The Journal of Community Cancer Care

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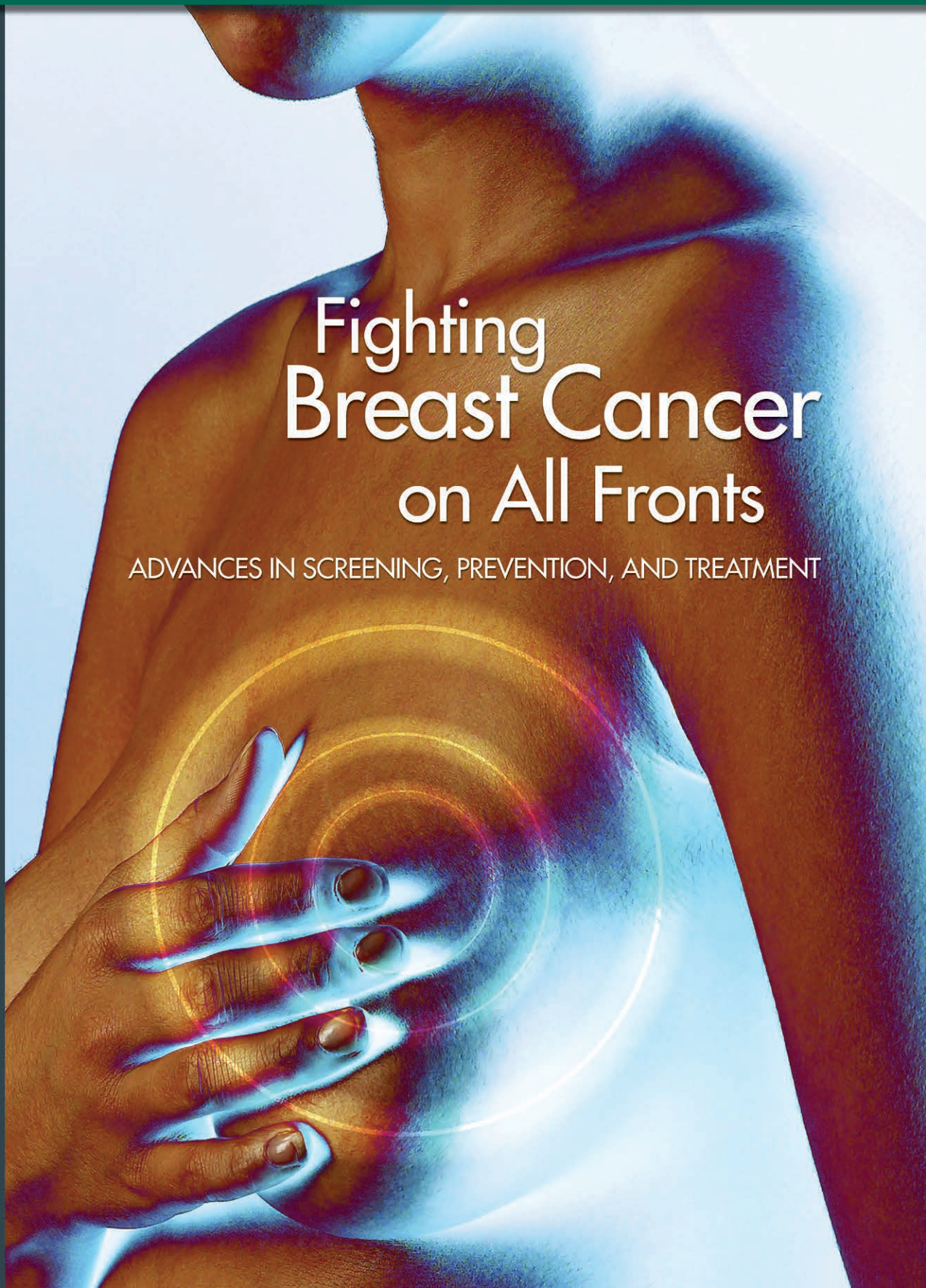


Fighting Breast Cancer on All Fronts

ADVANCES IN SCREENING, PREVENTION, AND TREATMENT

IN THIS ISSUE:

The Journal of Community Cancer Care

A publication of

COMMONWEALTH HEMATOLOGY-ONCOLOGY P.C.

Headquarters:
10 Willard Street
Quincy, MA 02169
617-479-3550
www.chomed.com

Commonwealth Hematology-Oncology (CHO) is New England's largest private practice cancer care group, with numerous offices and hospital affiliations throughout Massachusetts and in southern New Hampshire. Developed for primary care physicians and their medical and surgical colleagues, *The Journal of Community Cancer Care* is an educational resource with disease-specific issues covering the latest developments in cancer care.

FRONT LINES

Welcome to Our Journal

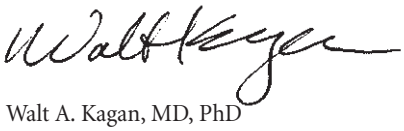
These are exciting and challenging times in the war against cancer. This excitement comes from the rapid development of more effective and less toxic drugs, as well as more advanced surgical procedures and radiation techniques that are improving survival rates and the quality of life for cancer patients. One of our many challenges is keeping up with the avalanche of new information and understanding how best to use this information in our own practices.

With this in mind, I am pleased to introduce you to *The Journal of Community Cancer Care*, a unique publication designed to inform busy, community-based primary care physicians and their medical and surgical colleagues about the latest developments in cancer care. This journal will provide timely educational material that is disease-specific, beginning with breast cancer in this premier issue.

While breast cancer survival rates have improved, this disease will claim the lives of more than 40,000 women in our country this year. More than 215,000 American women will learn they have breast cancer this year, with more than three-quarters of all cases occurring in women aged 50 and older. Women today are becoming more active partners in their medical treatment, but they still rely on their clinicians to manage their care.

To provide an optimal level of care, all members of our patients' medical team — PCPs, medical and surgical specialists, hospital administrators, and insurers — need to be updated about the topics featured in this journal: cancer prevention, screening, chemotherapy, targeted therapies, hormonal treatments, and technology that reduces chemotherapy errors.

We thank you for reviewing this material and visiting our web site, *www.chomed.com*, to find additional resources and download copies of our journal. We also thank our many colleagues and allied institutions for contributing to this publication. We look forward to sharing future editions with you as we collectively strive to provide world-class care that's close to home.



Walt A. Kagan, MD, PhD
President, Commonwealth Hematology-Oncology
Editor, *The Journal of Community Cancer Care*

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IN THIS ISSUE

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Chemoprevention

REDUCING THE RISK OF BREAST CANCER

By Susan A. Sajer, MD

Chemoprevention is a relatively new but exciting and effective strategy for reducing the incidence of breast cancer. Tamoxifen, used for more than 20 years for breast cancer treatment, was approved by the U.S. Food and Drug Administration (FDA) in October 1998 for reducing the incidence of breast cancer in women 35 years or older who are at elevated risk for the disease. Approximately two-thirds of breast cancers are estrogen receptor-positive (ER+), and their growth is enhanced by estrogen.

A selective estrogen-receptor modulator (SERM), tamoxifen works by binding to estrogen receptors in breast tissue and blocking the tumor-promoting activity of estrogen. Tamoxifen is known to mimic the effects of estrogen in tissues other than breast, contributing to some of the negative as well as positive side effects of the drug. Clinical researchers are comparing raloxifene, a SERM used to treat osteoporosis, with tamoxifen in a large clinical trial to determine which drug is better able to prevent breast cancer with the fewest side effects in postmenopausal women.

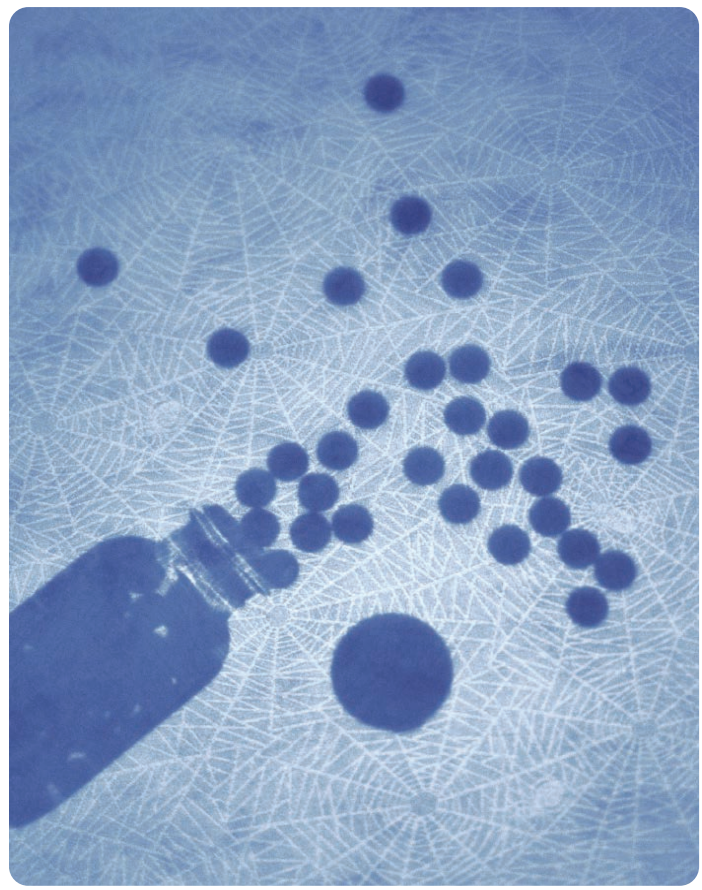
Tamoxifen

The first evidence of the chemopreventative properties of tamoxifen came from retrospective analysis of randomized, controlled clinical trials of adjuvant tamoxifen therapy in patients with breast cancer. This analysis showed that women taking tamoxifen developed fewer contralateral second primary breast cancers. This finding led to the 1992 launch of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) to test whether tamoxifen could prevent the development of breast cancer in healthy women at increased risk for the disease.

The BCPT was a randomized, double-blind, placebo-controlled clinical trial of healthy women 35 years or older with at least a 1.7% cumulative, five-year risk for developing breast cancer. Commonwealth Hematology-Oncology P.C. (CHO) was among the more than 500 sites to participate in the BCPT, which enrolled 13,388 premenopausal and postmenopausal women who met entry criteria for age and breast cancer risk.

Women in the trial were randomized to take either 20 mg of tamoxifen or a placebo daily for five years. After a median of 54.6 months of follow-up, BCPT researchers reported in 1998 that the incidence of invasive breast cancer was reduced by 49% in women taking tamoxifen compared with women taking placebo.[1]

Other benefits of tamoxifen included a 50% decreased risk of noninvasive breast cancer, a significant reduction in the diagnosis of benign breast conditions, a decreased incidence of breast biopsies, and a slight decrease in bony fractures. Negative side effects from tamoxifen were more severe in women 50 years and older who had an intact uterus than in younger women. The most common side effects were hot flashes and vaginal discharge. Other side effects included deep vein thrombosis, pulmonary embolism, and cataracts. Postmenopausal women, but not premenopausal women, had an increased risk of uterine malignancies, including endometrial cancer and, rarely, uterine sarcomas (1 per 500 patients per year).



Raloxifene

Raloxifene is a SERM used to treat osteoporosis that may help prevent the development of breast cancer in women at increased risk for the disease. Researchers with the Multiple Outcomes of Raloxifene Evaluation (MORE) study were the first to report a preventative effect of raloxifene on breast cancer development. The MORE study was designed to assess the anti-osteoporotic properties of raloxifene in postmenopausal women when taken for four years, compared with placebo.

After a median follow-up of 40 months, MORE researchers found that women taking raloxifene had an approximately 50% decreased incidence of invasive breast cancer compared with placebo. Raloxifene appeared to provide marked protection against ER+ but not ER- breast cancers. Side effects reported included hot flashes, influenza-like syndromes, endometrial cavity fluid, peripheral edema, and leg cramps. There were also increases in deep vein thrombosis and pulmonary emboli. There was, however, no increased risk reported for the development of endometrial cancer.

The NSABP initiated the Study of Tamoxifen and Raloxifene (STAR) in 1999 to compare five-year regimens of raloxifene and tamoxifen for reducing breast cancer incidence in postmenopausal women at high risk for the disease. The study enrolled 19,000 postmenopausal women 35 years or older at high risk for breast cancer. CHO was one of more than 500 STAR sites located in the United States, Puerto Rico, and Canada, and it successfully enrolled women from the Boston area. STAR researchers anticipate releasing data as early as 2006.

Aromatase Inhibitors

Aromatase inhibitors (AI) reduce the concentration of circulating estrogen in postmenopausal women and are effective for breast cancer treatment. Studies have shown that women taking AIs for the treatment of breast cancer developed fewer contralateral breast cancers. Currently, CHO is participating in a DFPCC study evaluating the AI letrozole (Femara®) in the prevention of breast cancer. This trial compares letrozole to placebo in high-risk postmenopausal women with elevated estradiol levels. Unlike tamoxifen and raloxifene, the AIs are not associated with an increased risk of uterine malignancies or clotting. They are associated with an increased risk of bone loss, so bone density is monitored closely in this study.

Breast Cancer Risk Assessment

Detailed guidelines for assessing a patient's risk for developing breast cancer are available in the National Comprehensive Cancer Network's Breast Cancer Risk Reduction Clinical Practice Guidelines in Oncology.[2] Risk assessment is based on several factors, including age, family history, and personal medical history. A qualitative risk assessment can be made for women who have a germline cancer susceptibility mutation, prior thoracic radiation, lobular carcinoma *in situ*, or a strong family history of breast cancer. Women who meet any of these criteria have an elevated risk of breast cancer and should be offered risk-reduction counseling, which includes discussion of the potential risks and benefits of tamoxifen therapy.

The web-based Gail model[3] can be used to estimate the breast cancer risk in women without qualitative risk factors. It uses patient-specific demographic characteristics to calculate five-year and lifetime levels of breast cancer risk. And for comparison, it calculates the average level of risk experienced by women of the same age and race. Women with a 1.7% or higher five-year risk for invasive breast cancer should be offered risk-reduction counseling. The Gail model should not be used to assess risk for women who have at least one family member diagnosed with breast cancer before the age of 50 years. The Claus model tables[4], which consider detailed family history, can be used instead.

The Genetics of Hereditary Breast Cancer Syndromes

There are three known hereditary syndromes that increase a woman's risk of developing breast cancer. Breast/ovarian cancer syndrome is associated with certain mutations in BRCA1 (BReast CAncer 1) or BRCA2 (BReast CAncer 2) genes. This syndrome is more prevalent in women of Ashkenazi Jewish ancestry and in some Netherlands and Icelandic populations. Women with these mutations have an increased risk of developing both breast and ovarian cancer, usually before menopause.

Li-Fraumeni syndrome is a rare condition that in most families is caused by a mutation of the tumor suppressor gene p53 (TP53). This syndrome predisposes patients to childhood sarcomas, brain tumors, leukemia, lung cancer, and adrenocortical carcinomas, in addition to premenopausal breast cancer.

Cowden syndrome is also rare and is associated with mutations of the tumor suppressor gene PTEN. Patients with this syndrome tend to develop characteristic skin lesions; breast, endometrial, and gastrointestinal cancers; and thyroid and cerebellar tumors. Women who have a family member known to have a mutation in a breast cancer-susceptibility gene, one or more family members who developed breast cancer before the age of 40 years, a family history of multiple cases of breast and/or ovarian cancer, Ashkenazi Jewish ancestry, or multiple cancers characteristic of Li-Fraumeni syndrome or Cowden syndrome, as well as women with early onset breast cancer, should be offered genetic counseling, including risk/benefit assessment of genetic testing for suspected mutations.

The web-based Gail model can be used to estimate the breast cancer risk in women without qualitative risk factors. It uses patient-specific demographic characteristics to calculate five-year and lifetime levels of breast cancer risk.

Risk-Reducing Surgery

Retrospective analysis has shown bilateral prophylactic mastectomy to decrease the risk of breast cancer by up to 90% in moderate-risk to high-risk women. However, because of the potential negative psychosocial effect, this procedure should be limited to women at very high risk for invasive breast cancer, such as patients with lobular carcinoma *in situ* or germline breast cancer susceptibility mutations.

Women with BRCA1 and BRCA2 mutations are at increased risk for both ovarian and breast cancer. Due to the absence of reliable methods of early detection for ovarian cancer and the poor prognosis associated with advanced ovarian cancer, women are advised to undergo bilateral prophylactic salpingo-oophorectomy after childbearing. Several studies in carriers of BRCA1 or BRCA2 mutations have demonstrated the effectiveness of prophylactic oophorectomy in preventing ovarian cancer. In addition, the risk of breast cancer was reduced by up to 50%, depending on the age of surgical menopause. Before choosing risk-reducing surgery, patients should undergo multidisciplinary counseling to help them assess the risks and benefits of prophylactic surgery and other prevention strategies.

Lifestyle Modifications

Although there is no sure way to avoid breast cancer, some healthy lifestyle choices may help lower breast cancer risk and, additionally, lower the risk of heart disease, diabetes, colon cancer, and osteoporosis. These include regular physical activity, maintaining a healthy weight, reducing consumption of saturated and trans fats, increasing consumption of polyunsaturated and monounsaturated fats, taking a multivitamin with folic acid, limiting alcohol intake to less than one alcoholic beverage per day, and choosing to breastfeed children. JCCC

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Susan A. Sajer, MD, *an oncologist at Commonwealth Hematology-Oncology's Concord office, is affiliated with New England Medical Center and Emerson Hospital, where she is the Chairperson for the Cancer Care Committee and a Principal Investigator for Cancer and Leukemia Group B. Dr. Sajer received her medical degree from Jefferson Medical College in Philadelphia and her Bachelor of Science degree from Lehigh University in Bethlehem. Board certified in hematology, medical oncology, and internal medicine, Dr. Sajer is an Assistant Professor of Medicine at Tufts University School of Medicine and a member of the American Medical Association, the American Society of Hematology, the American Society of Clinical Oncology, the Massachusetts Medical Society, and the Massachusetts Society of Clinical Oncology.*

Breast Cancer Screening Guidelines

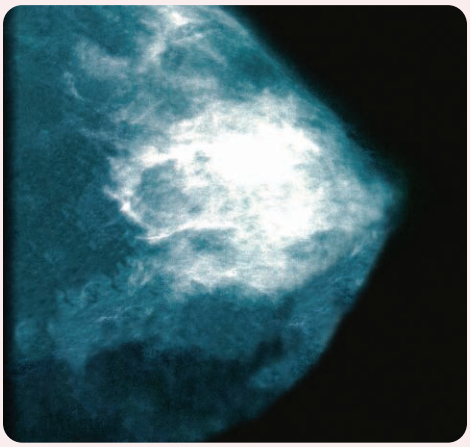
RECOMMENDATIONS EMPHASIZE EARLY DETECTION

By Sarah K. May, MD

The risk of developing breast cancer in the United States has reached a steady state with roughly 200,000 new cases detected each year. Approximately 20% of these patients are predicted to die from the disease.[1] In spite of these alarming numbers, breast cancer mortality has been decreasing somewhat in recent years due to new technologies and an increased emphasis on early detection. It remains the second leading cause of death from cancer among American women.[1,2]

Breast Cancer Guideline Controversies

Despite almost universal agreement that screening and an early, accurate evaluation of breast abnormalities saves lives, screening guidelines as developed by the National Comprehensive Cancer Network (NCCN)[2] and the American Cancer Society (ACS)[3] for the diagnosis of breast cancer are continually changing and, at times, controversial.



Modeling studies of the benefits of annual mammography screening in women aged 40 to 49 years estimated a long-term 30% to 40% decrease in breast cancer mortality.

Breast self-examination (BSE) has been the subject of a number of studies that have reached conflicting conclusions, particularly when decreased mortality is the endpoint. A large, 10-year BSE screening study has shown that there was no significant difference in the cumulative breast cancer mortality rates between a group of patients given instructions for BSE and a control group given no instructions. However, a higher number of benign lesions were detected by the women in the BSE group, leading some to speculate that BSE does not assist in diagnoses and may lead to higher levels of worry, depression, and anxiety.

Although there is agreement between the ACS and the National Cancer Institute (NCI) on the benefits of breast cancer screening, the interval of screening remains controversial. The ACS and NCCN guidelines recommend yearly mammograms for women 40 years and older. Other studies suggest an interval of every one to two years for women aged 50 to 74 years.

According to the U.S. Preventive Services Task Force, the potential benefits of annual mammography increase as a woman ages and the likelihood of harm from false-positive results decreases from the ages of 40 to 70 years; thus it recommends a screening interval of one to two years for women aged 40 to 49 years and annually thereafter. These intervals have been generally adopted by most guidelines.[2, 3, 4]

Recent metaanalysis of the accuracy of screening mammography reported a true positive rate ranging from 83% to 95% and a false-positive rate ranging from 0.9% to 6.5%. Modeling studies of the benefits of annual mammography screening in women aged 40 to 49 years estimated a long-term 30% to 40% decrease in breast cancer mortality. Though not considered a stand-alone screening tool, it remains the mainstay for breast cancer screening.

Recommendations for Average-Risk Women

The ACS 2005 guidelines place a strong emphasis on the role of the health care professional in raising and regularly reinforcing awareness about breast cancer, early breast cancer detection, and the importance of prompt reporting of any new symptoms. For women at normal risk between the ages of 20 and 39 years, a clinical breast examination (CBE) is recommended every one to three years, with periodic BSEs between CBEs.

The CBE should be utilized to assess risk, to raise awareness of breast symptoms and the importance of early detection, and to review the patient's technique for BSE. For women aged 40 and older, annual CBE and screening mammography are recommended, with periodic BSEs encouraged. These annual screenings are recommended as long as the patient is in good health and a candidate for treatment.

Recommendations for High-Risk Women

While breast cancer screening guidelines can be applied broadly to the general population, patients who are at increased risk should be identified through formal risk assessment. Women at increased risk for breast cancer may benefit from earlier initiation of screening, screening at shorter intervals, and screening with additional modalities such as ultrasound or MRI.

Significant risk factors include inherent genetic mutations (BRCA1 or BRCA2), a personal history of breast cancer (lobular carcinoma *in situ*, or LCIS), and two or more first-degree relatives with breast cancer diagnosed at any age. Lesser but still significant risk factors include one first-degree relative with breast cancer, nodular densities on a mammogram, and atypical hyperplasia.[1, 2, 3]

For women aged 25 years or younger in the high-risk group, annual CBEs are recommended and periodic BSEs are encouraged. For women aged 26 years or older, annual mammograms and CBEs every six to 12 months are recommended. CBEs every six to 12 months and annual mammography with optional BSEs are recommended for women 35 years of age or older with a risk factor greater or equal to 1.7% based on the NCI's Gail model.[5] The Gail model assesses a woman's risk of developing breast cancer using computerized probabilities derived from specific patient demographic characteristics.

Other specific risk factors that drastically increase the risk of breast cancer compared with the general population are prior exposure to irradiation at a young age (75 times greater risk), women with LCIS (approximately eight to 10 times greater risk), or women with atypical hyperplasia (a fourfold to fivefold increase in relative risk). These women should receive an annual mammogram and CBEs every six to 12 months with BSEs encouraged, and should also consider chemoprevention.[2]

Role of MRI in Screening High-Risk Women

Several studies have compared the effectiveness of CBE, ultrasound, mammography, and MRI in high-risk women. The use of MRI was reported to detect significantly more incidences of invasive breast cancer compared with mammography (2:1), ultrasound (2:1), and CBE (4:1). More importantly, MRI was superior to mammography

For women aged 25 years or younger in the high-risk group, annual CBEs are recommended and periodic BSEs are encouraged.

in finding tumors smaller than 1 cm and detecting cancerous tissue while it was still localized to the breast.

When all four screening methods were used, sensitivity increased to 95% compared with 45% for mammography combined with CBE. Although MRI screening offers increased sensitivity, the decreased specificity, cost, duration of the examination, and injection of contrast material prohibit its use as a routine, population-based screening technique.

Conclusion

Breast cancer screening programs are controversial at the present time. The effectiveness of these programs may be buffered by a variety of demographic factors, including age and ethnic, social, and educational background. There are several areas where breast cancer imaging practices can be improved, namely in reducing over-treatment of potentially nonlethal cancers, in monitoring the effectiveness of nonsurgical therapies, and in guiding noninvasive therapies.

The current guidelines place a strong emphasis on the role of the health care professional in raising and regularly reinforcing awareness about breast cancer, early breast cancer detection, and the importance of prompt reporting of any new symptoms. Women are encouraged to make informed choices. JCCC

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Sarah K. May, MD, *an oncologist at Commonwealth Hematology-Oncology's Quincy office, is affiliated with Milton Hospital, Quincy Medical Center, Carney Hospital in Dorchester, and the New England Sinai Hospital and Rehabilitation Center in Stoughton. Dr. May received her medical degree from Tufts University School of Medicine and her Bachelor of Arts degree from Oberlin College in Ohio. She is board certified in medical oncology and hematology, and she is a Diplomate of internal medicine with the American Board of Internal Medicine. A faculty member at Tufts University School of Medicine and the Boston University School of Medicine, Dr. May is also a member of the American Society of Clinical Oncology and the Massachusetts Society of Clinical Oncology.*

Hormonal Therapy

SEARCH CONTINUES FOR TAMOXIFEN ALTERNATIVES

By Carmen L. Pisc, MD

For more than 25 years, tamoxifen has been the gold standard for the endocrine treatment of all stages of estrogen receptor-positive (ER+) breast cancer. Approved in the United States in 1977 for the treatment of advanced breast cancer in postmenopausal women and in 1998 for reducing the incidence of breast cancer in women at high risk for the disease, tamoxifen therapy is credited with saving the lives of more than 400,000 women. As the first nonsteroidal anti-estrogen developed for clinical use, tamoxifen has proved to be a pioneering medicine with ubiquitous applications as an endocrine therapy for breast cancer.

Tamoxifen is a selective estrogen-receptor modulator (SERM), and it has anti-estrogenic action on the breast and estrogenic agonistic action on the bones and circulating cholesterol. Despite protective action against bone loss and elevated blood cholesterol levels, tamoxifen therapy is not without major concerns. In the mid-1980s, tamoxifen was found to enhance the growth of endometrial cells, and it was predicted to increase the risk of endometrial cancer in postmenopausal women.

Further, recent studies indicate that 50% of recurrent ER+ cancers are resistant to tamoxifen. Thus, although tamoxifen remains the initial endocrine treatment of choice for premenopausal women who have advanced disease and postmenopausal women who are intolerant of the newer aromatase inhibitor (AI) therapies, the search continues for additional hormonal therapies.

Aromatase Inhibitors

AIs represent a new class of drugs that act by inhibiting aromatase, a cytochrome P450 enzyme that catalyses the conversion of androgens to estrogens in body fat; liver, breast, and muscle cells; and breast tumor tissue. The AIs reduce the synthesis and the output of estrogen in postmenopausal women, resulting in a marked decrease in the level of circulating estrogen. The third-generation AIs, which include the nonsteroidal agents anastrozole (Arimidex®) and letrozole (Femara®) and the steroidal compound exemestane (Aromasin®), are the most recent to become available.

Anastrozole and letrozole have been studied extensively in women with metastatic breast cancer and are approved by the U.S. Food and Drug Administration (FDA) for the first-line and second-line treatment of hormone receptor-positive metastatic breast cancer. Two phase III clinical trials have assessed the efficacy of anastrozole over tamoxifen as a first-line therapy in postmenopausal women with advanced breast cancer.

In the two trials, which were similar in design and prospectively designed for combined analysis,[1] anastrozole showed superior efficacy to tamoxifen in terms of time-to-progression (TTP) in patients with hormone receptor-positive tumors in addition to a number of tolerability benefits. Results of the only phase III trial assessing the efficacy of letrozole versus tamoxifen[2] in postmenopausal women with advanced breast cancer showed letrozole to be superior to tamoxifen with respect to TTP (both overall population and patients with hormone receptor-positive tumors), objective response, and clinical benefit rates (overall population).

Exemestane is a steroidal aromatase inactivator approved in the United States for hormonal therapy for women with metastatic breast cancer after disease progression with an anti-estrogen. A phase III randomized trial has demonstrated the superiority of exemestane over tamoxifen as a first-line treatment in terms of progression-free survival.[3] Preclinical studies have suggested that it may have a different toxicity profile than the nonsteroidal agents; however, these findings have not been confirmed by clinical studies.

Adjuvant Therapy

Because of their efficacy and safety as first-line and second-line therapies in advanced disease settings, the third-generation AIs are now being evaluated as adjuvant therapies. Four phase III, randomized, adjuvant trials have assessed the third-generation AIs compared with tamoxifen or placebo after five years or less of tamoxifen therapy: The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial, the Italian (ITA) Trial, the Intergroup Exemestane Study (IES), and the MA-17.

In the ATAC trial, more than 9,000 postmenopausal women were randomly assigned to treatment with anastrozole plus placebo, tamoxifen plus placebo, or anastrozole plus tamoxifen. After a median follow-up of 47 months, treatment with anastrozole resulted in a significant reduction of breast cancer events and an improvement in disease-free survival compared with treatment with tamoxifen. There was no difference in disease-free survival between the combination arm and the tamoxifen arm. After six years, anastrozole still shows further reduction in second breast cancers.

In the IES trial, 4,742 women who had received two to three years of tamoxifen were randomly assigned to either continue tamoxifen for a total of five years or switch to exemestane to complete their five-year courses of hormonal therapy. After a median follow-up of 37.4 months, switching to exemestane resulted in significantly superior disease-free survival (Hazard Ratio [HR]: 0.73; p=0.0001), breast cancer-free survival (HR: 0.70; p=0.00005), and time to second breast cancer (HR: 0.50; p=0.04). Overall survival favored switching to exemestane (HR: 0.83; p=0.08).

The MA-17 trial enrolled 5,187 postmenopausal women who had completed five years of tamoxifen therapy and were disease-free at the beginning of the study. Subjects were randomly assigned to receive either letrozole or placebo for an additional five years. The study was halted after a median follow-up of 2.4 years because of a significant reduction in breast cancer events in patients treated with letrozole.

Fulvestrant

A relatively new addition to the inventory of endocrine therapies is the estrogen receptor antagonist fulvestrant (Faslodex®), which entered clinical development after preclinical studies suggested that it was active in tamoxifen-resistant breast cancers. Fulvestrant blocks the trophic actions of estrogen without exerting any partial agonist effects. It completely binds to the estrogen receptor with a much greater affinity than tamoxifen, preventing estrogen-receptor dimerization, inhibiting estrogen-receptor DNA binding, and leading to down-regulation of estrogen-regulated genes.

Two large, phase III trials (Trial 0021: North American and Trial 0020: Rest of World [Europe, South Africa, Australia]) have compared the efficacy and tolerability of fulvestrant with anastrozole in postmenopausal women with advanced breast cancer that had progressed on prior endocrine treatment (mainly tamoxifen). Patients were randomly assigned to receive either 250 mg of fulvestrant by monthly injection or a daily 1-mg dose of oral anastrozole. Patients continued treatment until disease progression or withdrawal.

In the North American trial (n=400), after a median follow-up of 16.8 months, fulvestrant was found to be as effective as anastrozole in terms of TTP (fulvestrant 5.4 months; anastrozole 3.4 months; HR: 0.92; 95% confidence interval [CI]: 0.74-1.14; p=0.043). Median duration of response (DOR; from randomization to progression) was 19.0 months for fulvestrant compared with 10.8 months for anastrozole. An analysis using all randomized patients showed the mean DOR was significantly greater for patients treated with fulvestrant compared with those treated with anastrozole.

In the Rest of World (open) trial, patients (n=451) were randomly assigned to receive either fulvestrant (5 mL intramuscular injection) or oral anastrozole. After a median follow-up of 14.4 months, fulvestrant was shown to be at least as effective as anastrozole in terms of TTP (HR: 0.98; 95% CI: 0.80-1.21; p=0.84). Median TTP was 5.5 months for fulvestrant and 5.1 months for anastrozole.

A prospective, combined analysis of the results of two phase III, multicenter, clinical trials in patients progressing on a prior anti-estrogen showed fulvestrant to be at least as effective as anastrozole in terms of TTP and overall survival. Fulvestrant is therefore at least as effective as anastrozole in the second-line treatment of postmenopausal women with advanced breast cancer.

Fulvestrant completely binds to the estrogen receptor with a much greater affinity than tamoxifen, preventing estrogen-receptor dimerization, inhibiting estrogen-receptor DNA binding, and leading to down-regulation of estrogen-regulated genes.

The American Society of Clinical Oncology Technical Assessment on the Use of Aromatase Inhibitors as Adjuvant Therapy for Postmenopausal Women With Hormone Receptor-Positive Breast Cancer: 2004 Status Report4 recommends the following:

> "Based on the results from multiple, large randomized trials, adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence. Neither the optimal timing nor duration of aromatase inhibitor therapy is established. Aromatase inhibitors are appropriate as initial treatment for women with contraindications to tamoxifen. For all other postmenopausal women, treatment options include five years of aromatase inhibitor treatment or sequential therapy consisting of tamoxifen (for either two, three, or five years) followed by aromatase inhibitors for two to three or five years. Patients intolerant of aromatase inhibitors should receive tamoxifen. There are no data on the use of tamoxifen after an aromatase inhibitor in the adjuvant setting. Women with hormone receptor-negative tumors should not receive adjuvant endocrine therapy. The role of other biomarkers such as progesterone receptor and HER2 [human epidermal growth factor receptor 2] status in selecting optimal endocrine therapy remains controversial. Aromatase inhibitors are contraindicated in premenopausal women; there are limited data concerning their roles in women with treatment-related amenorrhea. The side effect profiles of tamoxifen and aromatase inhibitors differ. The late consequences of aromatase inhibitor therapy, including osteoporosis, are not well characterized."

Though treatment advances for breast cancer continue, women and their physicians must weigh the risks and options of all therapeutic approaches thoroughly. JCCC

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Carmen L. Pisc, MD, *an oncologist at Commonwealth Hematology-Oncology's Haverhill office, is affiliated with Merrimack Valley Hospital in Haverhill, Anna Jacques Hospital in Newburyport, Lawrence General Hospital in Lawrence, and Caritas Holy Family Hospital in Methuen. Dr. Pisc received her medical degree from Carol Davila Medical School in Bucharest, Romania. She was a resident in internal medicine at the University of Massachusetts Memorial Medical Center in Worcester, a Fellow in endocrinology at District Hospital in Romania, a Postdoctoral Fellow at the Massachusetts General Hospital Cancer Center, and a Fellow in hematology-oncology at the University of Massachusetts Memorial Health Care university campus in Worcester. Board certified in internal medicine and board eligible in medical oncology and hematology, Dr. Pisc is a member of the American College of Physicians.*

Targeted Cancer Therapies

EXAMINING THE DEVELOPMENT AND MOLECULAR CHARACTERISTICS OF TARGETED AGENTS

By Vijay Kasturi, MD

Many medical and scientific experts anticipate the imminent arrival of an era of personalized medicine in which individualized cancer treatments will be based on the molecular features of a patient's disease. It is now known that histologically similar cancers, previously considered one disease, may be comprised of multiple molecular subclasses that respond differently to various treatments. One of the most obvious examples is breast cancer. Two histologically identical tumors will respond differently based on the presence or absence of estrogen receptors.

Recent rapid advances in the science and technology of molecular genetics and molecular oncology are generating increasingly detailed knowledge of the molecular pathways that contribute to the initiation and progression of cancer. This knowledge is providing the basis for the development of patient-specific, targeted therapies to kill or arrest the growth of cancer cells with minimal harm to healthy tissues.

Targeted anticancer therapies are designed to disrupt molecular attributes of cancer cells that are critical to the malignant phenotype and, ideally, not present in vital organs and tissues. However, many agents target molecular features that are present in healthy tissue but usually to a lesser degree than in tumor tissue.

More than a dozen agents that target specific molecular attributes of various cancers have been approved by the U.S. Food and Drug Administration (FDA), and several hundred more are in preclinical or clinical trials. These targeted agents are generally one of two types: anticancer antibodies and small-molecule drugs. Anticancer antibodies bind with high affinity to specific molecular features of cancer cells and initiate cell death by various mechanisms. Small-molecule drugs are designed to interfere with the function of proteins integral to the growth of cancer cells.

Many of these agents have received FDA fast-track approval, which is usually based on surrogate markers of survival, such as time-to-progression (TTP) or tumor volume. In these cases, the FDA requires follow-up clinical testing to determine whether the therapy prolongs patient survival and to demonstrate that the potential therapeutic benefits outweigh the risks.

Some of the molecular targets of agents approved by the FDA include tyrosine kinases (TKs), components of the human epidermal growth factor receptor (HER) signaling pathway, and vascular endothelial growth factor (VEGF). For a summary of the features of each of these targets, see Table 1. Targeted agents cause cancer cell death by a variety of mechanisms, including apoptosis (programmed cell death) and inhibition of angiogenesis. The mechanism of cell death caused by some targeted agents is not known. This article summarizes the development and molecular characteristics of many of the FDA-approved targeted agents.

Tamoxifen and Other Anti-Estrogen Agents

The prototype for molecularly targeted cancer drugs can be said to be tamoxifen therapy for estrogen receptor-positive (ER+) breast cancer. Tamoxifen is a selective estrogen-receptor modulator (SERM) that has been used to treat ER+ metastatic breast cancer since the 1970s and is also used as a surgical adjuvant in early-stage ER+ breast cancer. Approximately two-thirds of breast cancers are hormone sensitive and grow more aggressively in the presence of estrogen.

Tamoxifen binds to estrogen receptors in breast tissue, blocking estrogen from activating the molecular pathways that lead to cell proliferation. Because tamoxifen mimics estrogen in other tissues, this drug has several rare but serious side effects, including increased incidence of endometrial cancer, deep vein thrombosis, and pulmonary embolism.

Researchers are searching for other anti-estrogen agents that may work as well as or better than tamoxifen and with fewer serious side effects. Promising candidate drugs include the SERM raloxifene and several aromatase inhibitors (AI). AIs act by blocking the conversion of androgens to estrogens in peripheral tissues, the main source of estrogen in postmenopausal women. Three AIs, anastrozole (Arimidex®), exemestane (Aromasin®), and letrozole (Femara®), as well as the estrogen receptor antagonist fulvestrant (Faslodex®) have been approved by the FDA for the treatment of breast cancer in postmenopausal women. Although AIs do not appear to increase risk for endometrial cancer, they may contribute to the development of osteoporosis.

Trastuzumab (Herceptin®)

Trastuzumab is a humanized monoclonal antibody that binds to the HER2 protein, which is overexpressed in approximately 25% to 30% of primary breast cancers. Trastuzumab mediates antibody-dependent cellular cytotoxicity, preferentially killing HER2-overexpressing cancer cells.

Clinical testing has shown trastuzumab to benefit patients with metastatic breast cancer who have experienced disease progression following one or two treatments of chemotherapy and whose primary tumors overexpress HER2. When given in combination with chemotherapy, (anthracycline plus cyclophosphamide or paclitaxel), trastuzumab improved median TTP, overall response rate, and median survival in comparison with chemotherapy alone. Another clinical trial showed that trastuzumab therapy alone elicited at least a partial response in 14% of patients.

The FDA granted fast-track approval to trastuzumab in 1998 as a second-line or third-line treatment of metastatic breast cancer in patients shown to overexpress HER2 in primary tumors. Serious side effects of trastuzumab include ventricular dysfunction, congestive heart failure, hypersensitivity reactions, and sometimes-fatal pulmonary events. Other reported adverse events

include anemia, leukopenia, diarrhea, infection, infusion reactions, and rare cases of nephrotic syndrome associated with glomerulopathy.

Early clinical trial results have shown the safety and efficacy of trastuzumab given in combination with paclitaxel as a presurgical treatment for early-stage breast cancers. One pilot study demonstrated a dramatically improved pathologic complete response rate in women with HER2 positive stage II or stage III breast cancer who were treated with trastuzumab plus paclitaxel, compared with women receiving chemotherapy alone. Phase II trials testing trastuzumab in combination with docetaxel and carboplatin have also shown promising results. Multiple phase III trials of trastuzumab therapy for HER2-positive early-stage breast cancer are in progress.

Recently, results of two large randomized phase III clinical trials testing the use of trastuzumab in combination with standard adjuvant chemotherapy (Adriamycin and Cytoxan followed by Paclitaxel) for high-risk, node-negative and node-positive patients with breast cancer were reported. In a pooled analysis of 3,351 patients, trastuzumab reduced the risk of tumor recurrence by 55%. This translated into a four-year, disease-free survival rate of 85% with the addition of trastuzumab to chemotherapy compared with 67% with chemotherapy alone. The results of these North American trials were confirmed by another worldwide clinical trial with a recurrence risk reduction on the order of 50%. Thus, trastuzumab is now standard therapy in both adjuvant and metastatic breast cancer for HER2-positive patients.

Lapatinib

A new class of targeted agents now is being developed that inhibit multiple HER receptors. Lapatinib is a small-molecule inhibitor of the TK of both HER1 and HER2. It has a significantly longer half-life than either gefitinib or erlotinib. One study in patients with previously treated metastatic breast cancer has shown a 13% response rate. Another study has shown a 30% clinical benefit rate in patients with trastuzumab-refractory metastatic breast cancer. Several phase III trials are underway combining lapatinib with chemotherapy compared with chemotherapy alone in advanced breast cancer.

Bevacizumab (Avastin®)

Bevacizumab was the first antiangiogenic cancer treatment to receive FDA approval. This humanized, monoclonal antibody received fast-track FDA approval in February 2004. Bevacizumab binds to VEGF, a protein that normally stimulates angiogenesis at times of tissue growth, such as during pregnancy or wound healing. This protein is also needed to supply tumors with new blood vessels required for continued growth. Bevacizumab prevents VEGF from interacting with the VEGF receptor, thus inhibiting the activation of angiogenesis.

Clinical trials have shown that bevacizumab, given in combination with standard therapy of ironotecan, leucovorin, and 5-fluorouracil (ILF), improved survival by approximately five months in patients with metastatic colorectal cancer compared with patients receiving ILF therapy alone. Clinical trials are testing the efficacy of bevacizumab in combination with other therapies for treatment of breast, prostate, pancreatic, head and neck, renal cell carcinoma, melanoma, and other cancers. Some researchers anticipate that recent improvements in technologies to detect angiogenesis may improve the assessment of patient response to this drug in early-stage clinical trials.

Recently, results of a randomized trial comparing chemotherapy (paclitaxel) to chemotherapy plus bevacizumab as first-line chemotherapy for patients with locally recurrent or metastatic breast cancer were reported. Significantly, response rates were improved from 14% to 28%, and progression-free survival improved from a median of 6.1 months to 11 months. Overall survival was significantly improved by approximately 32%. Side effects of bevacizumab include gastrointestinal perforation, impaired wound healing, hemorrhage, infusion reactions, congestive heart failure, nephritic syndrome, thromboembolism, myocardial infarction, angina, proteinuria, and a variety of other adverse events usual to cytotoxic chemotherapy. Hypertension was common in patients receiving bevacizumab in clinical trials.

Cetuximab (Erbitux®)

Cetuximab is a recombinant human/mouse monoclonal antibody that binds to EGFR. This protein is expressed in many normal epithelial cells and is often overexpressed in colorectal and other cancer cells. The binding of cetuximab to EGFR blocks growth factor activation of the receptor. This binding inhibits activation of a cellular proliferation signaling pathway and also induces apoptosis.

The FDA gave fast-track approval to cetuximab in February 2004 for use in combination with the chemotherapeutic drug irinotecan to treat patients with metastatic colorectal cancers that have progressed despite prior chemotherapy. Only patients with confirmed overexpression of EGFR in primary tumors are eligible for treatment with cetuximab. Although clinical trial data show that cetuximab can shrink tumors in some individuals

TABLE 1. MOLECULAR TARGETS OF CANCER THERAPY

Tyrosine Kinases (TKs): TKs belong to a class of enzymes that regulate molecular pathways controlling cell growth. The phosphorylation of tyrosine by TKs activates cellular events leading to proliferation. There are many TKs, each associated with one or more signaling pathways. Some cancers are caused by errors in one of these pathways. For example, chronic myelogenous leukemia (CML) is commonly caused by a genetic translocation that results in the Bcr-Abl TK gene which produces an enzyme that continuously stimulates cell proliferation. Other commonly targeted TKs include those associated with the proteins c-kit, PDGF, and FLT3. Targeted cancer agents that inhibit TKs include imatinib and erlotinib.

Human Epidermal Growth Factor Receptor (HER) Signaling Pathway: The HER signaling pathway is a critical regulator of normal cell growth. Epidermal growth-factor receptor (EGFR) is one component of this pathway that is overexpressed in many cancer cells, contributing to excess proliferation. Gefitinib and cetuximab are two anticancer agents that disrupt the activity of EGFR. Trastuzumab targets HER2, a component of the HER signaling pathway that is overexpressed in some breast cancers.

Vascular Endothelial Growth Factor (VEGF): VEGF is known to stimulate angiogenesis to meet perfusion requirements at times of tissue growth such as during pregnancy or wound healing. However, angiogenesis is also required for the continuing growth of tumors. Bevacizimab targets VEGF to prevent the formation of new blood vessels needed to supply growing tumors.

Proteasomes: Proteasomes are large cellular protein complexes that help break down proteins tagged by the cell for destruction. Disruption of cell homeostasis through proteasome inhibition often results in cell death. Bortezomib is a proteasome inhibitor.

Hormone Receptors: Hormone receptors are proteins residing in the cytoplasm of cells that are capable of binding hormones such as estrogen and progesterone and directly activating gene transcription. Tamoxifen and aromatase inhibitors (AIs) such as Arimidex, Femara, and Aromasin are selective estrogen receptor modulators (SERMs).

TABLE 2. SELECTED CANDIDATE TARGETED CANCER AGENTS IN CLINICAL TRIALS

Drug/Source	Drug Type	Target(s)	Mode of Action	Disease	Clinical Trial Phase
SU11248/ Pfizer, New York, NY	Small molecule	RTKs	Antiangiogenesis	Refractory GIST	III
				Metastatic renal clear-cell carcinoma	III
				Metastatic NSCL	II
				Metastatic Breast Cancer	II
				Metastatic colorectal cancer	II
				Neuroendocrine tumors	II
PKC412/ Novartis	Small molecule	RTKs/FLT3 protein	Antiangiogenesis, other	AML	II/I
MLN518/ Millennium	Small molecule	RTKs	Other	Relapsed or refractory AML	II/I
MLN2704/ Millennium	Monoclonal antibody conjugated with the drug maytansinoid	PSMA	Targeted delivery of chemotherapeutic drug	Metastatic androgen-independent prostate cancer	II/I
ZD6474/ Astra Zeneca	Small molecule	EGFR/VEGF	Antiangiogenesis	Advanced or metastatic NSCLC	II
				Small-cell lung cancer	II
				Thyroid cancer	II
Oblimersen (Genesense®)/ Genta, Berkeley, CA	Small molecule	Bcl-2 protein	Apoptosis inducing	AML	III
				B cell NHL	II/I
				Advanced or metastatic breast cancer	II/I
				Advanced esophageal or gastric cancer	II/I
				Small-cell lung cancer	II
				Hepatocellular carcinoma	II
				Relapsed or refractory multiple myeloma	II
				Unresectable GIST	II
				Hormone refractory prostate cancer	II
Lapatinib	Small molecule	RTK	Antiangiogenic	Metastatic breast cancer, renal, lung, bladder, gastric cancers	
Lasofoxifene	SERM	Estrogen receptor	Estrogen receptor modulator	Prevention of breast cancer	III
Pertuzumab	Monoclonal antibody	ERBB2	EGFR inhibition	Metastatic breast cancer, ovarian, lung	II
Zarnestra	Small molecule	Ras	Farnesyltransferase inhibitor (FTI)	Metastatic breast cancer	II
Sorafenib	Small molecule	Raf	FTI, Antiangiogenesis	Metastatic renal, breast, melanoma	II/III

in this patient population, it is not yet known whether the drug will improve survival. Dermatologic toxicities were common in clinical studies of cetuximab. Other reported adverse events include infusion reactions, pulmonary toxicity, fever, sepsis, kidney failure, breathing difficulties, low blood pressure, dehydration, and diarrhea. A clinical trial of cetuximab in combination with chemotherapy for patients with refractory metastatic breast cancer is now underway.

Gefitinib (Iressa®)

Gefitinib is a small-molecule drug that targets the epidermal growth factor receptor (EGFR), a component of the HER1 signaling pathway that is often overexpressed in non–small-cell lung cancer (NSCLC). The FDA granted fast-track approval to gefitinib in May 2003 for the treatment of patients with advanced NSCLC who experienced disease progression after two or more courses of chemotherapy.

However, follow-up studies in this patient population did not show a survival benefit for patients taking gefitinib compared with patients taking a placebo. The FDA directed in December 2004 that other drugs, including the small-molecule inhibitor erlotinib, should be used to treat patients with advanced NSCLC who have shown disease progression despite prior chemotherapy.

Recently, EGFR mutations have been associated with dramatic responses to gefitinib in patients

with lung cancer. However, the rate of mutations in patients with breast cancer remains unclear. Prolonged stable disease has been observed in patients with advanced breast cancer treated with gefitinib; however, gefitinib may have more activity against earlier-stage breast cancer, and phase II trials testing this are underway.

Erlotinib (Tarceva®)

Erlotinib is a small-molecule inhibitor of a TK that is associated with EGFR. Researchers conducted a clinical trial to compare erlotinib with placebo in patients with locally advanced or metastatic lung cancer with disease progression following prior treatments. They reported that median survival in patients taking erlotinib was 6.7 months compared with 4.7 months in patients in the placebo group. The mechanism of action of this drug is not fully known.

The FDA granted fast-track approval to erlotinib in November 2004 for the treatment of patients with NSCLC with disease progression following at least one chemotherapy regimen. Adverse events reported for erlotinib therapy include diarrhea, rash, nausea, and vomiting. A phase II trial of erlotinib in patients with otherwise refractory breast cancer did show a low clinical benefit rate; combination trials of erlotinib and chemotherapy are now underway for this patient population.

Imatinib (Glevec®)

Imatinib was the first small-molecule targeted agent to receive FDA approval. This TK inhibitor was granted fast-track approval in 2001 for the treatment of CML. Most cases of CML are caused by a genetic mutation that produces the abnormal Bcr-Abl TK protein. This malfunctioning protein continuously stimulates cellular proliferation. Imatinib binds to a crucial portion of the Bcr-Abl TK, inhibiting protein function and inducing cellular apoptosis.

Clinical research has shown imatinib to produce durable, complete hematologic or cytogenic remission in many patients with CML, with few side effects. Patients must be tested to confirm expression of the Bcr-Abl TK gene in leukemic cells to be eligible for treatment with imatinib. The FDA has since approved imatinib for the treatment of relapsed and metastatic gastrointestinal stromal tumors (GIST), another malignancy caused by an abnormal TK. Researchers have also shown imatinib to inhibit receptor TK for platelet-derived growth factor (PDGF), which is overexpressed in many other cancers. Potential serious side effects from imatinib include fluid retention, edema, hemorrhage, and hepatotoxicity. Imatinib therapy may also cause dermatologic toxicities, anemia, neutropenia, and thrombocytopenia.

Bortezomib (Velcade®)

Bortezomib is a small-molecule anticancer drug and the first proteasome inhibitor to be approved by the FDA. Bortezomib received fast-track approval in May 2003 for the treatment of patients with relapsed multiple myeloma. Proteasomes are large protein complexes that help break down proteins tagged by the cell for destruction. Disruption of cell homeostasis through proteasome inhibition often results in cell death. Because proteasomes are present in cells throughout the body, proteasome inhibitors can also kill healthy cells. However, preclinical testing showed that bortezomib is particularly toxic to a variety of cancer cells.

Early clinical trials showed that this drug can reduce tumor volume in patients with multiple myeloma with disease progression following two prior treatments. Subsequent clinical trials showed bortezomib to lengthen TTP by almost three months in patients with relapsed multiple myeloma compared with treatment with dexamethasone. Serious adverse events documented for this drug include peripheral neuropathy, hypotension, cardiac disorders, and thrombocytopenia. To date, phase II clinical trials of bortezomib in breast cancer have not shown responses, but trials in combination with chemotherapy are ongoing.

Thalidomide

Thalidomide is also being tested as an antiangiogenic cancer treatment and has proven effectiveness against multiple myeloma. While thalidomide is notorious for causing birth defects in the late 1950s, researchers are now using its antiangiogenic properties to stunt tumor growth. Thalidomide also has some effects on the immune system and might synergize with immunotherapy.

Targeted Therapies in Clinical Trials

Many small-molecule drugs and anticancer antibodies are undergoing clinical testing to determine whether they are effective against various cancers. Some of these agents are listed in Table 2, along with a summary of molecular targets, modes of action, and clinical trial information. Preclinical research has demonstrated that these agents interact with their designated targets and produce a desired effect *in vitro* and *in vivo*.

However, many agents that show promise in preclinical or early clinical testing are ultimately not approved by the FDA for use in humans because of excessive toxicity or lack of efficacy. Nevertheless, the mounting information available about the molecular biology of cancer development and progression is steadily improving researchers' abilities to identify candidate agents that will provide safe and effective patient-specific cancer therapies in humans. JCCC

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Vijay Kasturi, MD, *an oncologist at Commonwealth Hematology-Oncology's Leominster and Worcester offices, has hospital appointments with UMass Memorial Medical Center in Worcester, UMass Memorial HealthAlliance Hospital, and Saint Vincent Hospital in Worcester. Dr. Kasturi received his medical degree from Rush Medical College in Chicago and his Bachelor of Science degree from the University of Illinois. He was a Clinical Fellow in medical oncology and hematology at the National Cancer Institute and a resident and intern in medicine at Rush Presbyterian St. Luke's Medical Center. Board certified in medical oncology and internal medicine, he is an Assistant Professor of Medicine at the University of Massachusetts, an Adjunct Instructor in Medicine at Dartmouth-Hitchcock Clinic in Keene, New Hampshire, and a member of the American Society of Clinical Oncology.*

Preventing Chemotherapy Errors

THE DANA-FARBER INCIDENT AND PROCEDURE REFORM

By Walt A. Kagan, MD, PhD

In November 1994, a 39-year-old health columnist for *The Boston Globe* and mother of two died shortly after receiving a drug overdose while undergoing chemotherapy at the Dana-Farber Institute, a world-renowned research and cancer-treatment facility. At the same time, a 53-year-old teacher suffered severe heart damage after receiving a similar overdose. Three years later, she died of cancer.

Both women were undergoing chemotherapy for breast cancer but, unfortunately, were given four times the appropriate dose of chemotherapy. The following year, an Illinois man seeking treatment for testicular cancer was administered four times the prescribed dose of chemotherapy. Although it was estimated that he had an 80% chance of recovery, he died due to the overdose.

The Dana-Farber Incident

As expected, these unnecessary deaths prompted numerous charges, countercharges, and finger pointing, as well as indictments. In the Dana-Farber incident, as it is now known, numerous deficiencies in the hospital system, including protocol violations, ineffective drug-error reporting, and poor quality assurance by hospital leaders, were identified. The nurses were following protocols from a typewritten order sheet on which the physician had handwritten the appropriate dose for each individual patient. The doses were misread.

At the end of the decade, the Institute of Medicine reported in *To Err Is Human: Building a Safer Health System*[1] that one million people in the United States suffer from preventable medical injuries while being treated in U.S. hospitals. Health Grades[2], which publishes rankings of hospitals and physicians, recently estimated that approximately 195,000 people die from these mistakes.

The Dana-Farber incident, and others like it, received extensive press coverage and set the stage for massive self-examination of the U.S. public health care system. It was soon recognized that iatrogenic injuries and deaths associated with medical errors and ill-prescribed medication were common, costly, and led to significant erosion of trust in health care institutions.

Classen *et al*[3] reported that adverse drug events, including medication errors, could increase hospital length of stay by an average of 1.7[4] days with an associated average cost of $2,262. This cost becomes even more significant in light of evidence that between 42% and 67% of serious adverse drug events or iatrogenic injuries are preventable.

Computer Aid for Reducing Errors

The development and application of computerized physician order entry (CPOE) systems and clinical decision support systems (CDSS) began in earnest with the goal of significant medication-error and adverse-outcome rate reductions. Recent statements by The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) support a "systems approach" to preventing medication errors from reaching patients in American health care facilities.[5]

The American Society of Health-Systems Pharmacists went further and defined "medication" errors to include errors in prescribing, dispensing, and administering medications, as well as errors in patient compliance. Its definition did not include therapeutic failures, intentional overdoses, adverse drug reactions, allergic responses, or errors that were prevented by the system.[6]

The challenge of preventing errors and the magnitude of those that do occur are even more pronounced in the oncology field. Chemotherapy errors may occur at various instances within the overall treatment course, beginning with the initial evaluation of the patient and extending throughout the ordering, preparation, administration, and monitoring of these agents. Four factors contribute to this phenomenon:[6]

(1) The narrow therapeutic window of cytotoxic agents creates the potential for serious adverse sequelae, even in the event of a "minimal" error.

(2) As research demonstrates the benefits of combination chemotherapy and dose intensification, the regimens being used have become more complex. Furthermore, these regimens often require concomitant ancillary medications for prophylaxis against adverse events related to chemotherapy.

(3) The acceptance of newer, high-dose therapies, particularly those with stem-cell rescue, has promoted a level of comfort among health care providers when prescribing high doses.

(4) Health care providers may not be fully familiar with the various agents available, especially given the proliferation of new drugs and unique therapeutic categories on the market in the past few years.

The Dana-Farber incident promoted a policy of "zero tolerance" for medication errors in the eyes of the public and prompted Dana-Farber to put in place a computerized system for drug and chemotherapy orders.[6] The primary focus became known as the "five rights": give the right drug to the right patient at the right dose through the right route at the right time. The deaths at Dana-Farber also motivated Walt A. Kagan, MD, PhD, President of Commonwealth Hematology-Oncology P.C. (CHO) and software designer Howard Silverman, MD, to think strategically of ways to error-proof the chemotherapy process.

IntelliDose™

Dr. Silverman founded IntrinsiQ Research and developed IntelliDose™, a software package designed to prevent chemotherapy errors. CHO became IntrinsiQ's partner and key testing site for IntelliDose.

IntelliDose is designed to monitor appropriate chemotherapy dosing schedules based on preloaded treatment plans derived from peer-reviewed literature, while checking for possible contraindications regarding the patient's current medical condition(s), allergies that may interfere with dosing, possible drug interactions, significant changes in weight or weight sets outside predetermined parameters, and lab values based on age and gender outside preset parameters.

IntelliDose performs all calculations and produces an electronic order that is accessible to all authorized individuals at any networked computer. The basis of IntelliDose order writing is treatment templates organized in cycles to produce a complete plan of treatment. Entire multicycle treatment plans can be built for virtually all levels of complexity related to polychemotherapy, supportive agents, laboratory studies, and schedules. It also provides an electronic report of the regimen, including specific instructions to nurses and other providers about when and how each drug should be administered. The e-nurse module provides step-by-step nursing instructions that increase standardization and decrease ambiguity while capturing charges for all billable services.

The program offers the physician not only increased patient safety and quality of care but also the ability to maintain an audit trail by documenting the treatment procedure. It also provides an easy, efficient means of coding correct charges. The current version is now used by more than 400 oncologists around the country in office, clinic, and academic settings. The next version will have the ability to interact with patient records and other electronic databases that already exist at medical facilities, and can be custom designed for each practice.

Despite its ease of use, relatively low cost (average cost is $2,000 to $3,000 per year per practice), and the fact that it is based on well-proven technology tested in numerous and diverse systems, early adoption of this new tool has been slow. According to its developer, IntelliDose has penetrated only approximately 5% of the potential market, in the face of a 90% reduction of error rate.

Eliminating Mistakes

Health care professionals must continuously strive to reduce iatrogenic errors, if not totally eliminate them, for many reasons. First and foremost is the basic ethical responsibility of health care providers to do no harm. Second, medication errors may be financially costly to an institution, whether due to litigation stemming from an error or due to iatrogenic effects requiring further treatment or prolonged hospitalization.

Testifying before the Health Subcommittee of the House Energy and Commerce Committee, JCAHO President Dennis S. O'Leary, MD, underscored the fact that health care must create an environment in which safety is always foremost and errors are viewed as opportunities for learning and improvement. "The knowledge of what to do differently and how to do it exists, but we are far closer to the beginning of the journey than we are to the end. We as a society must ramp up our efforts if we are to successfully bridge the chasm between the current state of health care and what is truly safe, high-quality care," he said. JCCC

CHEMOTHERAPY ORDERS

Chemotherapy	Dose Basis	WT Type	Dose	Route	Daily Freq and Schedule	Initials Time
	Special Instructions					
Anzemet	100 mg/dose	NA	100 mg	IV	X1 on d1	
	Administer by infusion over 15 minute(s) in 100 mL 0.9% sodium chloride. Admix with Decadron if Decadron ordered.					
Decadron	10 mg/dose	NA	10 mg	IV	X1 on d1	
	Administer by infusion over 15 minute(s) in 100 mL 0.9% sodium chloride. Admix with Anzemet if Anzemet ordered.					
capecitabine DOSED AT 53% OF ___ mg (diarrhea)	530 mg/m2	real	1002 mg	PO	BID on d1 to d7	
	Verify that patient has prescription. #QS Refills: NONE. Interrupt therapy for grade 2 nausea, vomiting, diarrhea, stomatitis, or hand-foot syndrome. Dose reduce for renal dysfunction.					
Oxaliplatin DOSED AT 50% OF 248 mg (diarrhea)	65 mg/m2	real	123 mg	IV	X1 on d1	
	Administer by infusion over 2 hour(s) in 500 mL 5% dextrose in water. Reconstitute Oxaliplatin with sterile water (10 mL for 50 mg vial, 20 mL for 100 mg vial), further dilute in 500 mL 5% dextrose. Do not use chloride-containing solutions, do not use aluminum needles or infusion sets containing aluminum. Assess for peripheral neuropathy.					

This is a snapshot of one section of a computer-generated order set.

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Walt A. Kagan, MD, PhD, *President of Commonwealth Hematology-Oncology, practices in the group's Quincy office. He has hospital appointments with Quincy Medical Center, Carney Hospital, Milton Hospital, and South Shore Hospital. Dr. Kagan received his medical degree from Cornell University Medical College and his PhD from Sloan-Kettering Division, Cornell University Graduate School of Medical Science. He is a Clinical Instructor in Medicine at Harvard Medical School and an Assistant Professor at Tufts University School of Medicine. Dr. Kagan is on the Board of Directors for the Massachusetts Society of Clinical Oncologists. He is a member of the American Medical Association, the American Society of Internal Medicine, the American Academy of Medical Administrators, and the American Society of Clinical Oncology.*

Radiation Therapy

PARTIAL-BREAST IRRADIATION TECHNIQUES MAY PREVENT RECURRENCE IN SOME PATIENTS

By Tatiana Lingos, MD

Research has demonstrated that breast-conserving therapy followed by whole-breast irradiation is as effective as total mastectomy for treatment of early-stage breast cancer. However, many patients eligible for breast-conserving therapy still opt for mastectomy, and up to 30% of patients who undergo breast-conserving therapy do not receive the recommended adjuvant radiation, which may put them at increased risk for local failure.

Factors contributing to these patient choices include the lengthy treatment times of up to six weeks of daily treatment, concerns about the potential side effects of radiation therapy, and the sometimes long travel distances to treatment centers. Emerging techniques for partial-breast irradiation may help address these concerns by offering shorter treatment times, conformal delivery of radiation to the targeted tissue, and lower, more homogeneous radiation dosages yet still confer the same degree of tumor control in certain carefully selected patients.

These techniques are based on growing evidence that regional radiation of the lumpectomy cavity and adjacent tissue may prevent recurrence as effectively as whole-breast irradiation in appropriately selected patients. This is an introduction to partial-breast irradiation techniques.

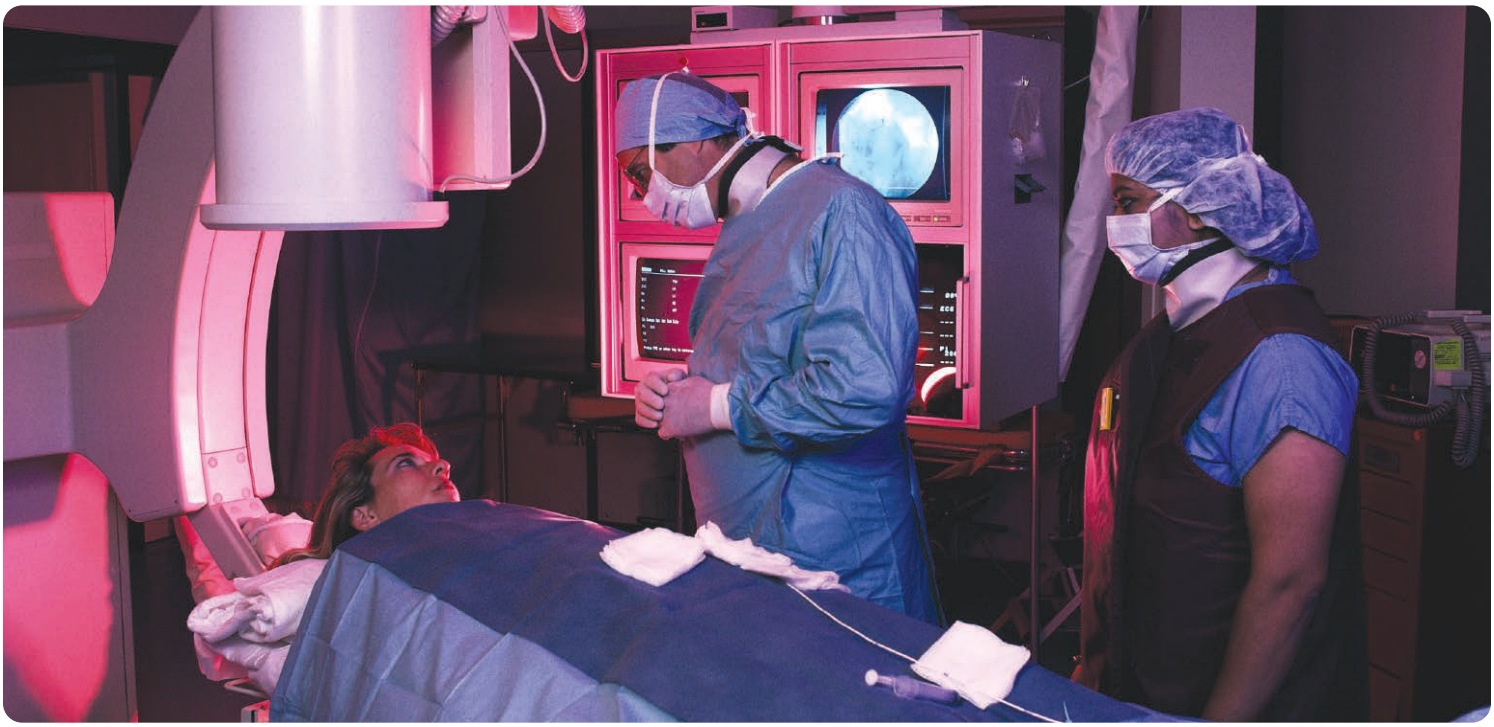
Brachytherapy

Accelerated partial-breast irradiation (APBI) techniques shorten treatment time to approximately five days. Multicatheter brachytherapy was the first APBI technique used in the United States. The catheters are strategically placed to deliver 45 Gy at a high-dose rate to a radius of 1 cm to 2 cm beyond the lumpectomy cavity. Advantages of this procedure include increased patient convenience and reduced exposure of the contralateral breast, heart, lung, and other surrounding tissues.

The use of 3-D treatment planning to guide catheter placement has helped mitigate the inherent startup learning curve associated with this technique. Some women may feel distress over the appearance of the breast while the catheters are in place. In the greater Massachusetts medical community, multicatheter brachytherapy is offered to women who are unable to manage the difficulties of whole-breast radiotherapy and as a boost to women at high risk for recurrence.

MammoSite®

The MammoSite Radiation Therapy System is a newer APBI technique that targets a treatment radius of 1 cm beyond the lumpectomy cavity at doses similar to multicatheter brachytherapy. The MammoSite system includes a catheter equipped with a balloon at the distal end. The balloon is surgically placed in the lumpectomy cavity and inflated to a spherical inflation of 4 cm to 6 cm. The radiation source is inserted into the balloon at the time of treatment, after which the entire apparatus is removed. The MammoSite technique is simpler to use than multicatheter brachytherapy and appears to improve the reproducibility of dose delivery to targeted breast tissue as well as the long-term cosmetic result.



There is growing evidence that regional radiation of the lumpectomy cavity and adjacent tissue may prevent recurrence as effectively as whole-breast irradiation in appropriately selected patients.

3-D Conformal Radiotherapy

The noninvasive 3-D conformal radiotherapy (CRT) uses 3-D imaging technologies and computerized planning software to design the delivery of a conformal radiation dose to the targeted area of breast tissue to approximately 1 cm to 2 cm beyond the lumpectomy cavity. One challenge presented by this APBI technique is the need to adjust for patient setup error and breathing motion. Continued research will focus on ensuring the irradiation of the full target volume and evaluating potential toxicities, tumor control, and cosmetic effects.

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) was developed not to accelerate postlumpectomy adjuvant radiation but to improve dose homogeneity, increase conformality, and reduce toxicity beyond levels achieved by other methods. Treatment times required for IMRT are comparable to those for standard whole-breast radiotherapy, but side effects are lessened. IMRT uses sophisticated computerization to optimally modulate the intensity of multiple radiation beams across the targeted treatment field.

A notable advantage of this technology is the reduced dose delivered to vital tissue, including the heart and lungs. It is important to weigh this advantage against the probable delivery of low-dose radiation to some normal tissues that would not receive exposure by standard methods. Clinical research reveals IMRT as particularly useful in the delivery of radiation to complex treatment volumes, such as those that include breast tissue and regional nodal areas in proximity to vital tissues, particularly in left-sided cancers. IMRT is used for this purpose at some facilities in the greater Massachusetts medical community. As technology evolves, image-guided radiation therapy (IGRT), an even newer technique, will automatically compensate for variations in position of the tumor with patients' movements and respirations.

Conclusion

These and other emerging techniques for delivering adjuvant radiation following breast-conserving therapy promise to improve patient quality of life through shortened radiation treatment times, reduced long-term and late-treatment effects, and reduced toxicity to vital organs. Future research will refine patient-selection criteria, investigate quality-assurance issues, and assess long-term outcomes. JCCC

Reference List

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Tatiana Lingos, MD, *is a graduate of Wellesley College and the University of Massachusetts Medical School. Following an internship at Mount Auburn Hospital, she completed her residency at Massachusetts General Hospital, where she served as Chief Resident. Board certified in radiation oncology, between 1987 and 1995, she was the Associate Director of the Metrowest Medical Cancer Center, was on the faculty of Harvard Medical School and the Harvard Joint Center for Radiation Therapy, and was an attending physician at Dana-Farber Cancer Center, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, and Children's Hospital. She was Medical Director of South Suburban Oncology Center in Quincy, Massachusetts, from 1995 to 2004 and is currently the Chief of Radiation Oncology at Roger Williams Medical Center in Providence, Rhode Island. Dr. Lingos is a Clinical Assistant at Massachusetts General Hospital and a Clinical Instructor in radiation oncology at Harvard Medical School.*

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

PROCRIT®
Epoetin alfa
FOR INJECTION

FOR FULL PRESCRIBING INFORMATION FOR ALL INDICATIONS, REFER TO THE *PHYSICIANS' DESK REFERENCE®*

INDICATIONS AND USAGE

PROCRIT® (Epoetin alfa) is indicated for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT® is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. 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, which should be managed appropriately.

CONTRAINDICATIONS

PROCRIT® is contraindicated in patients with: 1. Uncontrolled hypertension; 2. Known hypersensitivity to mammalian cell-derived products; 3. Known hypersensitivity to Albumin (Human).

WARNINGS

Pediatric Use: The multidose preserved formulation contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in premature infants, which are sometimes fatal.

Thrombotic Events and Increased Mortality

A randomized, prospective trial of 1265 hemodialysis patients with clinically evident cardiac disease (ischemic heart disease or congestive heart failure) was conducted in which 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 these studies is unknown, however, the incidence of non-fatal myocardial infarctions (3.1% vs 2.3%), vascular access thrombosis (39% vs 29%), and all other thrombotic events (22% vs 18%) were also higher in the group randomized to achieve a hematocrit of 42%.

Increased mortality was also observed in a randomized placebo-controlled study of PROCRIT® in adult patients who did not have chronic renal failure (CRF) 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. While the extent of the population affected is unknown, in patients at risk for thrombosis, the anticipated benefits of PROCRIT® treatment should be weighed against the potential for increased risks associated with therapy.

In a randomized, prospective trial conducted with another Epoetin alfa product, in 939 women with metastatic carcinoma of the breast who were receiving chemotherapy, patients were assigned to receive either Epoetin alfa or placebo for up to a year, in a weekly schedule, with the primary goal of showing improved survival and improved quality of life in the Epoetin alfa treatment arm. This study utilized a treatment strategy designed to maintain hemoglobin levels of 12 to 14 g/dL (hematocrit 36 to 42%). Increased mortality in the first 4 months after randomization was observed among 469 patients who received the erythropoietin product [41 deaths (8.7% mortality)] compared to 470 patients who received placebo [16 deaths (3.4% mortality)]. In the first four months of the study, the incidence of fatal thrombotic vascular events (1.1% vs 0.2%) and death attributed to disease progression (6.0% vs 2.8%) were both higher in the group randomized to receive Epoetin alfa as compared to placebo. Based on Kaplan-Meier estimates, the proportion of subjects surviving at 12 months after randomization was lower in the Epoetin alfa group than in the placebo group (70% vs 76%), p = 0.012, log rank. However, due to insufficient monitoring and data collection, reliable comparisons cannot be made concerning the effect of Epoetin alfa on overall time to disease progression, progression-free survival, and overall survival.

Pure Red Cell Aplasia

Pure red cell aplasia (PRCA), in association with neutralizing antibodies to native erythropoietin, has been observed in patients treated with recombinant erythropoietins. PRCA has been reported in a limited number of patients exposed to PROCRIT®. This has been reported predominantly in patients with CRF. Any patient with loss of response to PROCRIT® should be evaluated for the etiology of loss of effect (see PRECAUTIONS: LACK OR LOSS OF RESPONSE). PROCRIT® should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of binding and neutralizing antibodies to PROCRIT®, native erythropoietin, and any other recombinant erythropoietin administered to the patient. Amgen/Ortho Biotech Products, L.P. should be contacted to assist in this evaluation. In patients with PRCA secondary to neutralizing antibodies to erythropoietin, PROCRIT® should not be administered and such patients should not be switched to another product as anti-erythropoietin antibodies cross-react with other erythropoietins (see ADVERSE REACTIONS).

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 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 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): 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 recombinant erythropoietins.

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 Interactions: 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 male and female rats treated intravenously (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: PEDIATRIC USE.

Pediatric Cancer Patients on Chemotherapy: Published literature has reported the use of PROCRIT® in approximately 64 anemic pediatric cancer patients ages 6 months to 18 years, treated with 25 to 300 Units/kg subcutaneously (SC) or IV, 3 to 7 times per week. Increases in hemoglobin and decreases in transfusion requirements were noted.

Geriatric Use: Among 1051 patients enrolled in the 5 clinical trials of PROCRIT® for reduction of allogeneic blood transfusions in patients undergoing elective surgery 745 received PROCRIT® and 306 received placebo. Of the 745 patients who received PROCRIT®, 432 (58%) were aged 65 and over, while 175 (23%) were 75 and over. No overall differences in safety or effectiveness were observed between geriatric and younger patients. The dose requirements for PROCRIT® in geriatric and younger patients within the 4 trials using the TIW schedule were similar. Insufficient numbers of patients were enrolled in the study using the weekly dosing regimen to determine whether the dosing requirements differ for this schedule.

Of the 882 patients enrolled in the 3 studies of chronic renal failure patients on dialysis, 757 received PROCRIT® and 125 received placebo. Of the 757 patients who received PROCRIT®, 361 (47%) were aged 65 and over, while 100 (13%) were 75 and over. No differences in safety or effectiveness were observed between geriatric and younger patients. Dose selection and adjustment for an elderly patient should be individualized to achieve and maintain the target hematocrit (See DOSAGE AND ADMINISTRATION).

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.

Hypertension: Hypertension, associated with a significant increase in hemoglobin, has been noted rarely in patients treated with PROCRIT®. Nevertheless, blood pressure (BP) 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® three times weekly (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 BP 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; Thrombotic Events and Increased Mortality).

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.

Tumor Growth Factor Potential: PROCRIT® is a growth factor that primarily stimulates red cell production. Erythropoietin receptors are also found to be present on the surface of some malignant cell lines and tumor biopsy specimens. However, it is not known if these receptors are functional. A randomized, placebo-controlled trial was conducted in 224 chemotherapy-naïve, non-anemic patients with small cell lung cancer receiving cisplatin-based combination chemotherapy, to investigate whether the concurrent use of PROCRIT® stimulated tumor growth as assessed by impact on overall response rate. Patients were randomized to receive PROCRIT® 150 Units/kg or placebo subcutaneously TIW during chemotherapy. The overall response rates, after 3 cycles of treatment, were 72% and 67%, in the PROCRIT® and placebo arms, respectively. Complete response rates (17% vs. 14%) and median overall survival (10.5 mos vs. 10.4 mos) were similar in the PROCRIT® and placebo arms.

Two additional studies explored effect on survival and/or progression of administrations of other exogenous erythropoietin with higher hemoglobin targets.

In a randomized, placebo-controlled study using another Epoetin alfa product, conducted in 939 women with metastatic breast cancer, study drug dosing was titrated to attempt to maintain hemoglobin levels between 12 and 14 g/dL. At four months, death attributed to disease progression was higher (6% vs 3%) in women receiving Epoetin alfa. Overall mortality was significantly higher at 12 months in the Epoetin alfa arm (See WARNINGS; Thrombotic Events and Increased Mortality).

In a randomized, placebo-controlled study using Epoetin beta, conducted in 351 patients with head and neck cancer, study drug was administered with the aim of achieving a hemoglobin level of 14 g/dL in women and 15 g/dL in men. Locoregional progression-free survival was significantly shorter (median PFS: 406 days Epoetin beta vs 745 days placebo, p = 0.04) in patients receiving Epoetin beta.

There is insufficient information to establish whether use of Epoetin products, including PROCRIT® have an adverse effect on time to tumor progression or progression-free survival.

These trials permitted or required dosing to achieve hemoglobin of greater than 12 g/dL. Until further information is available, the recommended target hemoglobin should not exceed 12 g/dL in men or women.

ADVERSE REACTIONS

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PROCRIT® with the incidence of antibodies to other products may be misleading.

A few cases of PRCA associated with antibodies with neutralizing activity have been reported in patients receiving PROCRIT® (see WARNINGS: PURE RED CELL APLASIA). These cases were observed in patients treated by either SC or IV routes of administration and occurred predominantly in CRF patients.

Adverse Experiences Reported in Clinical Trials

Adverse experiences reported in clinical trials with PROCRIT® administered TIW in cancer patients were consistent with the underlying disease state. 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: Event followed by Patients Treated With PROCRIT® (n = 63) first, Placebo-treated Patients (n = 68) second:
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%; Paresthesia 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 treatment and placebo arms.

OVERDOSAGE

The maximum amount of PROCRIT® that can be safely administered in single or multiple doses has not been determined. Doses of up to 1500 Units/kg TIW for 3 to 4 weeks have been administered to adults without any direct toxic effects of PROCRIT® itself. Therapy with PROCRIT® can result in polycythemia if the hemoglobin is not carefully monitored and the dose appropriately adjusted. If the suggested target range is exceeded, PROCRIT® may be temporarily withheld until the hemoglobin returns to the suggested target range; PROCRIT® therapy may then be resumed using a lower dose (see DOSAGE AND ADMINISTRATION). If polycythemia is of concern, phlebotomy may be indicated to decrease the hemoglobin.

DOSAGE AND ADMINISTRATION

Although no specific serum erythropoietin level can be stipulated above which patients would be unlikely to respond to PROCRIT® therapy, treatment of patients with grossly elevated serum erythropoietin levels (eg, > 200 mUnits/mL) is not recommended. The hemoglobin should be monitored on a weekly basis in patients receiving PROCRIT® therapy until hemoglobin becomes stable. The dose of PROCRIT® should be titrated to maintain the desired hemoglobin.

Two PROCRIT® dosing regimens may be used in adults; 150 Units/kg SC TIW or 40,000 Units SC Weekly. For pediatric patients, see PRECAUTIONS: PEDIATRIC USE.

TIW Dosing

Starting Dose:	
Adults	150 Units/kg SC TIW
Pediatric Patients	See PRECAUTIONS: Pediatric Use.
Reduce Dose by 25% when:	1. Hgb approaches 12 g/dL or, 2. Hgb increases > 1 g/dL in any 2-week period
Withhold Dose if:	Hgb exceeds 13 g/dL, until the hemoglobin falls to 12 g/dL, and restart dose at 25% below the previous dose
Increase Dose to 300 Units/kg TIW if:	response is not satisfactory [no reduction in transfusion requirements or rise in hemoglobin] after 8 weeks
Suggested Target Hgb Range:	10 g/dL to 12 g/dL

During therapy, hematological parameters should be monitored regularly (see PRECAUTIONS: Laboratory Monitoring).

Weekly Dosing

- The starting dose in adults is 40,000 Units SC Weekly. If after 4 weeks of therapy, the hemoglobin has not increased by ≥ 1 g/dL, in the absence of RBC transfusion, the PROCRIT® dose should be increased to 60,000 Units Weekly.
- If patients have not responded satisfactorily to a PROCRIT® dose of 60,000 Units Weekly after 4 weeks, it is unlikely that they will respond to higher doses of PROCRIT®.
- PROCRIT® should be withheld if the hemoglobin exceeds 13 g/dL and reinitiated with a 25% dose reduction when the hemoglobin is less than 12 g/dL.
- If PROCRIT® treatment produces a very rapid hemoglobin response (e.g., an increase of more than 1 g/dL in any 2-week period), the dose of PROCRIT® should be reduced by 25%.

STORAGE

Store at 2° to 8°C (36° to 46°F). Do not freeze or shake.

◆

ORTHO BIOTECH

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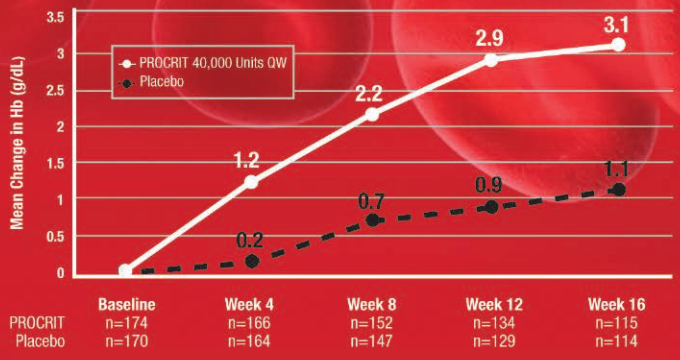
638-10-979-4BC

When treating patients with chemotherapy-induced anemia...

Efficacy Means *More*

Mean Increase in Hb From Baseline*†‡[1,2]



	Baseline	Week 4	Week 8	Week 12	Week 16
PROCRIT	n=174	n=166	n=152	n=134	n=115
Placebo	n=170	n=164	n=147	n=129	n=114

More Red Blood Cells for Increased Hb vs Placebo*†‡[1]

More Patients With Reduced Transfusion Requirements vs Placebo§[1]

PROCRIT®
EPOETIN ALFA
Strength for Living®

PROCRIT is indicated for the treatment of anemia in patients with nonmyeloid malignancies where anemia is due to the effect of concomitantly administered chemotherapy. PROCRIT is indicated to decrease the need for transfusions in patients who will be receiving concomitant chemotherapy for a minimum of 2 months. PROCRIT is not indicated for the treatment of anemia due to other factors such as iron or folate deficiencies, hemolysis or gastrointestinal bleeding which should be managed appropriately.

Important Safety Information

PROCRIT is contraindicated in patients with uncontrolled hypertension. PROCRIT and other erythropoietic therapies may increase the risk of thrombotic events and other serious events. The target hemoglobin (Hb) should not exceed 12 g/dL. The dose of PROCRIT should be reduced by 25% if the Hb approaches 12 g/dL or increases by more than 1 g/dL in any 2-week period. The dose of PROCRIT should be withheld if the Hb exceeds 13 g/dL, until the Hb falls to 12 g/dL; dosing may then be restarted, with a 25% dose reduction. During treatment with all erythropoietic therapies, the Hb should be monitored weekly until it becomes stable. In a study where patients were treated with another Epoetin alfa product to a target Hb range of 12 to 14 g/dL, there was an increased incidence of mortality attributed to disease progression seen in the Epoetin alfa treatment group compared to placebo.

Pure red cell aplasia (PRCA) has been reported in a limited number of patients exposed to PROCRIT, predominately in patients with chronic renal failure. PROCRIT should be discontinued in any patient with evidence of PRCA and the patient evaluated for the presence of antibodies to erythropoietin products. Prior to and during PROCRIT therapy, the patient's iron status should be evaluated. Hypertension associated with rapid increases in Hb has been rarely noted in cancer patients treated with PROCRIT. Nevertheless, blood pressure should be monitored carefully, particularly in patients with an underlying history of hypertension or cardiovascular disease. The most commonly reported side effects (>10%) for PROCRIT in clinical trials were pyrexia, diarrhea, nausea, vomiting, edema, asthenia, fatigue, shortness of breath, paresthesia, and upper respiratory infection.

Please see adjacent page for Brief Summary of Prescribing Information.

* A pivotal, randomized, double-blind, multicenter, placebo-controlled trial of 344 cancer patients receiving chemotherapy in an intent-to-treat population evaluated transfusion requirements and Hb response. A primary endpoint of the study was transfusion avoidance.[1]

† The mean change in Hb from baseline to study end was 0.9 g/dL in the placebo group and 2.8 g/dL in the Epoetin alfa group; the difference between groups was statistically significant ($P<.0001$).[1]

‡ Initiation dose 40,000 Units weekly, with escalation to 60,000 Units weekly if the Hb did not increase >1 g/dL by week 4 or if the subject received a transfusion during the first 4 weeks of therapy. The majority of patients (57%) treated with PROCRIT did not require escalation.[1]

§ Between days 29 and study end ($P=.001$).

References: 1. Witzig TE, Silberstein PT, Loprinzi CL, et al. Phase III, randomized, double-blind study of Epoetin alfa compared with placebo in anemic patients receiving chemotherapy *J Clin Oncol.* 2005;23:2606-2617. 2. Data on file, Ortho Biotech Clinical Affairs, LLC.

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Commonwealth Hematology-Oncology
10 Willard Street
Quincy, MA 02169