**).

**Genitourinary System**:

**In Men**:
Prepubertal: Phallic enlargement and increased frequency of erections.
Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, bladder irritability and decrease in seminal volume.

**In Women**:
Clitoral enlargement, menstrual irregularities.

**In Both Sexes**:
Increased or decreased libido.

**CNS**: Excitation, insomnia.

**Gastrointestinal**: Nausea, vomiting, diarrhea.

**Hematologic**: Bleeding in patients on concomitant anticoagulant therapy, iron-deficiency anemia.

Leukemia has been observed in patients with aplastic anemia treated with oxymetholone. The role, if any, of oxymetholone is unclear because malignant transformation has been seen in patients with blood dyscrasias and leukemia has been reported in patients with aplastic anemia who have not been treated with oxymetholone.

**Breast**: Gynecomastia.

**Larynx**: Deepening of the voice in women.

**Hair**: Hirsutism and male-pattern baldness in women, male-pattern of hair loss in postpubertal males.

**Skin**: Acne (especially in women and prepubertal boys).

**Skeletal**: Premature closure of epiphyses in children (see **PRECAUTIONS**, **Pediatric Use**), muscle cramps.

**Body as a Whole**: Chills.

**Fluid and Electrolytes**: Edema, retention of serum electrolytes (sodium, chloride, potassium, phosphate, calcium).

**Metabolic/Endocrine**: Decreased glucose tolerance (see **PRECAUTIONS**), increased serum levels of low-density lipoproteins and decreased levels of high-density lipoproteins (see **PRECAUTIONS**, **Laboratory Tests**), increased creatine and creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Reversible changes in liver function tests also occur, including increased Bromsulphalein (BSP) retention and increase in serum bilirubin, glutamic-oxaloacetic transaminase (SGOT) and alkaline phosphatase.

## DRUG ABUSE AND DEPENDENCE

### Controlled Substance:

ANADROL®-50 Tablets is considered to be a controlled substance and is listed in Schedule III.

## OVERDOSAGE

There have been no reports of acute overdosage with anabolics.

## DOSAGE AND ADMINISTRATION

The recommended daily dose in children and adults is 1-5 mg/kg of body weight per day. The usual effective dose is 1-2 mg/kg/day but higher doses may be required, and the dose should be individualized. Response is not often immediate, and a minimum trial of three to six months should be given. Following remission, some patients may be maintained without the drug; others may be maintained on an established lower daily dosage. A continued maintenance dose is usually necessary in patients with congenital aplastic anemia.

## HOW SUPPLIED

ANADROL®-50 (oxymetholone) Tablets is supplied in bottles of 100 (NDC 68220-055-10) white scored tablets embossed with 0055 and ALAVEN. **Keep out of reach of children**. Dispense in a tight, light-resistant container.

## STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP].

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ALAVEN™ PHARMACEUTICAL

055 Rev 12/06

# Hematologic Cancers

## Unraveling the Complexities of Non-Hodgkin's Lymphomas. Part 2.

### *Recent Advances and Clinical Implications of Pathobiology*

BY **SANDRA E. KURTIN, RN, MS, AOCN, ANP-C**
ARIZONA CANCER CENTER, UNIVERSITY OF ARIZONA, TUCSON

Non-Hodgkin's lymphomas (NHLs) represent a group of heterogeneous lymphoid malignancies with variable clinical presentation, pathologic characteristics, prognosis, and recommended treatment. The diseases arise from either B or T lymphocytes at different stages of maturation. Normal B-cell development is an organized process requiring interactions between the cell and the microenvironment, with specific events that define differentiation, function, and survival. A number of these processes are thought to represent key transforming events that provide an opportunity for abnormal development and lymphoma pathogenesis.[1,2]

Characterization of the normal and abnormal elements of the process of differentiation and the tumor microenvironment are critical to the diagnosis of NHL. The tissue diagnosis, which may include any lymphatic tissue (lymph nodes, spleen, other tissue biopsy, bone marrow, peripheral blood if circulating lymphocytes), is critical for an accurate diagnosis and characterization of the morphologic, immunophenotypic, cytogenetic, and molecular characteristics of the disease necessary to classify the specific subtype of NHL. Wide variances in disease trajectory, prognosis, indications to initiate treatment, and treatment selection exist among subtypes of the disease. The key elements of the pathobiology of NHL and the implications for pathologic diagnosis, patient prognosis, and treatment will be reviewed.

### Key elements of the tissue diagnosis of NHL

NHLs arise from either B or T lymphocytes. B-cell NHL is the most common (90%) (Table).[3] Lymphatic tissues are commonly found throughout the body, including in the lymph nodes, lymphatic fluids, liver, spleen, and tonsils. Extensive lymph node networks exist in the kidneys and lungs and encase or run parallel to most vascular networks throughout the body. Lymphadenopathy, organomegaly, or lymphocytosis is common in the presentation of NHL. Imaging techniques are useful in localizing disease for biopsy and determining the extent of disease and will be discussed in future articles in this series.

Ultimately, a pathologic diagnosis will require a tissue sample to characterize the disease, assign a subtype, and estimate prognosis. Several studies documenting the complexity of an accurate pathologic diagnosis have identified limited tissue availability or an inadequate specimen as the primary factors limiting precise diagnosis.[4-7]

Because of its structure, different regions within a single lymph node may contain variable pathologic changes

*Continued on page 16*

**Table. Most Common Subtypes of Non-Hodgkin's Lymphoma with Selected Diagnostic and Prognostic Attributes**

| Lymphoma subtype | Morphology | Immunophenotyping | Common cytogenetic abnormalities | Molecular testing |
|---|---|---|---|---|
| Diffuse large B-cell lymphoma | Diffuse pattern with distortion of the normal architecture of the lymph node or extranodal site | $CD20^{+}$, $CD45^{+}$, $CD3^{-}$ | t(14;18), t(3;v), t(8;14) | Testing for Bcl-2, Bcl-1, c-Myc; all offer a survival advantage to the lymphoma cells* |
| Follicular lymphoma | Nodal lymphoma with a follicular growth pattern | $CD10^{+}$, $CD20^{+}$, $slg^{+}$, $CD23^{+/-}$, $CD22^{+}$, $CD25^{+/-}$ | t(14;18)(q32;q21) 85% | IgH rearrangement with Bcl-2 expression that leads to cellular resistance to apoptosis* |
| Small lymphocytic lymphoma/ chronic lymphocytic leukemia | Usually appear normal, may be large, smudge cells may be present, prolymphocytes common | $CD5^{+}$, $CD20^{dim+}$, $slgdim^{+}$, $CD23^{+}$, $CD22^{-}$, $CD25^{-(+)}$ $CD38^{+}$ -* | Trisomy 12<br>t(11q;v)*<br>del(11q)*<br>del(17p)*<br>del(13q)† | Patients with variable region Ig mutations have a more favorable prognosis* |
| Mantle cell lymphoma | Cells populate the mantle zone of the follicle | $CD5^{+}$, $CD20^{+}$, $slg^{+}$, $CD22^{+}$, $CD45^{+}$, $CD10^{-}$, $CD23^{-}$, $CD25^{-}$ cyclin $D1^{+}$ | t(11;14)(q13;q32)<br>Deregulates cyclin D1 expression interfering with cell-cycle regulation | IgH rearrangement with Bcl-1 (increased cell proliferation) and Bcl-6 expression (resistance to apoptosis)* |
| Peripheral T-cell lymphoma | Peripheral T cells with no features of other subtypes | $CD4^{+}$, $CD7^{-}$, $CD8^{-}$ | | Clonal rearrangements of the receptor genes seen in noncancerous T-cell disease are common |
| Marginal zone B-cell lymphoma | Cells resemble marginal zone or monocytoid B cells, may be small or large | $CD20^{+}$, $slg^{+}$, CD22+ $CD5^{-}$, $CD10^{-}$, $CD23^{-}$, CD $25^{-}$ cyclin $D1^{-}$ | t(11;18),* Associated with resistance to treatment | IgH—MALT 1*<br>Bcl-10 = t(14;18)(q32;q21)* |
| Mucosa-associated lymphoid tissue (MALT) | Most commonly arise in secondary lymphoid structures | $CD20^{+}$, $slg^{+}$, CD22+ $CD5^{-}$, $CD10^{-}$, $CD23^{-}$, CD $25^{-}$ | t(1;14)(p22;q32)<br>t(11;18)(q21;q21) | IgH rearrangement with Bcl-10 expression* |

**Unfavorable, †Favorable*
*Sources: References 1-5.*

HEMATOLOGIC CANCERS

# Recent Advances and Clinical Implications

*Continued from page 15*

that may affect the final diagnosis. For example, diffuse large B-cell lymphoma (DLBCL) is characterized by diffuse involvement by malignant B cells, which distort the normal architecture of the lymph node or extranodal site. These cells tend to be large and express common B-cell receptors, which distinguish them from other subtypes of NHL and allow further characterization of the DLBCL variants.[8]

For these reasons, an excisional lymph node biopsy is recommended for the initial diagnosis of NHL. For disease confined to the retroperitoneal region, spleen, or other extranodal sites, laparoscopic biopsies have provided an alternative to open surgeries. The tissue is best analyzed when submitted fresh (not in formalin), and will be used for hematopathology, immunophenotyping, and molecular testing.

A bone marrow biopsy and aspirate is necessary to complete the diagnostic profile and should include analysis similar to that of the lymphatic tissue, with the addition of selected cytogenetic and molecular tests if positive for lymphoma. In some cases, this is the only source for diagnostic evaluation. An adequate specimen must include bone marrow aspirate with evidence of spicules to allow evaluation of normal and synchronous trilineage hematopoiesis or the presence of abnormal populations of cells. The aspirate is then used for flow cytometry to obtain immunophenotyping, which is critical to the differentiation of lymphoma subtypes because it identifies key surface receptor molecules known as clusters of differentiation (CD). This testing is also performed on lymphatic tissue. The CD, in essence, provide a "ZIP code" of their precise location because individual CD are found only in selected regions of lymphatic tissue at different points in the process of maturation and are associated with key transforming events. The bone marrow core is critical in the diagnosis of NHL; it provides tissue for analysis of architecture, lymphoid aggregates, cell type, and cellularity.

Additional molecular testing now is recommended for specific subtypes of NHL.[8] In particular, the characterization of immunoglobulin (Ig) loci or protooncogenes offers critical diagnostic and prognostic information, and Ig loci and protooncogenes are now being targeted for therapy. Targets include the Bcl-2 gene (antiapoptotic gene correlating to t(14;18)(q32;q21), frequently occurring in follicular lymphoma) and Bcl-6 gene (common in DLBCL and associated with a proliferative advantage). Bcl-6 most commonly is associated with translocation involving the Ig heavy-chain promoter region. Mutations in the Ig genes occur during germinal center B-cell development and most often are associated with chromosomal translocations that allow the Ig to control these genes that are critical to apoptosis.[9]

## Conclusion

Complete pathologic analysis of lymphatic tissue is essential to the accurate diagnosis of NHL. Adequate tissue samples are essential. Incorporation of more recent technologies that allow characterization of cytogenetic and molecular attributes of the disease, including chromosomal translocations, gene rearrangements, oncogene expression, and Ig loci, have provided critical prognostic information and the opportunity for refinement of targeted therapies. Familiarity with the diagnostic process will promote an understanding of the variability in treatment of each subtype of NHL and provide the opportunity to educate the patient and family about the importance of the diagnostic process. Future articles in this series will provide examples of treatment selection based on the pathobiology of the disease.

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**Erratum: In the article on non-Hodgkin's lymphoma in the October/November issue, Table 2 was printed incorrectly. The corrected table is reproduced in entirety below.**

**Table 2. Prognostic Indexes for Non-Hodgkin's Lymphoma**

| International Prognostic Index (IPI) | | | |
|---|---|---|---|
| **Risk factors (one point each)** | **Score** | **CR (%)** | **5-year survival (%)** |
| 1. Age >60 | | | |
| 2. Ann Arbor Stage III or IV | 0-1 | 87 | 73 |
| 3. > 1 extranodal site | 2 | 67 | 51 |
| 4. Elevated LDH | 3 | 55 | 43 |
| 5. ECOG PS ≥ 2 | 4-5 | 44 | 26 |
| *Age-adjusted risk for >60 yrs | | | |
| 1. Ann Arbor Stage III or IV | 0 | 92 | 83 |
| 2. Elevated LDH | 1 | 78 | 69 |
| 3. ECOG PS > 2 | 2 | 57 | 46 |
| | 3 | 46 | 32 |

| Follicular Lymphoma International Prognostic Index (FLIPI) | | | |
|---|---|---|---|
| **Risk factors (one point each)** | **Score** | **5-year survival (%)** | **10-year survival (%)** |
| 1. Age >60 | | | |
| 2. Ann Arbor Stage III or IV | 0-1 | 86 | 71 |
| 3. Hgb < 12 g/dL | 2 | 70 | 40 |
| 4. > 4 nodal areas | 3 | 51 | 37 |
| 5. Elevated LDH | | | |

LDH indicates lactic dehydrogenase; ECOG, Eastern Cooperative Oncology Group; Hgb, hemoglobin.
Source: Solal-Celigny P, et al. *Blood*. 2004;104:1258-1265.

## Recent FDA Approvals

- **Pralatrexate for Diffuse Large B-Cell Lymphoma**

The US Food and Drug Administration has granted pralatrexate (PDX, Allos) orphan drug status for treatment of diffuse large B-cell lymphoma. Under this designation, the drug, if approved, will have 7 years of market exclusivity. The novel antifolate agent already has orphan drug status to treat T-cell lymphoma.

- **Dual-action Oral Analgesic**

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The US Food and Drug Administration has approved tapentadol (Johnson & Johnson) immediate-release tablets for relief of moderate to severe acute pain in adults. The centrally acting oral analgesic has two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition. Tapentadol tablets in 50-mg, 75-mg, and 100-mg doses are approved. As with all controlled substances, tapentadol will be reviewed by the US Drug Enforcement Agency for scheduling and cannot be sold until it receives a scheduling classification.

# Breast Cancer

## Changes in Receptor Status Argue for Retesting Breast Cancer Recurrences

When breast cancers recur or metastasize, practitioners should retest them for receptor status, study results indicate. In up to one third of cases, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status may differ from the primary tumor. Two studies that were presented at the Breast Cancer Symposium in Washington, DC, in September, one prospective and one retrospective, demonstrated the advisability of retesting. Discordance in receptor status between recurrences and the primary lesion can have a major impact on patient management.

Christine Simmons, MD, clinical associate at Sunnybrook Hospital in Toronto, prospectively measured discordance in ER, PR, and HER2 status between primary and metastatic lesions (ML) among 29 patients identified at the time of first clinical/radiologic suspicion of metastatic recurrence who had lesions amenable to biopsy. Biopsies of ML were also analyzed for disease confirmation. Patients' oncologists were surveyed pre- and postbiopsy to see if the biopsy results altered their treatment plan.

**Discordance in receptor status between recurrences and the primary lesion can have a major impact on patient management.**

Twenty-five of the 29 biopsies confirmed a breast cancer metastasis. Of these, 40% had a change in hormone receptor status (three had loss of ER, seven had loss of PR), and 8% had a change in HER2 receptor status (two of 25 became HER2 positive). Three biopsies revealed benign disease in the supposed ML, and one other demonstrated low-grade lymphoma.

"So we did demonstrate a statistically significant alteration in hormone receptor status and HER2 status, actually higher than had been reported in previous retrospective reviews, which report usually about a 20% change in hormone receptor status," Simmons said.

These results led to a significant change in management for 20% of patients (6 of 29, $P = .002$), many of

*Continued on page 18*

## CANCER CONCEPTS

# Cancer Self-seeding

*Continued from cover*

The idea is that when epithelial tumors release cells into the bloodstream and lymphatic system, some of which may establish distant metastases, some cells may also circulate back and settle in the area of the primary mass. Self-seeding is a close relative of, but different from, metastasis.

Delivering one of the keynote talks at the 2008 Breast Cancer Symposium in Washington, DC, in September, Joan Massagué, PhD, chairman of the Cancer Biology and Genetics Program at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, said that metastatic invasion is a difficult process because the target organ is a different cellular environment from the tissue of tumor origin. Most cells that enter bone marrow, lung, or brain from another organ do not thrive. "However, if the cells that have been released from the tumor recirculate...through the tumor that they departed from, they are going to recognize that as a very friendly territory," he explained. "A tumor would be enriching itself with the most aggressive cells that it has produced." These cells survived in the circulation and can re-establish themselves in the originating tumor (ie, "self-seed").

Massagué and his colleague Larry Norton, MD, of the Department of Medicine at MSKCC, have demonstrated self-seeding in a mouse model system by implanting human breast cancer cells labeled with fluorescent markers into the animals on two sides, using a different color marker for each side. Cells from one side found their way into the tumors on the other side, as evidenced by their different color under the microscope. When the investigators injected tumor cells into the heart, the cells circulated and seeded only into the mammary tumors and not into other tissues. When mammary tumor cells were put into the lung, circulating cells homed back to an existing mammary tumor. These experiments demonstrated the tissue-specificity of the homing and therefore "self-seeding."

Using this experimental system, the researchers are now investigating which class of cells in a tumor are best at self-seeding, what capabilities they have to have, and what are the consequences of a tumor being seeded by its own cells. They have found that these tumors grow faster, not because the seeded cells themselves proliferate so much, but because they release chemical factors that promote tissue invasion and stimulate the original tumor cells to grow by a paracrine effect. Massagué and colleagues are also trying to identify the genes that need to be activated for these processes to take place and to determine if the same processes occur in human patients.

### Therapeutic implications

As genes and factors are identified that allow cells to re-enter tumors, therapies may be developed to minimize their effects. And even if a primary tumor is resected and therefore gone, Massagué warned that self-seeding could also happen in metastases or even in micrometastases. "Let's not forget, the metastasis is itself a tumor," Massagué said, so it has the potential to seed itself, as well. "Any drug that blocks the ability of cells to re-enter anything, be it the tumor or another organ, that's something that would be very valuable to try and target," he said.

In an interview with *The Oncology Nurse*, Massagué advised that tumor self-seeding is a concept that has so far been shown only in animals. If it proves to occur in human beings, he said it would have a number of clinical implications and would explain some long-standing questions about patterns of tumor growth and risk of metastasis. He said he does not doubt that the same phenomenon occurs in people since the mouse model has been consistent whenever human or mouse tumors of various tissue types have been tested.

Self-seeding is different from metastasis in that metastatic cells not only have to be able to survive in the circulation, but they also have to be able to establish themselves in an environment that is not their natural one, in a tissue different from where they came, and then thrive and take over. But self-seeding may be a precursor to development of metastases. "The tumor is acting as an incubator. It's enriching itself in further propelling the expansion of the most aggressive children to be born out of the model cells in the tumor," Massagué said.

In his part of the keynote address, Norton hypothesized that self-seeding may help to explain why the response rate to a chemotherapeutic drug or regimen often correlates poorly with overall survival. "We have not developed drugs that affect self-seeding," he said. "We have developed antimitotic drugs but not antiseeding [ones]." Present drugs may be able to affect seeding but have not been optimized in dose or scheduling to do so, Norton proposed.

Joan Massagué, PhD

Eric Winer, MD, director of the Breast Oncology Center at Dana-Farber Cancer Institute in Boston, chaired the session at which Massagué and Norton presented their work. He cautioned that self-seeding is a new concept and demonstrating it in people will be challenging. "The key here is that this is different from the way we've thought about how breast cancer spreads and how breast cancer grows in the past, and we really need new approaches," he said.

In the animal experiments, the researchers at MSKCC have been investigating self-seeding mainly using breast tumors. "I think in principle it could apply to absolutely every tumor type," Massagué predicted. "Like everything in biology, every phenomenon has a range, and I'm sure that some tumors will be quite... aggressive that way, others won't do it very much, and time will tell."

### Reference

Norton L, Massagué J. Is cancer a disease of self-seeding? *Nat Med.* 2006;12:875-878.

—*Daniel M. Keller*



BREAST CANCER

# Retesting Breast Cancer Recurrences

*Continued from page 17*

whom had a change in receptor status between primary and metastatic lesions. she said, and for the one with lymphoma, it completely changed treatment.

**Biopsy should be performed at the time of any metastatic recurrence and should be analyzed for ER, PR, and HER2 receptor status.**

For the three patients with benign disease, "It actually changed their overall prognosis and was life altering for them,"

Bone was the site of ML in 38% of these cases. Simmons noted that in many retrospective studies, "a lot of the tissue that's used to make up these tumor banks are soft-tissue specimens or tissues that [are] easy to achieve with a biopsy and not really representative of the true metastatic population, where most patients present with bone metastases from breast cancer." Therefore, retrospective studies, especially ones that report a lower discordance rate in receptor status, may suffer from some sampling bias.

Simmons advised that a biopsy should be performed at the time of any metastatic recurrence and should be analyzed for ER, PR, and HER2 receptor status. "This study did demonstrate prospectively that there is a discordance rate in ER, PR, and HER2 status, and that that discordance significantly alters management," she concluded.

The study also found that 87.5% of biopsies were feasible in patients who consented to the study, and the results of a patient survey showed that patients tolerated the procedures well, most reporting only mild-to-moderate discomfort. "In fact, we had incredible patient buy-in.... It provides further evidence that yes, biopsies should be done. They change management, they're acceptable, and it's feasible to do this," she said.

Results of this study have led to a second study to assess for potential changes in management at the time of treatment failure in the metastatic breast cancer setting, repeating biopsies as patients progress at the time of failure to see if the disease has changed.

Another study, this one retrospective using archived tumor specimens, also indicated the need to retest as breast cancer progresses. It found a 6% discordance rate in HER2 overexpression between primary tumor or involved axillary lymph nodes (PT/ALN) and local recurrence or metastatic recurrent disease (RD). Ricardo Alvarez, MD, a third-year medical oncology fellow at M.D. Anderson Cancer Center, reviewed the records of 82 patients seen at the center who had fluorescent in situ hybridization (FISH) performed to determine HER2 gene amplification in their PT/ALN and RD tissues.

Most patients (88%) had invasive ductal carcinoma, and 46% had more than stage II disease at initial diagnosis. Most (78%) recurrences were distant, most commonly to lung, bone, or liver.

Five cases (6%) showed discordance in FISH results between PT/ALN and RD tissues. All five went from HER2 positive to HER2 negative. None of these patients received adjuvant trastuzumab, and only one was treated with trastuzumab-based therapy for RD, experiencing stable disease for >15 months. Two of the five patients also had changes in ER/PR status, one having a loss of both receptors and one a gain of both in the metastatic tissue.

"This is extremely important because we guide our therapy depending on the expression of these three factors, [and] we have data that these receptors can change," Alvarez said. "We are [now] treating our patients depending on the first clinical diagnosis and our first molecular diagnosis....In the future [for] patients who come with metastatic disease, we need to repeat all of the molecular biomarkers." He predicted that some patients will benefit from additional treatment and others from changing or withholding specific treatments, such as in the case of loss of a receptor.

He plans to do additional analyses until he has a total of 200 evaluable cases. And he will also investigate other biomarkers in signal transduction pathways such as PTEN, Akt, and PI3K to see if these changes correlate with changes in HER2 status.

*—DMK*

# Bone Metastases

## Certain Types of Cancer Linked to Higher Risk for Bone Fracture

MONTREAL—Patients with primary bone cancer, multiple myeloma, and metastases to the bone are approximately three to five times more likely than others to suffer a fracture within 12 months of their diagnosis, according to a new Danish study. The investigators, who presented their findings at the American Society for Bone and Mineral Research 30th Annual Meeting, also found that patients with metastases to organs other than bone, as well as those with lung, liver, gallbladder, and pancreatic cancers were at elevated risk of fracture within 12 months of diagnosis.

On the other hand, patients with breast cancer, skin cancer, and cancer of the colon or rectum were not found to be at elevated risk, said study investigator Lars Rejnmark, MD, who is an attending physician at Aarhus University Hospital, Denmark. He said these findings should be of special interest to oncology nurses because they suggest that patients at elevated risk should be managed more aggressively and counseled thoroughly.

"If fracture is a main feature of the cancer, then it needs to be prevented," said Rejnmark in an interview with *The Oncology Nurse*. "Nurses are very important information providers on these types of findings. They are the ones who need to counsel the patients about healthy living and the importance of adequate vitamin D. I think vitamin D malabsorption may be playing a role in some of these cancer patients, and that is easily treated with supplementation of vitamin D, either through tablets or injections."

He advised that all patients with the types of cancer associated with elevated risk for fracture should not only be screened thoroughly for bone mineral density levels but also for serum vitamin D levels.

Rejnmark noted that there have been few studies on the risk of fracture in patients with cancer and little is known on the mechanisms of fractures in patients with cancer. He and his colleagues studied the risk of fracture in almost 500,000 cancer patients. The case-control study included 124,655 fracture cases and 373,962 age- and sex-matched controls.

**If fracture is a main feature of the cancer, then it needs to be prevented.**

The investigators found that within 12 months of diagnosis, the risk for a fracture among primary bone cancer patients was 3.51 times greater than the controls, 5.21 times greater for patients with multiple myeloma, and 5.28 times greater for patients with metastases to the bone. In addition, the risk for fracture was elevated in patients with metastases to organs other than bone (1.85 times greater), in patients with lung cancer (1.90 times greater), and in patients with cancer of the liver, stomach, gallbladder, and pancreas (2.14 times greater).

"We found that with prostate cancer there was a difference. Patients with prostate cancer did not have any increased risk during the first 12 months after diagnosis. However, they did have an increased risk after the first year," explained Rejnmark. He said all other types of cancer, including skin and breast, were not associated with an increased risk for fracture within 12 months after their cancer diagnosis.

He said these findings are important because they suggest those patients with elevated risk should be selected for prevention strategies and that bone health needs to be addressed by both nurses and physicians earlier rather than later in the course of their treatment.

—*JS*

# Strength Training May Help Prevent Bone Loss in Older Breast Cancer Patients

MONTREAL—Preliminary data presented at the American Society for Bone and Mineral Research 30th Annual Meeting are suggesting that strength training exercises may help prevent bone loss in older women who have been treated for breast cancer. This is the first study of its kind, and while it is ongoing, the current results show that for the first time there may be a proactive, nonpharmacologic approach a breast cancer survivor can take to lower her risk for osteoporosis and subsequent fractures.

"This is a big deal. Because of age, these women are at higher risk for osteoporosis and related fractures," said lead study investigator Kerri Winters-Stone, PhD, associate professor and research scientist, School of Nursing at Oregon Health & Science University, Portland. "This is something they can do on their own. They can preserve their bone health so they may never be a candidate for medications for preventing bone loss."

Winters-Stone said that is a very important issue to breast cancer survivors. She said many do not want to take any more medications than they have to because they have suffered so many side effects from their breast cancer treatments. Until now, few studies have focused on how different types of exercise interventions, particularly strength training, may benefit older patients with breast cancer.

Winters-Stone and her colleagues conducted a 12-month randomized controlled trial of strength (STR) training versus flexibility (FLEX) training in early-stage, older breast cancer survivors. The mean age of the women was 63.7 years, and the majority had stage I (40%) or stage II (41%) disease. On average, all the women were 12.5 years past diagnosis. Among these women 78% had undergone radiation therapy, 74% were currently on hormone manipulation therapy, and 48% had received chemotherapy.

Exercise training was done three times per week, with two onsite sessions and one at-home session. Each session was 60 minutes in duration. The STR group performed progressive lower-body and upper-body strength training, and each woman did one to two sets of nine exercises. The FLEX group performed progressive flexibility and relaxation exercises.

After 12 months, the researchers found that spine and hip bone mineral density (BMD) was maintained in women who performed regular strength training exercises (0.3% and –0.8%, respectively). Conversely, BMD decreased at both sites in the control group that performed only flexibility exercise (–1.7% and –1.6% at the spine and hip, respectively).

"So after 1 year of strength training, these older breast cancer survivors maintained bone at the spine and hip, in contrast to a group that performed flexibility exercises. They lost bone density over that same time period," said Winters-Stone in an interview with *The Oncology Nurse*. "Regular strength training can help maintain bone health and possibly reduce the risk of fracture after the treatment of breast cancer. This is a nonpharmacologic strategy for reducing fracture, and that is important for a couple of reasons. Many women are looking for nonpharmacologic strategies because they get tired from the treatments. Another reason women may like this is that this is something they can do on their own."

She noted that breast cancer survivors overall may have higher risk for fracture and osteoporosis compared with similarly aged women with no breast cancer history. She cautioned, however, that these findings are preliminary, and the study is ongoing. Winters-Stone also said this study included only women who had normal to low bone mass, but no osteoporosis.


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—*John Schieszer*

BONE METASTASES


# Fox Chase Cancer Center

Fox Chase Cancer Center in Philadelphia was designated a comprehensive cancer center by the National Cancer Institute in 1974. It is devoted to the detection and treatment of cancer; basic, clinical, and prevention research is conducted in more than 80 laboratories in the facility.

Fox Chase offers a number of multidisciplinary treatment options to patients with all types of cancers, including rare and difficult-to-manage tumors. Specialists at Fox Chase are recognized nationally and internationally in medical, radiation, and surgical oncology; diagnostic imaging; diagnostic pathology; pain management; oncology nursing; and social work.

Approximately 4100 patients are admitted annually to this 100-bed hospital, and outpatient visits number more than 69,000 yearly.

Fox Chase was ranked eleventh in the country by *US News & World Report* in its 2007 list of "America's Best Hospitals." It was the highest ranking cancer center in the Pennsylvania, Delaware, and New Jersey area.

In 2000, Fox Chase Cancer Center received Magnet status for nursing excellence, the first comprehensive cancer center to do so, and this honor was renewed in 2004.

Fox Chase Cancer Center has been designated as one of the Blue Distinction Centers for Complex and Rare Cancers by the BlueCross and BlueShield companies. The Blue Distinction designation helps patients identify institutions with expertise in rare cancers. Fox Chase has earned the Blue Distinctions Center for Complex and Rare Cancers designation for esophageal cancer, pancreatic cancer, gastric cancer, rectal cancer, bladder cancer, head and neck cancers, thyroid cancer, and soft tissue sarcoma.

The prostate cancer program at Fox Chase is well known for the development of three-dimensional conformal radiation therapy and new generations of image-guided radiation therapies, such as intensity-modulated radiation therapy.

Also, Fox Chase was the first in the region to offer a specialized localization and sterotactic system, magnetic resonance spectroscopy, and a four-dimensional computed tomography treatment simulator, all of which are used to deliver targeted radiation therapy.

An advanced imaging system to detect microscopic abnormal lung lesions is used at Fox Chase, with the goal of earlier detection and more precise surgery, including video-assisted thoracic surgery. Innovative new thoracic therapies being used include laser and photodynamic therapy.

## Stem cell transplant program

The Fox Chase-Temple Bone-Marrow Transplant Program offers bone marrow and peripheral blood stem cell transplantation. The program has performed more than 900 transplants since opening in 1988. The program performs both autologous and allogeneic transplants in adults. The National Marrow Donor Program has designated the Fox Chase-Temple program an adult transplant and stem cell collection center to perform matched unrelated donor transplants.

The Fox Chase-Temple Bone Marrow Transplant Program offers treatment protocols for patients aged 16 through 70 years. For patients older than 40 years of age or those who would not qualify for high-intensity regimens, low-intensity or mini-transplant programs are available using matched related or unrelated donors.

## Keystone Institute for Translational Medicine

In August 2008, a research collaboration with Temple University and Geisinger Health System was announced, resulting in the formation of the Keystone Institute for Translational Medicine. The intent of the collaboration is to design and implement research on the genetic, behavioral, and social causes of diseases and specific cancers that disproportionately affect urban and rural Pennsylvania. An overarching goal will be to engage in patient research as part of the healthcare delivery process.

Some of the programs that comprise the Keystone Program are Epigenetics and Progenitor Cells, with the goal of investigating two new views of the origins and maintenance of tumor cells; Personalized Kidney Cancer Therapy, which is investigating the mechanisms of kidney cancer metastasis and attempting to uncover the molecular signals that anticipate how a kidney tumor will respond to therapies; and Personalized Risk and Prevention, which is searching for molecular markers that predict cancer risk in an attempt to develop risk reduction strategies tailored to the profile and personal values of the patient.

A Seed Program initiative, in which funding is provided for up to 2 years for investigators with new ideas that require further exploration, was also launched recently.

## Recent discoveries and clinical trials

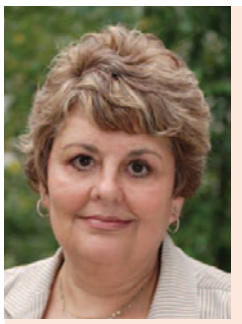
A recent discovery made by Fox Chase researchers is the mitotic checkpoint factor 2, which appears to be integral in preventing cells that are unable to equally separate their chromosomes from dividing. Cancer cells tend to bypass the mitotic checkpoint, allowing them to reorient the chromosomes that promote their ability to divide uncontrollably, said Tim J. Yen, PhD, a senior researcher at Fox Chase. The hope is that the discovery leads to an increase in the efficiency of drugs such as paclitaxel and gemcitabine, which exploit the mechanisms of mitosis to kill cancer cells.

Fox Chase researchers have also demonstrated that mutations in functional areas of a protein called BubR1, which take part in cell division, lead to a genetic rearrangement similar to a process that allows cancer cells to evade destruction by medical treatment. Inhibiting BubR1 could be a strategy to enhance the killing power of current therapeutics, according to Yen.

Researchers at Fox Chase Cancer Center have been able to halt the growth of breast cancer cells in the laboratory by creating a small, antibody-like molecule (ALM) that simultaneously attacks two separate targets (ErbB2 and ErbB3) on the surface of cancer cells. ALM may provide a means to slow the spread of cancer or create a guidance system for delivering more aggressive drugs directly to cancer cells.

Involved in more than 170 clinical trials of new prevention, diagnostic, and treatment techniques, Fox Chase also participates in national trials testing new agents that may prevent cancer. Approximately 800 new Fox Chase patients per year participate in clinical trials.

Current research includes the use of magnetic resonance imaging–guided focused ultrasound and alleviating bone pain caused by cancer metastasis to the bone.



### Director of Graduate Nurse Transition Program

### Deena Damsky Dell, RN, MSN, AOCN, BC

When Deena Damsky Dell, RN, MSN, AOCN, BC, came to Fox Chase in 1989, following a long stint as a nursing school professor, "it was the first time in my life that I was able to give the kind of nursing care that I taught students to give," she said.

The 2-week orientation program at Fox Chase was far superior to that in other hospitals in the area and signaled an opportunity for professional development that she could not get elsewhere, she believes.

In 2000, she started a program at Fox Chase for graduate nurses, and remains director of the popular Graduate Nurse Transition Program. "We had two goals for the program," noted Dell. "We didn't want to 'eat our young' by putting them into positions they weren't ready for, and we also didn't want to subject our patients to less than excellent care."

Her intensive care unit (ICU) skills and background make her a valuable resource at Fox Chase. She coordinates and teaches life support and telemetry classes, and helps in research in the ICU. "I do whatever is needed," said Dell.

As a former patient with breast cancer, Dell is uniquely qualified to work with other patients with breast cancer pre- and postoperatively. She serves on the medical advisory board of the nonprofit organization Living Beyond Breast Cancer. "Because I'm busy with the grad program only twice a year, I have the time to do breast cancer education," she said. The small size of Fox Chase, with only 100 beds, enables such variety in her career, which drives her.

According to Dell, "If it was a big hospital, any one of [the] things I do would be a full-time job," but at Fox Chase, "I get to do all of the different things I love."

The shared governance means that staff nurses have many opportunities for committee memberships, nursing grand rounds, and workshops. "We encourage professionalism, and you can pick what you want to do," said Dell regarding the support from nursing management. "The environment here encourages nurses to grow and expand their horizons."

*—Wayne Kuznar*

# Finally in the treatment of higher-risk MDS*...

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

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

# ...A Breakthrough in

Vidaza®

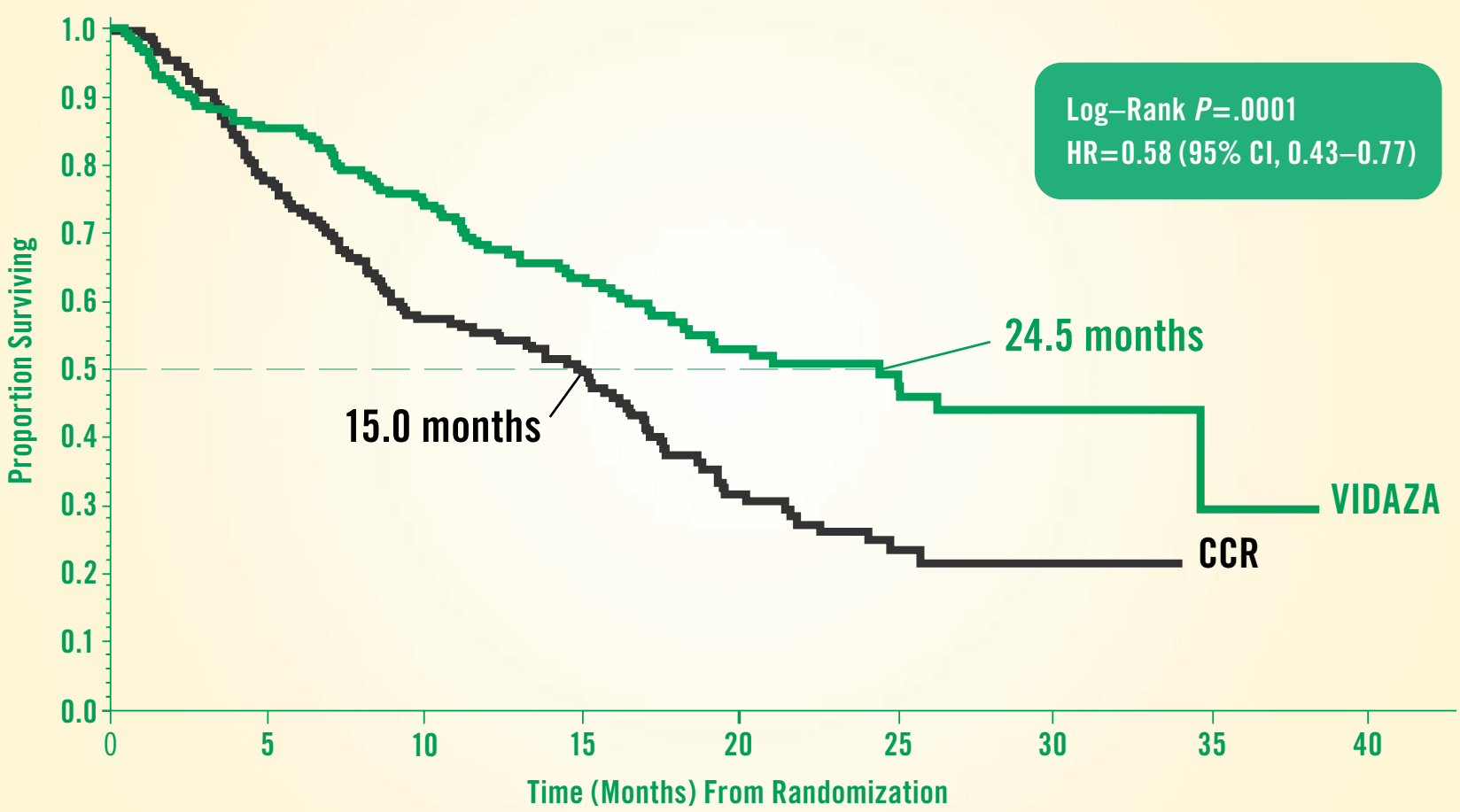
azacitidine for injection

**Proven Results. Extended Survival.**

# S U R V I V A L

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

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




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

* French-American-British classification for MDS.

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

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

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

*For proven survival in higher-risk MDS*

# There's only VIDAZA®

## VIDAZA significantly extended median overall survival vs CCR

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

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

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

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

- To optimize patient benefit, investigators aimed to treat patients with VIDAZA for at least 6 cycles[1]
- Patients receiving VIDAZA were treated for a median of 9 cycles (range 1-39)

### Important Safety Information

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

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

**Reference: 1.** Data on file, Celgene Corporation.

Celgene



Vidaza®

azacitidine for injection

**Proven Results. Extended Survival.**

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

## 1 INDICATIONS AND USAGE

### 1.1 Myelodysplastic Syndromes (MDS)

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

## 4 CONTRAINDICATIONS

### 4.1 Advanced Malignant Hepatic Tumors

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

### 4.2 Hypersensitivity to Azacitidine or Mannitol

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Anemia, Neutropenia and Thrombocytopenia

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

### 5.2 Severe Preexisting Hepatic Impairment

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

### 5.3 Renal Abnormalities

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

### 5.4 Monitoring Laboratory Tests

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

### 5.5 Pregnancy

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

### 5.6 Use in Males

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

## 6 ADVERSE REACTIONS

### 6.1 Overview

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

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

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

### 6.2 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data described below reflect exposure to VIDAZA in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (SC administration), Studies 2 and 3 were single arm studies (one with SC administration and one with IV administration), and Study 4 was an international randomized trial (SC administration) [see Clinical Studies (14)]. In Studies 1, 2 and 3, a total of 268 patients were exposed to VIDAZA, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). VIDAZA was studied primarily in supportive-care controlled and uncontrolled trials (n=150 and n=118, respectively). The population in the subcutaneous studies (n=220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the IV study (n=48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 mg/m$^2$. In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to VIDAZA. Of these patients, 119 were exposed for 6 or more cycles, and 63 for at least 12 cycles. The mean age of this population was 68.1 years (ranging from 42 to 83 years), 74% were male, and 99% were white. Most patients received daily VIDAZA doses of 75 mg/m$^2$.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 8 USE IN SPECIFIC POPULATIONS
### 8.1 Pregnancy
**Pregnancy Category D**

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

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

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

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

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

### 8.6 Gender Differences
There were no clinically relevant differences in safety and efficacy based on gender.

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

## 13 NONCLINICAL TOXICOLOGY
**Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

## 17 PATIENT COUNSELING INFORMATION
Instruct patients to inform their physician about any underlying liver or renal disease.

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

Manufactured for: Celgene Corporation
Summit, NJ 07901

Manufactured by: Ben Venue Laboratories, Inc. Bedford, OH 44146 Or Baxter Oncology GmbH 33790 Halle/Westfalen Germany

VidPlyPI.001 BS 08/08

# Nursing Career Specialist at Fox Chase Increases Recruitment, Retention

## An interview with Maureen Mullin, BSN, RN, OCN, CHCR

To meet the growing demands of nurse recruitment and retention, Fox Chase Cancer Center in Philadelphia has created a unique position—nursing career specialist. Although performing some of the duties of the traditional nurse recruiter, the nursing career specialist plays a more comprehensive role, including collaborating on marketing initiatives, developing relationships with community partners, and conceptualizing and implementing special nursing administrative projects. Maureen "Mickey" Mullin, BSN, RN, OCN, CHCR, has held the position since its inception in 2000. She spoke with *The Oncology Nurse* recently about what the role involves and the impact it has had on nurse recruitment and retention.

**What exactly does your position entail?**

The nursing career specialist was a position that was developed out of a need for increased nurse recruitment and retention here at Fox Chase. It's a multidimensional role. I do some of the duties of a traditional nurse recruiter, but it's much more comprehensive than that.

I collaborate with marketing departments on advertisements and marketing initiatives, and I work with community partners like schools and corporations to encourage students to enter the nursing field. I also work with the nursing department overall for the conceptualization and implementation of different kinds of nursing projects.

For example, I'm involved in the nursing satisfaction survey, which is part of the National Database of Nursing Quality Indicators. Hundreds of thousands of nurses are surveyed every year, and I am the coordinator for that here at Fox Chase to be sure that all of our nurses have their say about their job satisfaction. It's a key retention item.

The nursing career specialist role here at Fox Chase involves many different projects. We came up with the title after reviewing jobs across the country, and we molded it to fit our needs.

**Do other hospitals or cancer centers have such a position?**

I think the nursing career specialist position is unique to Fox Chase. Some hospitals have positions that are similar, which they call retention specialist or retention coordinator, but I think what I do as a nursing career specialist is more comprehensive. Although our outpatient department is huge and we are growing, Fox Chase is a relatively small hospital with 100 inpatient beds. So, we were able to combine all these duties and responsibilities together in one role.

In some of the larger centers, one person works with the community, another person focuses on education, and another does recruitment. But, for us here and for other smaller centers, this kind of collaborative role works better.

**Do you have any measure of what impact your program has had on nurse recruitment and retention?**

We do. In 2000 when I took the role, we had a very high vacancy rate. We hadn't had a nurse recruiter for a couple of years because the vacancy rate was low, but as the nursing shortage started to impact the country, the Philadelphia area was affected as well, and it came upon us rather quickly.

When I first took the role, we had a high rate of vacancy, from 13% to 20% depending on the area. In contrast, this month, our vacancy rate was only 4%, and our turnover rate was less than 1%. I would love to take credit for that, but it's actually the result of several factors.

At the same time my role was created, we also implemented a Graduate Nurse Transition Program, which is a very comprehensive training program for new nurses right out of school to learn about oncology. Deena Damsky Dell developed that program, teaches the coursework, and mentors the students [see page 20]. I recruit students for the program. The creation of the nursing career specialist position and the graduate nurse program coming at the same time had a significant impact on the vacancy and turnover rates.

The graduate nurse program has a dedicated budget to hire eight new nurses a year. Although it's quite an expensive program, in the end, it's cost-effective because the cost of replacing a registered nurse in the United States is usually equivalent to 1 year's salary. If you can train new nurses and have them in place when vacancies arise, your money is better spent than it would be on sign-on bonuses or advertising.

**When you're looking for a nurse for the program, what qualities do you look for beyond the basic educational requirements?**

We're looking for nurses who want to care for cancer patients and to work in a professional practice environment. Our nurses have a lot of autonomy and authority to be patient advocates. And so, we are looking for nurses who want to be in that type of environment. We're looking for qualities like a caring nature, compassion, critical thinking ability, and, of course, clinical excellence.

When we hire graduate nurses, we require a completed resume, their full transcript from college up to the point of application, and two clinical letters of reference, so that we can validate their academic credentials as well as clinical experience. We also require a brief essay explaining why they want to work here and what they have to offer our patients and their families.

For experienced nurses the application process is simply an online form. I screen every applicant we might consider in a telephone conversation before we bring them in for an interview to be sure they're interested in working here for the right reasons.

We don't require nurses to have oncology certification to start with, but we do encourage them to seek it once they are hired. We reimburse fully for nurses who take their oncology and other specialty certification.

**Philadelphia is a very competitive marketplace with a lot of opportunities for nurses. What factors do you find are important in recruiting nurses?**

Our environment is all about professional practice and advancing our nurses. So, we invest in the staff that we have. We do not provide any type of monetary incentives for hiring. The most we would offer would be reimbursement for a state board examination preparation course for a new graduate. We don't do sign-on bonuses in any way, shape, or form. Instead, we invest our money in our staff because we want to keep their knowledge and expertise right here. We offer a competitive salary and an excellent benefit package.

Although the compensation issues are important, what we really like to do is provide an environment that supports excellence in clinical practice. We were one of the first hospitals in the country to be part of the Magnet Recognition Program® [see sidebar] and the first cancer hospital to achieve Magnet status. The 14 forces of magnetism are what constitute an outstanding nursing facility and an excellent nursing department.

The Magnet program recognizes hospitals with a supportive nursing administration, a well-developed shared decision-making model, and policies

*Continued on page 28*

**We're looking for qualities like a caring nature, compassion, critical thinking ability, and, of course, clinical excellence.**

## Magnet Recognition Program®

The American Nurses Credentialing Center (ANCC) created the Magnet Hospital Recognition Program for Excellence in Nursing Services in 1990 to recognize hospitals with 14 characteristics that have been shown to attract and retain professional nurses. The program has since been broadened to include long-term care facilities and healthcare organizations abroad, and, in 2002, the name was changed to the Magnet Recognition Program®. Approximately 5.1% of all US healthcare organizations have achieved ANCC Magnet Recognition® status based on appraisal of quality indicators and standards of nursing practice known as the Forces of Magnetism.

The goals of the Magnet program are to promote quality in a setting that supports professional practice; identify excellence in the delivery of nursing services to patients/residents; and disseminate "best practices" in nursing services.

More information about the Magnet Recognition Program® and the application process can be found at www.nursecredentialing.org/Magnet/ProgramOverview.aspx.



NURSING CAREERS

# Books and Media

## "So, You Want to Be an Oncology Clinical Nurse Specialist?!"

Oncology Nursing Society. Pittsburgh, PA; ONS Publishing Division; 2008.
98 pages. Spiral bound. $19.00 ONS members; $25 nonmembers.

*Reviewed by* **BETH FAIMAN, RN, MSN, APRN-BC, AOCN**

Imagine that it is 8:30 AM on a Friday morning, and you are back in high school. The teacher proudly exclaims that today, you will be taking an impromptu test, the most important test of your life. You are ready to panic, but she advises that this is not an exam that you needed to study for. Answering all of the questions, however, will confirm what career path you are supposed to follow in life, based on your strengths and weaknesses, likes and dislikes. And, if you pursue the suggested vocation, you will be satisfied in life and become a success. If only happiness and success were as easy to find as through taking a test!

Each of us has a story to share, as to how we evolved in our jobs as oncology nurses. Whether it resulted from personal experience, through a series of events, or by answering questions on a career test, taking care of cancer patients has become our profession. Upon achieving a degree, we are led to believe that nursing will enable job satisfaction and security, which is generally true for most oncology nurses. But until you work with this special group of patients, you cannot truly realize the personal reward in addressing their needs and supporting them in many ways. This devotion to our patients is what allows many of us the ability to excel in a more advanced role, such as an advanced practice nurse (APN).

Many nurses consider obtaining an advanced degree, and are searching for insight and career guidance from the experts in the field. For those nurses who are considering an advanced degree, or have recently obtained one, I recommend a recent publication of the Oncology Nursing Society (ONS) entitled, "So, You Want to Be an Oncology Clinical Nurse Specialist?!" This is a comprehensive review that reflects upon the diverse role of an Oncology Clinical Nurse Specialist (CNS). These specially trained APNs not only serve as mentor, educator, problem solver, and consultant, but also are able to conduct clinical research and answer important questions in their area of expertise. This spiral-bound book is lightweight, easy to read, and provides the prospective oncology CNS with the necessary background information and tools required to guide your career.

In each chapter, the authors describe the stepwise evolution from the competent nurse to the expert facilitator, with accurate descriptors and role delineation to educate those less familiar with CNS practice. Real-world applications are readily found within each section, with helpful tips on time management strategies, organizational skills, and mentoring. The book uses catchy titles, with chapters prepared in an informal writing style, which makes this an easy read for the prospective CNS and a good reference for the new graduate who is evolving in the role.

As with many future APNs, I myself had debated which advanced role to select, and, although I ultimately chose to become an adult Nurse Practitioner (NP), the CNS role is also one of distinction. Reading a quality publication such as this may lead to future CNS leaders, as this book may help clarify the career path, without taking another test. There's more time for testing later…in school!

**This book is lightweight, easy to read, and provides the prospective oncology CNS with the necessary background information and tools required to guide your career.**

# NURSING CAREERS

# Nursing Career Specialist

*Continued from page 27*

that support recruitment and retention, such as full reimbursement for certification and a tuition reimbursement program. Our nurses are provided time to attend the meetings.

For new nurses, our main recruitment effort is our Graduate Nurse Transition Program, and a feeder for that is our Student Nurse Extern Program. I recruit at all of the local colleges, the National Student Nurse Association, and the Student Nurse Association of Pennsylvania for these programs.

**What sorts of educational and training opportunities do you provide for your staff?**

We offer a lot of professional development on site. We offer continuing education programs at lunchtime as well as 2- and 3-day continuing education courses that are nationally recognized. Our nurses may attend free of charge and they are also paid for the conference time. Nurses from all over the country attend our courses on such topics as chemotherapy, hospice care, and radiation therapy. Our nurses also have the opportunity to attend the conventions and conferences of professional nursing organizations like the Oncology Nursing Society.

**How important are factors such as flexible schedules and opportunities for advancement in recruiting and retaining nurses?**

In this day and age, nurses are looking for work/life balance, so we try to provide that, keeping in mind the needs of our patients because our patients' needs come first. Shared decision-making supports self-scheduling. And we have an excellent career ladder here called our Clinical Ladder program. As you rise on the clinical ladder, increasing your level of expertise, you're rewarded with a financial incentive.

**You mentioned your role involves community outreach. What form does this take?**

In addition to recruitment and retention, there's a big component of community outreach, reaching out to students about the field of nursing and encouraging them to enter our field. We go to school career fairs and health fairs and talk about the nursing field.

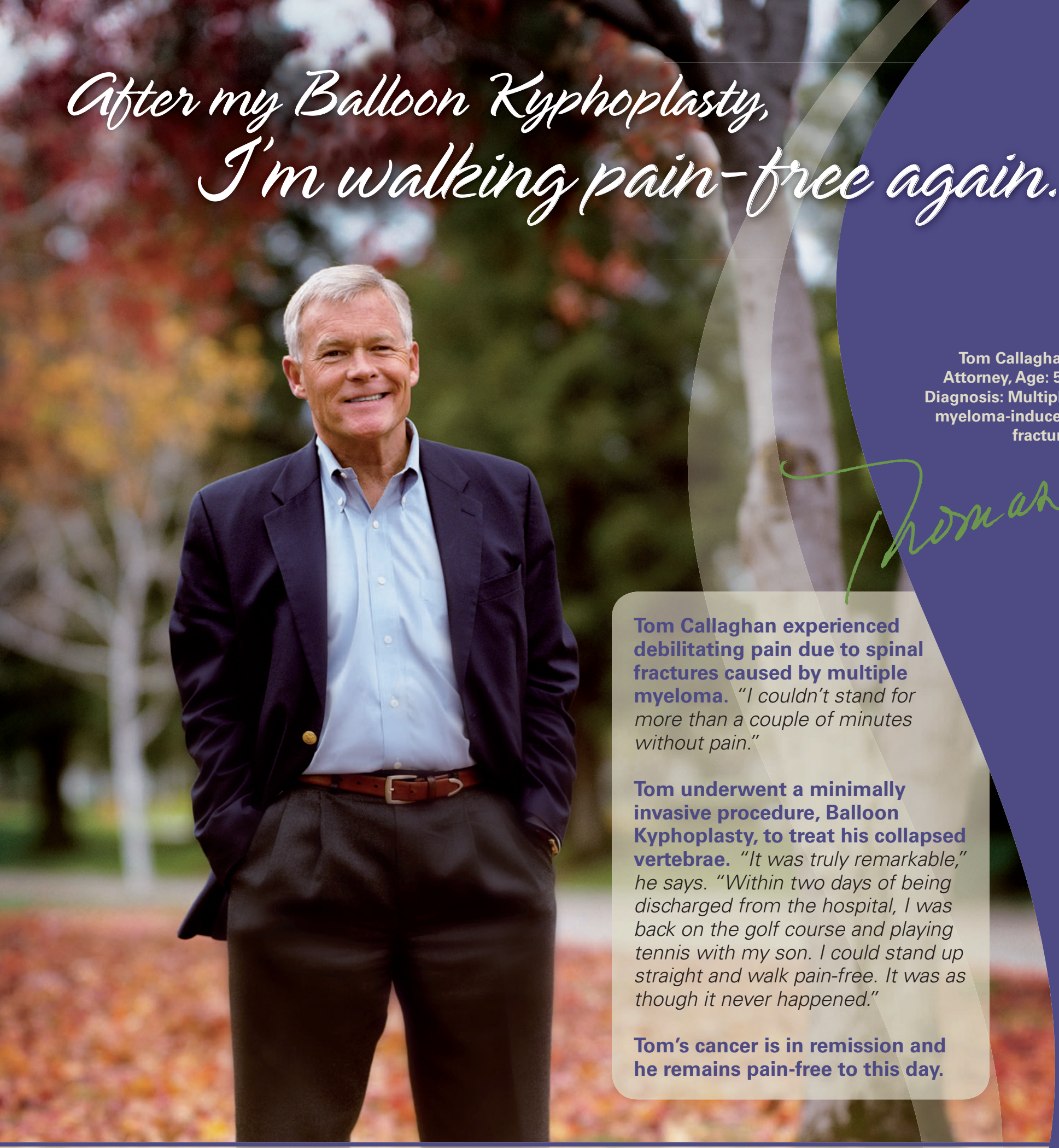
**There's a big component of community outreach, reaching out to students about the field of nursing and encouraging them to enter our field.**

One of the unique programs we have here is a nursing education fair, which we host every year or every other year. For the fair, all the colleges that offer nursing programs and nursing schools in the Philadelphia and surrounding suburbs come to Fox Chase. We have an open setting, somewhat like an open house, and students can walk around and talk to all the nursing programs in the area.

High school students can come and learn about the requirements for nursing school, and nurses can find out about nursing programs like RN to BSN completion programs, master's degrees, and doctoral programs in nursing.

*—Karen Rosenberg*

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



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

Tom

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

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

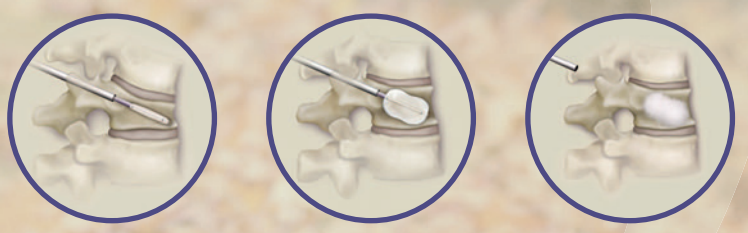
**Tom's cancer is in remission and he remains pain-free to this day.**

**A vertebral compression fracture (VCF)** occurs when the vertebral body collapses because the bone is too weak due to primary bone cancer, metastatic bone disease, and cancer and chemotherapy-related osteoporosis.

**To learn more about Balloon Kyphoplasty, visit our website at www.kyphon.com.**

Although the complication rate with Balloon Kyphoplasty has been demonstrated to be low, as with most surgical procedures, there are risks associated with Balloon Kyphoplasty, including serious complications. For complete information regarding indications for use, warnings, precautions, adverse events and methods of use, please reference the devices' Instructions for Use. *Kyphon* and *KyphX* are registered trademarks and *Ahead of the Curve* is a trademark of Kyphon Inc.  16000846-01

**Balloon Kyphoplasty**



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# Quality of Life in Metastatic Renal Cell Carcinoma: Sunitinib vs Interferon alfa

BY **DAVID CELLA, PhD**

*Center on Outcomes, Research, and Education (CORE), NorthShore University HealthSystem and Northwestern University Feinberg School of Medicine, Evanston, Illinois*

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**PROGRAM GOAL**

To educate oncology nurses about treatments for metastatic renal cancer and how they affect patients' quality of life.

**LEARNING OBJECTIVES**

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

- List current approved treatment options for metastatic renal cell carcinoma (RCC).
- Summarize clinical trial findings on the safety and efficacy of sunitinib vs interferon alfa in patients with metastatic RCC.
- Explain differences in quality of life with sunitinib vs interferon alfa in patients with metastatic RCC.

**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.

Renal cell carcinoma (RCC) is the most common form of kidney cancer, and at least 25% of patients have metastases at their initial presentation. The disease has a dismal prognosis. Notably, recurrence occurs in nearly half of patients treated for localized disease, and fewer than 20% of patients remain alive at 5 years.[1-3]

Metastatic RCC is usually unresponsive to standard chemotherapy, and, as a result, patients frequently die within a year of diagnosis.[4,5] Cytokines, such as interferon alfa, were accepted as standard first-line therapy for metastatic RCC for about 20 years until the recent introduction of targeted therapies. Cytokines, however, have significant limitations in terms of both efficacy and quality of life. Response rates generally do not exceed 20%, and the median overall survival is roughly 12 months. In addition, although 5% to 10% of patients treated with cytokines achieve long-term remission, most either gain no clinical benefit or discontinue treatment because of adverse side effects.[6] In fact, adverse effects, which range from influenza-like symptoms to neurocognitive deficits, may significantly impair quality of life.[2,7]

Today, the treatment landscape for patients with metastatic RCC is much better. Several targeted therapy options for effective therapy are available, including sunitinib malate (Sutent), sorafenib tosylate (Nexavar), and temsirolimus (Torisel). The clinical trials that led to the approval and adoption of these newer agents have included studies of patient-reported benefits, such as symptom relief and quality of life, and have examined cost-effectiveness relative to the cytokine therapy comparator. This brief article summarizes patient-reported and cost-effectiveness results from one of these newer agents: sunitinib malate.

Sunitinib malate is an oral inhibitor of tyrosine kinases, including vascular endothelial growth factor receptor and platelet-derived growth factor receptor. Both receptors are known to play a key role in the pathogenesis of clear-cell carcinoma, the major type of RCC and, thus, are considered rational targets for the treatment of clear-cell RCC. The drug is approved by the US Food and Drug Administration for treatment of both RCC and imatinib-resistant gastrointestinal stromal tumor and was the first cancer drug simultaneously approved for two different indications.[8]

## Phase 3 trial

In an international phase 3 trial, Motzer and associates compared sunitinib with interferon alfa in 750 patients 18 years of age or older who had metastatic RCC and a clear histology and had not undergone prior systemic RCC therapy.[9] All participants had measurable

**FACULTY/PLANNER DISCLOSURES**

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disease and an Eastern Cooperative Oncology Group performance status of 0 to 1. Most patients were white men approximately 60 years of age.

Patients were randomized to sunitinib or interferon alfa every 6 weeks. Sunitinib was administered orally at a starting dose of 50 mg/day for 4 weeks followed by 2 weeks off treatment. Interferon alfa was administered subcutaneously on 3 nonconsecutive days each week. Patients in the interferon alfa group received doses of 3 million units (MU) the first week, 6 MU the second week, and 9 MU thereafter. Doses could be adjusted if toxicity developed for both treatments.

Sunitinib produced a significantly longer progression-free survival (11 months vs 5 months) and a higher objective response rate (31% vs 6%) than interferon alfa and was well tolerated.

### Quality-of-life findings

Patients who received sunitinib also reported a better quality of life than those who received interferon alfa, and these findings were published in a subsequent report.[10] We believe our trial was the first direct comparison of quality of life in patients treated with an oral tyrosine kinase inhibitor or a systemic cytokine as first-line treatment of metastatic RCC. Earlier studies of quality of life in metastatic RCC involved case series and evaluations of other treatment options, such as surgery or immunotherapy.

**We believe our trial was the first direct comparison of quality of life in patients treated with an oral tyrosine kinase inhibitor or a systemic cytokine as first-line treatment of metastatic RCC.**

For our analysis, we used three patient-administered questionnaires, all of which have been validated widely:

1. the Functional Assessment of Cancer Therapy-Kidney Symptom Index-15 item (FKSI-15)
2. the Functional Assessment of Cancer Therapy-General (FACT-G)
3. the EuroQoL self-reported health status measure (EQ-5D) and its visual analog scale (EQ-VAS).

The FKSI-15 questionnaire is a validated symptom index for patients with kidney cancer. The Functional Assessment of Cancer Therapy-Kidney Symptom Index–Disease-related Symptoms (FKSI-DRS) subscale, which measures symptoms predominantly related to kidney cancer, including lack of energy, fatigue, pain, bone pain, weight loss, shortness of breath, cough, fever,

*Continued on page 32*

## COMMENTARY

# Quality of Life in Metastatic Renal Cell Carcinoma: Sunitinib vs Interferon alfa: A Nurse's Perspective

BY **LYSSA FRIEDMAN, RN, MPA, ONC**
*Veracyte, Inc, South San Francisco, California*

Renal cell carcinoma (RCC), although infrequent, remains a disease with a poor prognosis. In 2008, cancers of the kidney and renal pelvis represented nearly 4% of all new US cancer cases, and approximately 13,000 Americans died of these cancers.[1] RCC is the most common kidney cancer, and, as Cella reports, is associated with a high incidence of metastatic disease at diagnosis, recurrence rates, and mortality. Determinants of prognosis include tumor grade, local extent of disease, and presence of local extension and/or distant metastases. The most common sites of metastasis are lung, bone, brain, liver, and adrenal gland.[2]

Patients with RCC typically present with a suspicious mass found radiographically. Common complaints include flank mass or pain and hematuria. Patients with metastases may present with bone pain, adenopathy, pulmonary symptoms related to lung involvement, fever, weight loss, anemia, or varicocele.[2]

The US Food and Drug Administration has approved three oral tyrosine kinase inhibitors for the treatment of advanced RCC: sunitinib malate (Sutent), sorafenib tosylate (Nexavar), and temsirolimus (Torisel).[3-5] The introduction of these compounds brings oncology nurses new opportunities to educate themselves, and thus to support patients more effectively.

First, the toxicities of these agents are different from those caused by traditional chemotherapy agents. Dermatologic and gastrointestinal reactions are common. Temporary or permanent discontinuation of these drugs is indicated for a variety of medical conditions; thus, routine agent-specific monitoring is critical. Additionally, certain medications, foods, and/or complementary therapies should be avoided when taking these drugs. Oncology nurses can find full safety information on package inserts,[3-5] and patient education materials can be found on manufacturers' Web sites. Patients are best served by a clinic-wide approach to teaching about, assessing, and managing side effects and dose modifications. Educational plan development sits squarely in the oncology nurse's domain.

Second, use of oral formulations shifts the locus of control from the healthcare provider to the patient. The provider may see the patient only on day 1, yet patients continue to self-dose throughout the cycle. Patient education should include:

- Correct capsule/tablet size(s)
- Schedule, including number of capsules/tablets per dose, number of doses per day, and number of days per cycle
- Concomitant medications, foods and/or complementary therapies to be avoided
- How to account for missed or extra doses
- Side effects, including self-monitoring guidelines and instructions for when to call or visit the clinic.

Oncology nurses are instrumental in designing creative patient education approaches, including dosing calendars and drug diaries, which are aligned with the clinic-wide patient education plan.

Finally, proactive consideration to reimbursement and procurement is critical. Although some payers cover oral anticancer agents under the prescription benefit, others assign benefits on the medical side. Ordering these treatments may require more than writing a prescription. Payers may contract with a single specialty pharmacy that receives the chemotherapy order, obtains insurance authorizations when needed, and ships direct to the patient. Approvals may be limited to a 30-day supply, so planning ahead for reorder and accommodating dose modifications is critical. Additionally, patient copayments can be exorbitant; early referral to a manufacturer-supported patient assistance program can help prevent treatment delays or missed doses in patients who lack adequate financial resources.

It may be beyond the scope of nurse clinicians' practices to be knowledgeable about payer details for their entire patient population. Missed doses or delayed treatment, however, can have a negative impact on patient outcome. Oncology nurses, therefore, play a critical role in ensuring that clinics provide informed and proactive financial counseling and in coordinating patient flow between the financial and clinical areas.

In summary, the introduction of new, targeted agents brings improved patient outcomes and, likewise, offers oncology nurses new opportunities to learn, teach, and advocate.

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and hematuria, was the primary quality-of-life end point, higher scores indicating better outcomes. The FACT-G assesses four health-related domains, including physical well-being, social/family well-being, emotional well-being, and functional well-being. The EQ-5D questionnaire assesses a patient's overall health status by examining five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Quality-of-life scores significantly improved on all three questionnaires in patients treated with sunitinib compared with interferon alfa. Notably, sunitinib-treated patients developed fewer disease-specific symptoms than those treated with interferon alfa, as shown by a significant overall mean difference of 1.98 points on the FKSI-DRS subscale between sunitinib-treated and interferon alfa–treated patients (Table). Results on secondary quality-of-life end points (FKSI-15, FACT-G, EQ-5D, EQ-VAS) also showed clinically meaningful differences between sunitinib and interferon alfa, indicating that patients perceived that their health states were superior with sunitinib. The use of validated generic and disease-specific quality-of-life instruments to measure RCC-related symptoms strengthens our results.

### Cost-effectiveness analysis

Remák and associates recently evaluated the cost-effectiveness and cost utility of sunitinib versus interferon alfa and interleukin-2 as first-line therapy for metastatic RCC.[11] Using a Markov model to simulate disease progression and to determine disease-free survival, total life-years (LYs), and quality-adjusted life-years (QALYs), they found that sunitinib provides a cost-effective alternative to interferon alfa as first-line therapy for metastatic RCC. Based on their analysis, compared with interferon alfa, the health benefits of sunitinib are

## COMMENTARY

# Quality of Life in Metastatic Renal Cell Carcinoma: Sunitinib vs Interferon alfa: A Pharmacist's Perspective

BY **HEIDI D. GUNDERSON, PHARMD, BCOP**
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The economic burden of metastatic renal cell carcinoma (mRCC) is estimated to be between $107 million and $556 million in the United States and between $446 million and $1.6 billion worldwide.[1] The incidence and mortality of mRCC has been steadily increasing by 2% to 3% per decade, prompting the need for more efficacious, quality-of-life–enhancing, and fiscally responsible treatments for mRCC. Therapy for mRCC now focuses on aberrant signaling of molecular targets present on tumor cells. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are two such targets that are key drivers of angiogenesis, tumor growth, and metastasis in mRCC.

Motzer and colleagues conducted a randomized, phase 3 trial of sunitinib, an oral tyrosine kinase inhibitor of VEGF and PDGF, which demonstrated significant improvement in progression-free survival and objective response rates compared with interferon alfa as first-line therapy in mRCC.[2] A recent update of this trial reinforced the superiority of sunitinib over interferon alfa by illustrating a median progression-free survival of 11 months versus 5 months ($P$ <.000001), an objective response rate of 47% versus 12% ($P$ <.000001), and a trend toward better median overall survival of 26.4 months versus 21.8 months ($P$ = .051).[3] Although the difference in overall survival was not statistically significant, the authors note that the median overall survival may have been "diluted" by the 59% of patients in the interferon group that received second-line therapy with a VEGF-inhibiting agent.[3]

Cella and colleagues reported a superior quality of life in patients receiving sunitinib versus interferon alfa in the international, randomized, phase 3 trial described above.[4] It should be noted that treatment was not blinded, so it is possible that patients perceived their health status and health-related quality of life was superior with sunitinib. The severity of dermatologic toxicity (hand–foot skin reaction, skin discoloration, rash, xerosis, dermatitis, phototoxicity, hair color changes, alopecia, and nail changes) and survival have been well correlated with monoclonal antibody and tyrosine kinase targeted therapies.[5-8] It is interesting to note that Humblet and colleagues recently associated higher-grade skin toxicity with better overall health-related quality of life in patients receiving targeted therapy for metastatic colorectal cancer.[9] As an oncology pharmacist who counsels patients on the prevention and management of dermatologic toxicities with these therapies, this seems somewhat counterintuitive. It may be prudent to conduct a dermatology-specific quality-of-life assessment that measures cutaneous effects of tyrosine kinase inhibition separately from cancer symptom assessment.[10]

Rémak and colleagues' economic evaluation suggested that sunitinib is a cost-effective alternative to interferon alfa as first-line therapy for mRCC.[11] Trippoli and Messori refute the gained survival advantage with the Markov model of economic evaluation used in Rémak and colleagues' report given that overall survival findings were not statistically significant for patients receiving sunitinib.[12] Regardless, the improvement in progression-free survival, objective response rate, and quality of life in patients with mRCC receiving sunitinib has thrust multitargeted kinase inhibitors to the forefront of treatment algorithms in mRCC. Novel agents like sunitinib, however, do not come without a significant cost. The average wholesale price of sunitinib is approximately $8300 per 6-week cycle of therapy. Oncology pharmacists are frequently responsible for collaborating with the patient and insurance company regarding sunitinib coverage, prior authorization, copays, and/or registration with Pfizer Oncology's drug assistance program FirstRESOURCE. This collaboration, while often labor intensive for both the patient and oncology pharmacist, is necessary to contain the rising cost of treatment of mRCC as previously described.

The new paradigm of oral multitargeted kinase inhibitors as first-line therapy for mRCC affords the oncology pharmacist unique opportunities. Sunitinib and its active metabolite are metabolized by the cytochrome P450 enzyme CYP3A4.[13] A consultation with an oncology pharmacist reviewing prescription, nonprescription, and herbal medications must be required to prevent unnecessary toxicity and treatment failure due to drug–drug interactions with concomitant CYP3A4 inhibitors and inducers. Oncology pharmacists can also direct the appropriate administration of oral multitargeted kinase inhibitors with regard to food and maximal drug absorption. It is vital that the oncology pharmacist play an active role in providing comprehensive care to patients receiving multitargeted kinase inhibitors such as sunitinib.

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**Table. Average Treatment Differences for Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-related Symptoms Items**

| | Least Square Means | | | | |
|---|---|---|---|---|---|
| **Item** | **Sunitinib** | **Interferon alfa** | **Difference** | **95% Confidence interval** | ***P*** |
| I have a lack of energy | 2.50 | 2.18 | 0.320 | 0.197 to 0.442 | <.0001 |
| I have pain | 3.04 | 2.96 | 0.0828 | –0.0264 to 0.192 | .137 |
| I am losing weight | 3.39 | 3.24 | 0.144 | 0.0425 to 0.247 | .006 |
| I have bone pain | 3.35 | 3.20 | 0.149 | 0.0400 to 0.257 | .007 |
| I feel fatigued | 2.49 | 2.20 | 0.286 | 0.158 to 0.415 | <.0001 |
| I have been short of breath | 3.29 | 2.97 | 0.323 | 0.210 to 0.437 | <.0001 |
| I have been coughing | 3.40 | 3.18 | 0.226 | 0.117 to 0.335 | <.0001 |
| I am bothered by fevers | 3.87 | 3.48 | 0.389 | 0.311 to 0.467 | <.0001 |
| I have had blood in my urine | 3.95 | 3.95 | –0.00379 | –0.131 to 0.124 | .954 |

*Least squares means are estimated from mixed-effects models, and higher scores indicated better outcomes (better quality of life or fewer symptoms); the average postbaseline scores for each outcome were computed at approximately week 17 (between cycle 3, day 28 and cycle 4, day 1).*

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achieved at an incremental cost of $18,611 per progression-free year gained, $67,215 per LY gained, and $52,593 per QALY gained.

## What we now know

- Metastatic RCC has a poor prognosis. The cytokines, long considered the best treatment option given RCC's high resistance to chemotherapy, have significant drawbacks with respect to efficacy and quality of life.
- The oral tyrosine kinase inhibitor sunitinib has been shown to be more effective than interferon alfa in metastatic RCC.
- Our recent analysis demonstrated that sunitinib also confers quality-of-life improvements over interferon alfa. We believe the results are bolstered by the fact that we used widely validated generic and disease-specific instruments to assess quality of life.
- Sunitinib has an acceptable cost-effectiveness profile relative to interferon alfa as first-line therapy for metastatic RCC.

## What we do not know

- We are not able to differentiate between treatment effects that are related to a drug's adverse effect profile from those effects that result from the drug's ability to reduce disease-related symptoms. We are, however, currently exploring ways to resolve the problem.
- We cannot know for certain that the results hold true for the entire study population. Because our study included patients from different countries and we did not control for potential cultural differences, it is theoretically possible that the findings do not apply to individual countries. This possibility, however, is unlikely given the randomized study design.
- Because patients knew which drug they were taking, we cannot be certain that sunitinib-treated patients did not overestimate the drug's quality-of-life benefit. However, we rigorously designed our analysis to minimize such a possibility.

## Summary

Treatment options for patients with metastatic RCC now include targeted agents that fundamentally alter the patient treatment experience with cytokine therapy. These agents increase the likelihood of efficacy, diminish the side effect burden, and provide a range of options that are cost-effective under current standards for acceptability. Future research comparing these agents with one another, combining them with other treatments, and exploring strategies for maximizing individual benefit (ie, personalized medicine) should help further improve the benefits realized to date.

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*Jill Stein contributed to the preparation of this manuscript.*

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# Supportive Care

## Pathfinders Guides Patients Along the Cancer Landscape

Pathfinders is a program of comprehensive psychosocial support for cancer patients integrated with clinical care. In a study presented at the 2008 Breast Cancer Symposium in Washington, DC, in September, researchers at Duke University Medical Center in Durham, NC, showed that patients "unanimously" found the program helpful and reported significant improvement in psychosocial and physical outcomes. Using validated instruments, the investigators discovered improvements in quality of life and other measures even in the face of stable or worsening physical symptoms and advanced disease. Clinicians, too, appreciated the program and readily referred patients to it.

Originally developed at a community hospital in Aspen, Colo., in 2003, the Pathfinders psychosocial model aims to optimize biomedical healthcare; manage the psychological, behavioral, and social aspects of illness and its consequences; and promote better health. Components of the program are: patient navigation and advocacy; individualized psychotherapy and counseling; guidance on healthy lifestyle, such as diet and nutrition; links to community and health system resources; referral to complementary and alternative services; and life review and end-of-life planning.

Coauthor Jane Wheeler, MS, a research associate in medical oncology and a medical instructor at Duke, said the Pathfinders intervention uses an individualized approach, primarily one-on-one monthly psychotherapeutic sessions with a social worker, as well as patient advocacy and support, navigation, and coaching, all interwoven with standard oncology care. This is done "so notes are exchanged regularly," Wheeler said. The main point of contact for the patient is the "pathfinder," who coordinates and refers out to other services.

The program has been well accepted in community oncology but had never been tested for feasibility and acceptability in an academic setting. The Duke researchers, led by medical oncologist Amy Abernethy, MD, therefore set out to determine the feasibility of implementing Pathfinders in their large academic setting by enrolling patients with metastatic breast cancer (N = 54) with a prognosis of ≥6 months' survival in a prospective single-arm pilot study. A secondary objective focused on the effectiveness of the program.

Participants completed assessments at five time points over 6 months, including evaluations of satisfaction with care, physical function, symptoms, fatigue, and whether Pathfinders has been helpful to them. Further surveys at baseline, 3 months, and 6 months included exercise behavior, nutrition, spiritual well-being, coping skills, interpersonal support, and other psychosocial parameters.

Of 19 measures reported, the scores of 16 showed a change for the better and no change for only three. Significant improvements ($P < .05$) occurred for distress, despair, quality of life, emotion, and fatigue. At 3 months, 78% of respondents replied that Pathfinders had been helpful to them (data missing from 22%).

**At 3 months, 78% of respondents replied that Pathfinders had been helpful to them.**

Wheeler said that providers were "hugely enthusiastic" about Pathfinders. "We found out that it is incorporated into the academic, busy, bustling clinic setting easily, so it did not interrupt patient flows," she said. It also alleviated some of the burden from medical staff to address psychosocial needs.

The ultimate goal is to develop a model that can be promoted to and adopted by different institutions. Another goal is to develop a way to deliver to patients the same tools for coping skills and self-empowerment training using the Internet. Coauthor Tina Staley, MSW, LCSW, director of Pathfinders at Duke, commented that patients are thrust into the cancer environment without any guidebook or "toolbox" of techniques. "You get a blender, you get a manual…but you get cancer, and no one gives you that," she said.

Staley noted that a report by the Institute of Medicine said that caregivers need a common language so they can help patients with quality of life. "Therefore, we teach nurses the coping skills, physicians the coping skills.... We're really about empowering the patient to be able to take control of their own life and take it back from cancer." As an example, she said that while giving an intravenous medication, nurses can talk with a patient about relaxation techniques to reduce stress or to discern a psychosocial problem that can then be referred to the pathfinder. "The nurses... are the ones that want to come to the training the most," Staley said.

"It also gets them reconnected with why they got into this profession to begin with. And at a time…when everything is so fast and moving, what are just a few things that they can do that still empowers them to empower the patient and be able to get their job done," she said. She also said that nurses are often using the techniques in their own lives and that Duke's top oncologists have commented that Pathfinders has helped the staff as well as the patients.

Pathfinders was originally designed to address a wide variety of cancers, and plans are to expand the Pathfinders model at Duke to other forms of cancer and ultimately to conduct a randomized controlled trial involving men and women with various cancers. Cost-effectiveness and the impact of Pathfinders on clinical flow and on providers are also being explored.

*—DMK*

# Giving Healthcare Safety Net to Prostate Cancer Patients Provides Large Dividends

Nurses are playing a pivotal role in a prostate cancer treatment program that is successfully helping underprivileged men in California navigate the healthcare system.

The Improving Access, Counseling and Treatment for Californians with Prostate Cancer (IMPACT) program was established in 2001 by Mark Litwin, MD, a urologist at the Ronald Reagan University of California, Los Angeles Medical Center. He started IMPACT after significant evidence had accumulated that men from lower socioeconomic strata are less likely to have their cancer identified at early stages and are more likely to have worse outcomes and overall poor experiences with the healthcare system.

Each man enrolled in the program is uninsured and has an income of less than 200% of the federal poverty level. Each is assigned a nurse clinical care coordinator who provides the patient with case management and help in navigating the healthcare system. In addition, patients are assigned a primary cancer care provider and given access to counseling and interpreter services, educational materials, transportation assistance, food security, and housing referrals. These services are provided at no cost to the patient. The program, however, costs approximately $5000 to $6000 per patient per year. For more information on the program, please visit http://www.california-impact.org.

In an examination of enrollees' healthcare use and satisfaction (*J Commun Health*. 2008;33:318-335), Litwin and his coinvestigators found that 82% of the 357 men enrolled in the program between 2001 and mid-2005 did not go to an emergency department for nonemergent care, and 72% had adequate surveillance prostate-specific antigen testing. Furthermore, a median of 8 months after enrollment—the average time to completion of the follow-up questionnaire—78% reported complete satisfaction with the healthcare provided, and 67% had complete confidence in their IMPACT provider(s).

The investigators found no association between race/ethnicity and either healthcare resource use or satisfaction with the healthcare received, although particularly high satisfaction was noted by Hispanic patients. In fact, they were five times more likely than non-Hispanic white men to express complete satisfaction with the care provided. There was a small but significant inverse association between cancer-related symptoms and distress and satisfaction with care. Men with more symptoms and distress due to their cancer were significantly less likely than others to be completely satisfied.

The team also has a study in press that indicates the program is "very cost-effective," Litwin noted.

"The central foundation of this program, apart from providing financial support, is that we provide every patient with a nurse case manager to help him negotiate the healthcare system.… That is one of the things that contribute to the higher levels of satisfaction," he concluded.

*—Rosemary Frei*

# Nursing Practice

## Navigating the Relationship Between Oncology and Managed Care: the Oncology Nurse as Patient Advocate

BY **KIRK McCONNELL**
THE ZITTER GROUP, SAN FRANCISCO, CALIFORNIA

Oncology patients find it increasingly difficult to navigate their treatment options. The number of therapeutic options and amount of available information is overwhelming. There are logistical hurdles as insurance companies manage the category more aggressively. Personal treatment goals are formed in the context of a society that casts death as the ultimate enemy, to be fought at any cost. Patients need help as they face an oncology landscape that is becoming increasingly tangled.

To provide clarity on the evolving issues, *The Managed Care Oncology Index*, a semiannual publication from The Zitter Group, looks at the oncology category from two distinct vantages: managed care executives and clinical oncologists. The report's findings generate significant insight on the relationship between private practice oncology and managed care and reveal opportunities for the oncology nurse to play an important role in ensuring that all stakeholders understand what the patient defines to be successful care, whether that is aggressive therapy, extended courses of treatment, or the graceful transition to palliative care.

The oncologist–patient relationship can be very asymmetric; patients facing a life-threatening disease may not be well-equipped to actively engage their physicians in a critical discussion of treatment options. For that reason, it is very important that an oncologist take the time to discuss therapeutic options with the patient. However, managed care executives, also known as payors, and healthcare providers express very different opinions about how often these conversations occur. More than 80% of oncologists report engaging their patients in adequate discussions. Conversely, nearly 75% of payers believe that oncologists are not taking sufficient time to educate patients about therapeutic choices.

### Payer/provider disconnect

This payer/provider disconnect becomes even more startling when the two are asked to define "survival benefit" within oncology care. Oncologists report that a therapy that extends a patient's life by 3 to 6 months should be considered as having a survival benefit. A plurality of payers put this figure at 10 or more months (Figure 1). These two points taken together begin to tell an interesting story.

The relationship between payers and oncologists is often marked by a mutual distrust. Payers believe that the private oncology practice business model, heavily dependent on drug revenue, motivates oncologists to overprescribe drugs or, at a minimum, choose the most expensive therapeutic options. At the same time, oncologists see payers as seeking to restrict prescriber autonomy, the drive for cost savings undermining the provider's clinical expertise and the patient's best interest. This payers versus provider rhetoric can be at least partially explained by a misunderstanding of motives.

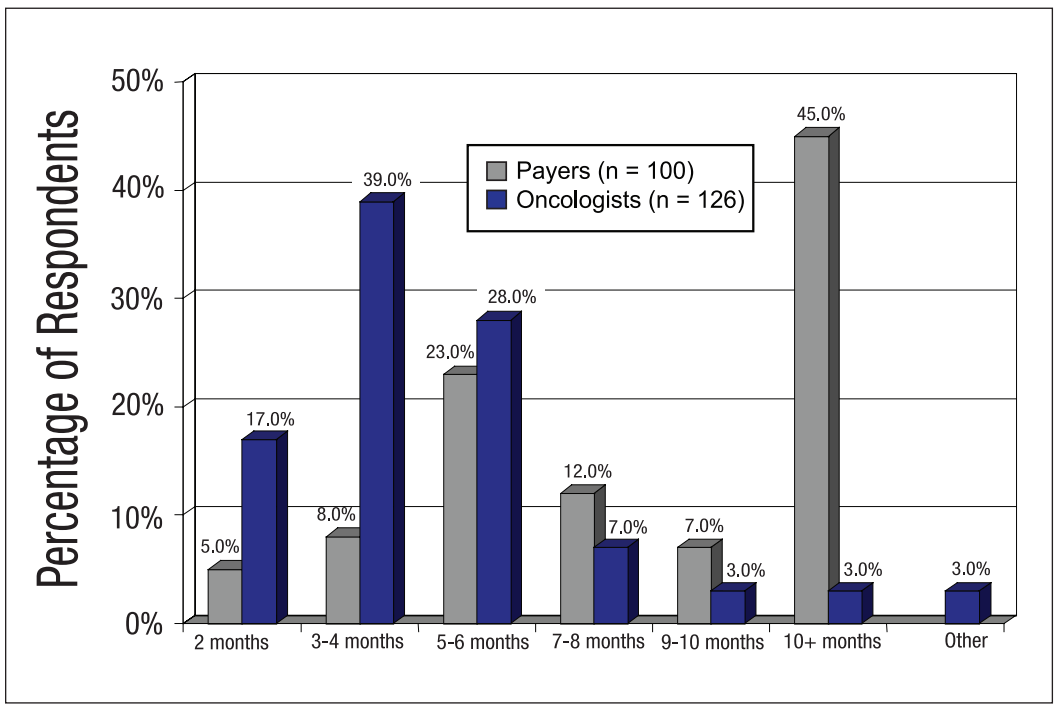


**Figure 1.** Differing definitions of survival
**Question:** By how long must a patient's life be extended for you to consider a product to have a survival benefit?

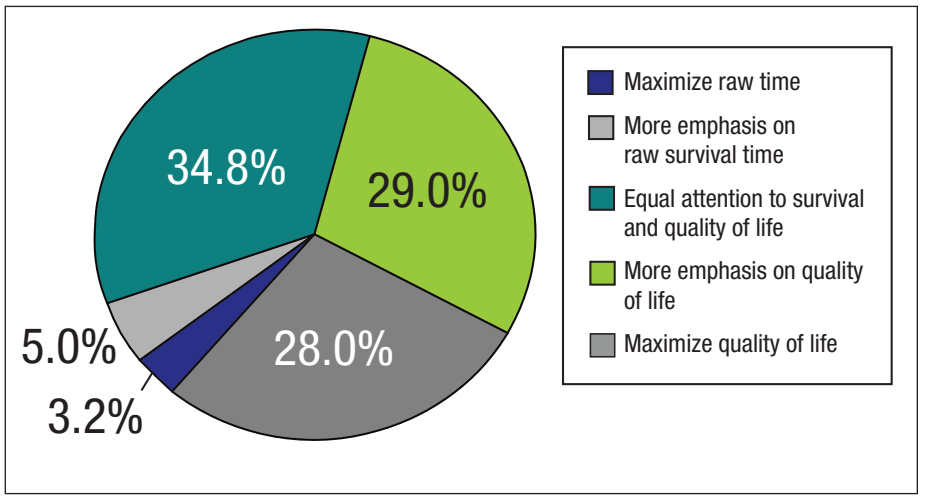


**Figure 2.** Priorities of terminally ill patients
**Question:** What do you see as the priority of terminally ill patients?

Payers' stated priority within oncology is the appropriate utilization of increasingly expensive therapies. If they see a discrepancy between cancer care guidelines and actual behavior, they will try to better align prescribing practices through tighter management of oncology, including through precertification and prior approval processes that require explicit evidence to justify treatment.

Managed care organizations believe that oncologists can get patient buy-in for nearly any treatment regimen, even if those recommendations go against the patient's personal preferences. For example, a patient may feel that he/she is disappointing his/her oncologists by asking about palliative care rather than the third- or fourth-line treatment options being presented to him/her.

### Promoting appropriate utilization

An important question becomes, how can appropriate utilization be promoted without limiting oncologist autonomy? One answer lies in the flow of information between patient and care team. Because of the time they spend with the patient, nurses play an essential role in facilitating this communication, making sure care is aligned with patient goals. Nurses are an essential check and balance in the oncology care continuum.

While oncology patients each have different definitions of successful treatment, trends are apparent when looking at patient subgroups. As shown in Figure 2, oncologists believe that patients in terminal situations are most interested in preserving quality of life, not maximizing raw survival time. As a consequence, there must be a constant discussion about the tradeoffs between clinical efficacy and side effect burden. The risks and dangers associated with therapies remain very real, often magnified in third- or fourth-line treatments. The care team must be sensitive to the needs of the patient and the patient's family, especially when it is time to transition from curative to palliative care.

### End-of-life care

When one looks at the cost of cancer care across the course of the disease, the final weeks of a patient's life consume a disproportionate amount of resources. While payers acknowledge

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NURSING PRACTICE

# Nurse as Patient Advocate

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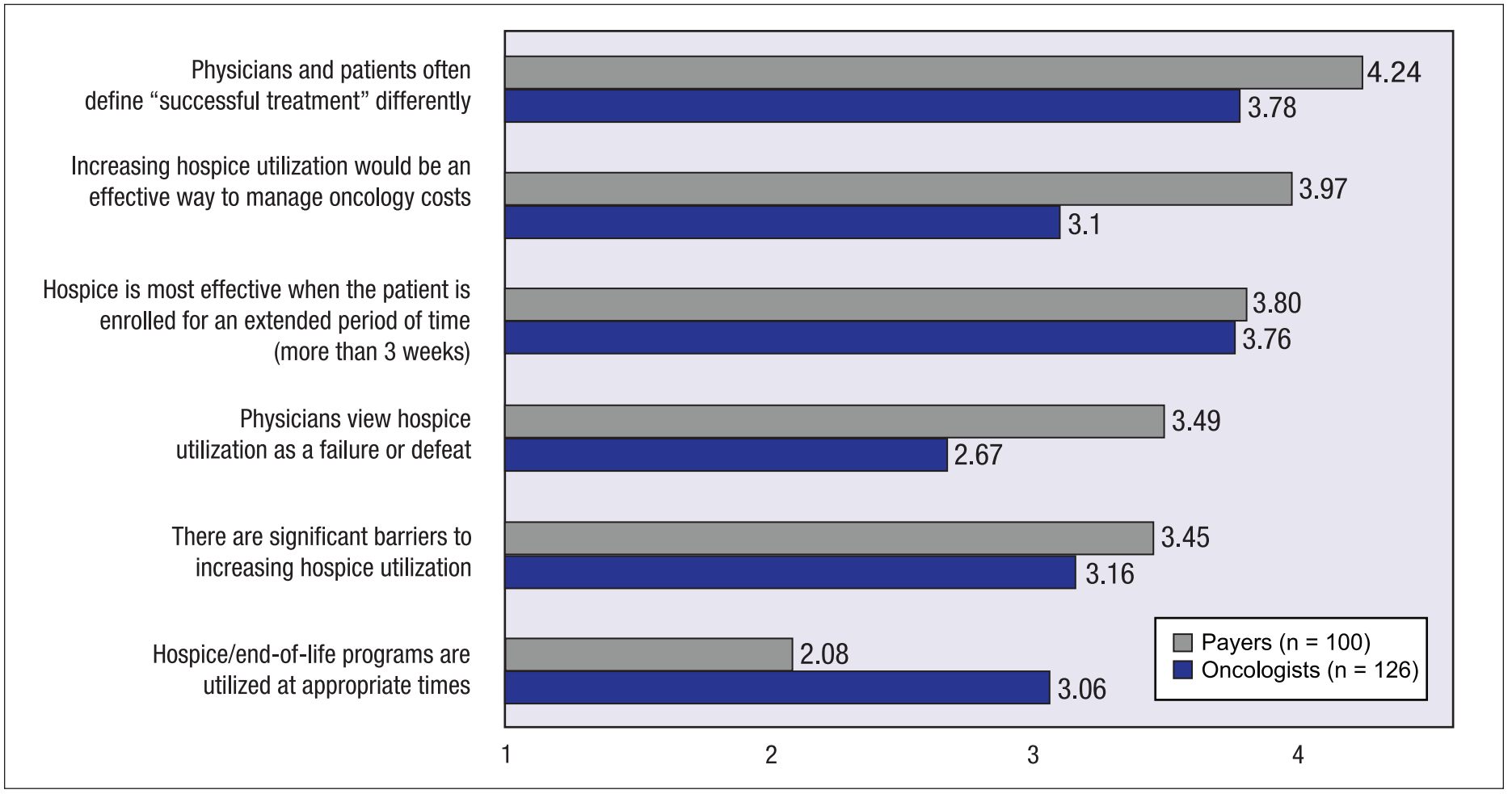
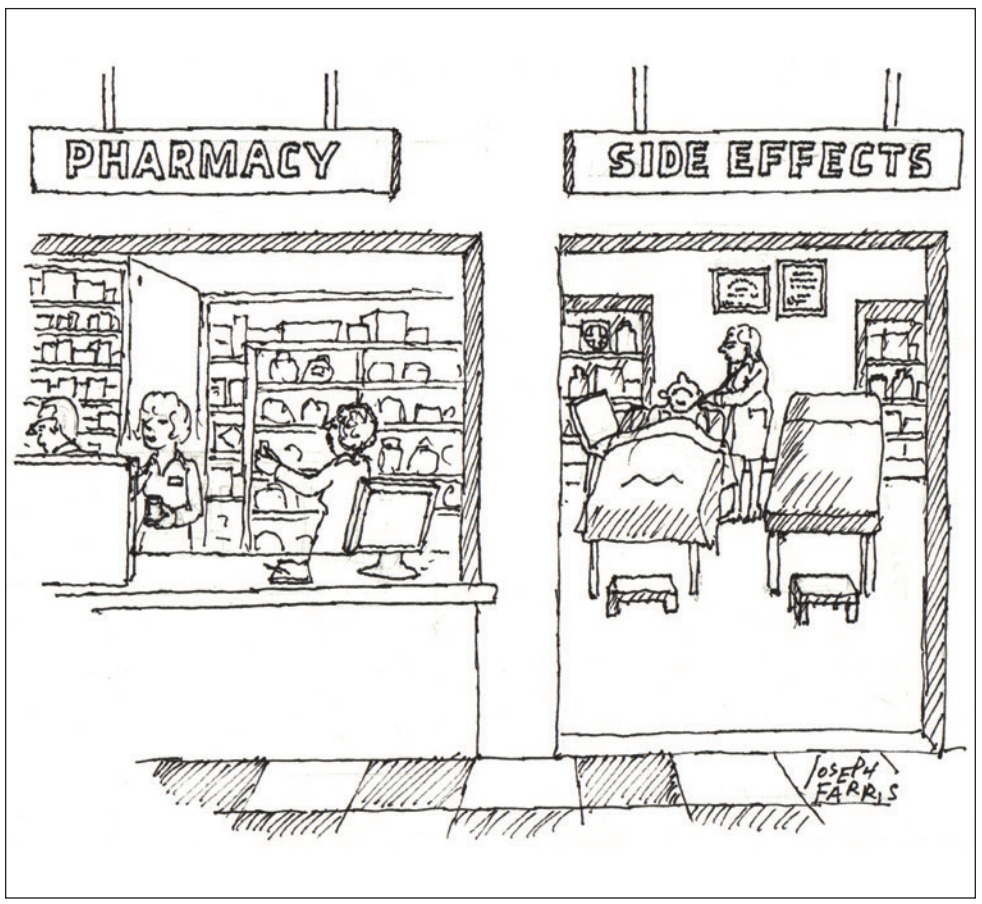



**Figure 3.** Payer/provider disconnects

that some of these costs are unavoidable, they question whether the increased spending generates improved outcomes or works to preserve the quality of remaining life. Is a patient best served by a complete exhaustion of curative options, or should palliative care play a larger role?

The payer/provider disconnect carries over to issues surrounding end-of-life care (Figure 3). In the sole point of agreement, both groups believe that hospice is most effective when the patient is enrolled for an extended period of time (more than 3 weeks). However, payers and providers answer very differently when asked if hospice programs are used at appropriate levels. Providers are neutral and payers believe that the programs are significantly underutilized.




**The payer/provider disconnect carries over to issues surrounding end-of-life care.**

There are two other striking points surrounding hospice care. First, payers believe that increasing hospice utilization would be an effective way to reduce oncology costs. Second, payers tend to believe that oncologists view hospice utilization as a failure or defeat. These two factors reinforce the role of the oncology nurse in ensuring that candid conversations about therapeutic options and treatment goals are taking place.

Payers are hesitant to push for expanded hospice utilization for fear of bad publicity. They do not want to be called out in the *Wall Street Journal* as an organization more committed to cost reduction than patient survival.

Conversely, oncologists also have significant motivation to delay hospice care. The standard private oncology practice business model relies heavily on drug revenue, which can account for up to three quarters of a practice's total revenue. A patient opting for palliative care represents a significant loss of potential income. While few oncologists are motivated primarily by money, perverse incentives do exist. It is worth questioning whether these incentives are keeping patients out of hospice programs that might be in the best interest of the patient or the patient's family.

Choice of a therapeutic regimen is typically more nebulous in oncology than other disease states. The disease is becoming more understandable and more treatable but there will continue to be a segment of patients who will die of cancer. For these patients, each will have his or her own definition of successful treatment. Some will push for exhaustion of curative options. Others will target making it to an important event, such as a grandchild's graduation or a son's wedding. Others will choose simply to stay as comfortable as possible, and to maximize the quality of the time they have left. In each instance, the care team must work to design a therapeutic regimen in keeping with the patient's goals.

In light of the often conflicting views voiced by payers and clinical oncologists, it is important that a cancer patient have an advocate to ensure that therapeutic decisions do not lose sight of the patient's interest. Whether the patient hopes to focus on quality of life and embrace the end, or fight through side effects and push for continued care, it is the oncology nurse who must work to elucidate these feelings, and promise that they be honored.

*Kirk McConnell is a senior analyst with The Zitter Group in San Francisco. He can be reached at kmcconnell@zitter.com.*

# Meetings

## FEBRUARY 2009

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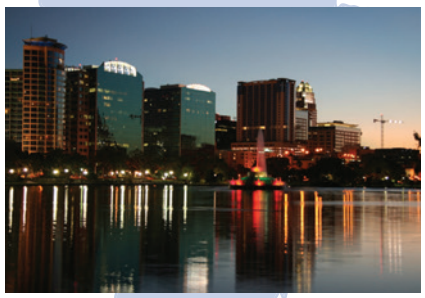
### 5 - 7 SCOTTSDALE, AZ
**4th Annual Community Oncology Conference**
**www.communityonc.com**

### 5 - 7 SAN DIEGO, CA
**11th International Symposium on Anti-Angiogenic Agents**
**www.antiangio2009.com**



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### 12 - 14 ORLANDO, FL
**10th National Conference on Cancer Nursing Research**
**www.ons.org**

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### 14 - 17 SAN DIEGO, CA
**29th Annual Clinical Hematology and Oncology Conference**
**www.scripps.org**

### 26 - 28 ORLANDO, FL
**2009 Genitourinary Cancers Symposium**
**www.asco.org**

## MARCH 2009

### 8 - 10 TAMPA, FL
**American Society of Preventive Oncology 33nd Annual Meeting**
**www.aspo.org**

### 11 - 15 HOLLYWOOD, FL
**NCCN 14th Annual Conference: Clinical Practice Guidelines & Quality Cancer Care**
**www.nccn.org**

### 14 - 18 LAS VEGAS, NV
**19th Annual National Interdisciplinary Breast Cancer Conference**
**www.breastcare.org**

# Leading patients toward improved outcomes

## You help patients reach their treatment goals

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

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

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

**RITUXAN is indicated for the treatment of patients with:**

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

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

**Please see brief summary of prescribing information on adjacent page.**

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

**BOXED WARNINGS and Additional Important Safety Information**

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

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