



A Report From the American Society of Clinical Oncology 2007 Annual Meeting

Managing Side Effects

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- 2** **Fatigue**
Using Ginseng to Manage Fatigue (*p 2*)
- 3** **Hot Flashes**
Tamoxifen (Nolvadex) and Hot Flashes (*p 3*)
Gabapentin (Neurontin, Gabarone) for Men With Prostate Cancer (*p 5*)
- 6** **Weight Loss**
Improving Weight Gain with Anamorelin (RC-1291) (*p 6*)
- 7** **Nerve Damage**
Controlling Treatment-Related Nerve Effects With Vitamin E (*p 7*)
- 7** **Blood Clots**
Venous Thromboembolism: A Concern in Hospitalized Cancer Patients (*p 7*)
- 8** **Anemia**
Safety of Erythropoietin for Treating Anemia (*p 8*)
Treating Anemia With Intravenous Iron (*p 10*)

contents continued on the following page

12 Bone Health and Cancer TreatmentOsteonecrosis of the Jaw (*p 12*)Reducing the Risk of Bone Breaks With Zoledronic Acid (Zometa) (*p 13*)**14** Infection in Older People With CancerRisk of Chemotherapy-Related Infection (*p 14*)**14** Follow-Up CareA Must for Childhood Cancer Survivors (*p 14*)

Each person with cancer reacts differently to chemotherapy and its various side effects. Fortunately, doctors have many ways to reduce and even prevent these side effects. Several new techniques are covered in this chapter.

At CancerCare® we often use the word “coping” to describe how people deal with their cancer situation. People sometimes mistakenly think that coping means just living with a problem, whether you like it or not. But coping actually means *managing* a problem and finding ways to take control of it.

Fatigue

USING GINSENG TO MANAGE FATIGUE

Many people with cancer experience fatigue, an extreme sense of tiredness that can be related to cancer treatment and/or to the cancer itself. Even though exercise is the treatment many doctors recommend for fatigue, a number of options are being studied. For example, the popular herb ginseng has shown some promise.

Researchers from the Mayo Clinic in Rochester, Minnesota, conducted a clinical trial using American ginseng in nearly 300 patients with various types of cancer. The people who took part in the study were receiving or had completed chemotherapy or radiation treatment. In an eight-week clinical trial, patients took

one of three different doses of ginseng twice daily or received a **placebo** (inactive substance) on the same schedule. People who took the higher doses of ginseng (1,000 and 2,000 mg) felt less tired than those who took the lower dose of ginseng (750 mg) or the placebo. The researchers believe that further study of American ginseng in people with cancer is worthwhile.

Hot Flashes

TAMOXIFEN (NOLVADEX) AND HOT FLASHES

Many women who take tamoxifen (Nolvadex) to prevent breast cancer recurrences find that they experience hot flashes. These sudden feelings of body heat occur when hormonal changes affect a person’s ability to adapt to normal internal body temperature fluctuations. This common and often uncomfortable side effect of tamoxifen may occur in up to 80 percent of women



being treated with this drug. Researchers at several medical centers in the United States are trying to discover why some women develop this side effect and others do not.

One possible **genetic** explanation is being considered by researchers at Johns Hopkins Kimmel Cancer Center in Baltimore, Maryland. According to their findings, premenopausal women with two exact copies of the gene referred to as CYP2D6 had an average of 17 more hot flashes each month

than did women with only one copy. Those with one copy had about five hot flashes a month. Similar results were seen in postmenopausal women. Postmenopausal women with two specific versions of CYP2D6 reported nearly 60 monthly hot

What's New, What's Important

- The popular herb ginseng may be effective in improving fatigue related to cancer and its treatment, but more study is necessary to confirm this.
- Differences in a certain gene type may predict which women taking tamoxifen (Nolvadex) for breast cancer will develop hot flashes, a side effect of the drug. Hot flashes may be a sign that the drug can effectively prevent the cancer from returning.
- Gabapentin (Neurontin, Gabarone), a drug used to treat epilepsy, appears to reduce hot flashes in men being treated for prostate cancer.
- An appetite-stimulating substance called anamorelin (RC-1291) may eventually become a promising new option for treating cancer cachexia, a condition in which a patient loses so much weight it can become life-threatening.

flashes—more than women with other gene types.

Being able to predict who might develop hot flashes when taking tamoxifen may make it possible for doctors to know when to prescribe drugs that might relieve this side effect.

The connection between tamoxifen treatment for breast cancer and the occurrence of hot flashes was of interest to another group of researchers. They wanted to find out two things. First, did hot flashes indicate that tamoxifen was working? And second, of the women treated with tamoxifen, did those who had hot flashes go longer without their cancer coming back compared with those who did not have hot flashes?

Part of the Women's Healthy Eating and Living Study, which included more than 3,000 women with breast cancer, focused on 900 women who were treated with tamoxifen after surgery. Nearly 80 percent of the patients who received tamoxifen reported having hot flashes. After seven years, a lower

percentage of these women developed recurrent or new breast cancer, compared with women who did not report hot flashes. Researchers think this may be because some women (about 10 percent) lack an enzyme that converts tamoxifen to a form of the drug that actually fights breast cancer. This same form of the drug also causes hot flashes. Thus, those without hot flashes may not have the ability to convert the drug to a form that fights cancer.

GABAPENTIN (NEURONTIN, GABARONE) FOR MEN WITH PROSTATE CANCER

Men being treated for prostate cancer often experience hot flashes. Results of a trial performed by the North Central Cancer Treatment Group, a national research group based at the Mayo Clinic in Rochester, Minnesota, may offer a possible solution.

More than 200 men took part in the study. All of the men had at least 14 hot flashes per week related to treatment for prostate cancer. Three different doses of gabapentin (Neurontin, Gabarone), a drug used to treat seizure disorders and some pain syndromes, were studied.

Men who received the highest dose (900 mg) had a significant improvement: the frequency of their hot flashes reduced by almost 50 percent. These men also were more satisfied with the level of control of their hot flashes than men who were not treated with gabapentin. This drug appears to be a reasonable option for men being treated for prostate cancer who are bothered by hot flashes.



Weight Loss

IMPROVING WEIGHT GAIN WITH ANAMORELIN (RC-1291)

Up to 75 percent of people with cancer may lose so much weight that the resulting extreme fatigue interferes with their quality of life. Called cachexia, this condition can complicate treatment and is closely associated with poor survival rates. So, researchers are searching for ways to help people with cachexia gain weight.

At Baylor College of Medicine in Houston, Texas, researchers have studied a promising option called anamorelin (RC-1291), which seems to act like an appetite-stimulating hormone.

About 75 people with cancer cachexia took part in a clinical

trial at 17 centers in the United States. Nearly two-thirds of the patients had lost between 5 and 15 percent of their body weight during the six months before they entered the clinical trial. About half the people in the clinical trial received anamorelin, and the others received a placebo.

By the end of the 12-week clinical trial, people who received anamorelin increased their weight by an average of a little over a pound. People who received a placebo decreased their weight by an average of slightly more than

a pound-and-a-half. Those who received anamorelin also had significant gains in total body mass (fat and muscle and other tissues) at 4, 8, and 12 weeks of treatment. On the other hand, those who received a placebo lost total body mass at all three points in time.

Further studies with anamorelin are needed.



Nerve Damage

CONTROLLING TREATMENT-RELATED NERVE EFFECTS WITH VITAMIN E

Many people with cancer who are treated with cisplatin (Platinol) are unable to receive their full treatment because of a side effect called **peripheral neuropathy**—nerve damage that may be felt as tingling, weakness, numbness, or pain in the arms and legs.

Researchers are continually searching for ways to prevent such side effects, and they may have just found one in vitamin E. For years, many researchers thought that vitamin E protected nerves by preventing the damage caused by chemotherapy. The results of the first formal clinical trial of vitamin E in people with nerve side effects from chemotherapy seem to support this idea.

This ongoing clinical trial, which was conducted in three cancer centers in Italy, included about 80 people with different cancers (two-thirds of them lung cancer). During chemotherapy with cisplatin, patients received either vitamin E supplements (400 mg a day) or a placebo. Vitamin E was continued for three months after chemotherapy.

Before treatment with vitamin E, both groups showed no nerve damage. In the first group of 25 people evaluated, 11 received vitamin E and 14 did not. The people who did not receive vitamin E had more severe signs of peripheral neuropathy than those who received vitamin E.

Researchers are looking forward to the final results of this trial to see whether these early positive results are confirmed.

Blood Clots

VENOUS THROMBOEMBOLISM: A CONCERN IN HOSPITALIZED CANCER PATIENTS

A frequent complication of chemotherapy is **venous thromboembolism (VTE)**, a blood clot that can travel

through the body's circulation. Such clots can be life threatening if they block the flow of blood to the lungs.

According to a review of more than one million hospital discharge summaries of cancer patients, the rate of VTE has risen from 3.6 percent in 1995 to 4.6 percent in 2003, an increase of almost 30 percent. The type and intensity of chemotherapy given seems to contribute to this increase. Medications such as darbepoetin alfa (Aranesp) and epoetin alfa (Procrit) to treat **anemia** in cancer patients may also play a part in the climbing rates of VTE.

In the review, certain cancers were associated with a higher rate of VTE, such as pancreatic, kidney, and ovarian cancers, as well as myeloma. The study also showed that African-Americans are especially susceptible to VTE. Researchers from the University of Rochester Medical Center in New York suggested that any person with cancer who is admitted to a hospital should be considered at high risk of VTE. They recommended preventive steps that would include wearing compression stockings or using a special hospital plastic stocking that intermittently fills with air and squeezes the leg to increase blood flow and reduce the risk of clots.

Anemia

SAFETY OF ERYTHROPOIETIN FOR TREATING ANEMIA

Many people with cancer often experience anemia, an abnormally low level of red blood cells that can lead to fatigue, shortness of breath, and other symptoms. Anemia can stem from the cancer itself and/or from chemotherapy and radiation treatments.

Cancer-related anemia has commonly been treated with blood transfusions or with medications that increase the body's production of red blood cells. The drugs are man-made versions of **erythropoietin (EPO)**, a chemical produced by the kidneys to encourage the production of red

blood cells by the bone marrow. In recent years, the safety of EPO drugs, particularly epoetin alfa and darbepoetin alfa, has come into question and is at the heart of a controversy in the medical community.

In 2003, several clinical trials involving people with cancer using EPO were stopped early because of an increased risk of cancer growth and death.

In response to these findings, in 2004 the U.S. Food and Drug Administration (FDA) issued a safety warning regarding the use of these drugs in situations that were not already approved by the FDA. The FDA identified a higher-than-expected number of cases of VTE in cancer patients who received these drugs.

In 2007, clinical trials with epoetin alfa and darbepoetin alfa have shown an increase in the growth of cancer and in deaths when these drugs were given to people with cancer.

To get a clearer picture of the safety issues of using these drugs, researchers from Northwestern University in Illinois, the University of South Florida, and the University of New Mexico analyzed a number of studies from different sources, including the FDA's own database. After reviewing 40 clinical trials of more than 7,500 people, the researchers found that these two EPO drugs were linked to an increased risk of VTE in patients who were treated for cancers of the bone marrow and in patients who received radiation or chemotherapy/radiation treatment. The drugs, however, are approved only for chemotherapy-induced anemia.

In another study, analyzing the information found in nearly 50 clinical trials conducted since 2003, the risk of death was



What's New, What's Important

- For people with cancer who are treated with cisplatin (Platinol), vitamin E may help protect them from peripheral neuropathy.
- Hospitalized cancer patients are at increased risk of venous thromboembolism, a potentially life-threatening complication. Preventive steps need to be taken.
- Many people who have developed anemia as a result of their cancer or cancer treatment use erythropoietin. The safety of erythropoietin, a drug that produces red blood cells to fight anemia, is being debated in the medical community. As studies continue, doctors should exercise caution and use erythropoietin only in cases approved by the FDA and treatment guidelines.
- Adding intravenous iron to erythropoietin for the treatment of anemia in people with cancer appears to lead to significant improvement in symptoms of fatigue.

increased with the use of these two EPO drugs in people with cancer treated for anemia. But these findings were also in situations that were considered “off-label” uses for these drugs.

Formal trials to evaluate the increased risks of using EPO drugs are needed and should help clarify the confusion surrounding this issue. At this time, it is important for doctors to use these drugs only in situations that have been approved by the FDA and accepted as standard treatment by such groups as the National Comprehensive Cancer Network.

TREATING ANEMIA WITH INTRAVENOUS IRON

Combining iron administered **intravenously** with EPO may improve fatigue symptoms and help people get the most out of such treatment, according to the findings of three separate clinical trials.

In the first clinical trial, researchers from Hungary tested various

forms of iron supplementation in almost 400 people who were being treated with darbepoetin alfa for anemia linked to chemotherapy. One group of patients received 200 mg of intravenous iron every three weeks (or two doses of 100 mg within three weeks). The other group received oral iron supplements or no iron. All the participants in the clinical trial received darbepoetin alfa every three weeks. Treatment lasted 13 weeks.

The 200 patients who received intravenous iron had a greater improvement in their symptoms of fatigue than the nearly 200 patients who received oral iron supplements or no iron. No unexpected side effects were seen with the combination including intravenous iron.

In the second clinical trial, the Iron Sucrose Study Group performed a similar comparison but with a different dosing schedule. During the first stage of the study, patients' anemia was treated with darbepoetin alfa or epoetin alfa for eight weeks. During the second stage of the study, the participants received either 12 weeks of EPO plus intravenous iron sucrose (a sugar) or just EPO alone.

Adding intravenous iron sucrose to EPO resulted in higher hemoglobin levels than treatment without iron sucrose. Hemoglobin is the part of the red blood cells that carry oxygen to the tissues in the body. Measuring the level of hemoglobin tells doctors whether a person has anemia. Specifically, low hemoglobin levels result in anemia.

In the third study, researchers from Pennsylvania Hospital in Philadelphia also tested the addition of intravenous iron to EPO in more than 175 people with anemia related to chemotherapy. Intravenous iron was compared with no iron treatment for eight weeks. Patients also received epoetin alfa for the first month of treatment.

By the end of the clinical trial, hemoglobin levels were significantly higher in people who received intravenous iron than

What's New, What's Important

- Doctors and the people they are treating with bisphosphonates should be aware that these drugs can cause jaw complications.
- In people with bone metastases who have higher levels of a substance called N-telopeptide, treatment with zoledronic acid (Zometa) can reduce the risk of bone complications.
- Certain factors place older people with cancer at higher risk of developing a complication from chemotherapy called neutropenia, a low white blood cell count that can increase their risk of infection. With this information, doctors can then treat them appropriately with myeloid growth factors to prevent neutropenia.
- All survivors of childhood cancer should be aware of their increased health risks and receive regular follow-up medical care.

in those who did not. Only patients treated with intravenous iron had a major improvement in their fatigue symptoms.

Bone Health and Cancer Treatment

OSTEONECROSIS OF THE JAW

Bisphosphonates are drugs often used to treat cancer that has spread to bone. These medications help prevent the loss of calcium from bone, reduce bone pain, strengthen bone, and reduce the risk of fractures. But researchers from Roswell Park Cancer Institute in Buffalo, New York, the University of Tennessee Health Science Center in Memphis, and M. D. Anderson Cancer Center in Houston, Texas, have found that bisphosphonates may increase the chances of developing a rare but potentially serious side effect called osteonecrosis (loss or breakdown of bone) of the jaw.

They studied the records of more than 5,000 people who were treated with intravenous bisphosphonates for many different

cancers. About 65 of these patients developed osteonecrosis of the jaw. Patients who developed this unusual side effect had received more injections than those who did not.

This finding suggests that any existing dental problems should be addressed before the start of treatment with bisphosphonates.

REDUCING THE RISK OF BONE BREAKS WITH ZOLEDRONIC ACID (ZOMETA)

Metastases from breast, prostate, lung, and kidney tumors can weaken bones. Patients can experience bone breaks, sometimes spontaneously, without any apparent injury. Studies have shown that elevated levels of a substance called N-telopeptide (NTX) in people with metastases to the bone are linked to an increased risk of bone fractures, cancer growth, and even death in some cases.

Researchers from around the world, including the United States, United Kingdom, and Canada, wanted to find out whether reducing NTX levels with the bisphosphonate zoledronic acid (Zometa) would reduce the risks.

They analyzed three large clinical trials of zoledronic acid that included people with bone metastases from cancers of the breast (nearly 380), the prostate (more than 300), and the lungs or other organs (more than 200). About half the patients had elevated NTX levels at the start of treatment with zoledronic acid. Within three months, NTX levels returned to normal in about 80 percent of those with cancer of the breast, lung, and other organs who previously had elevated NTX levels. NTX levels returned to normal in 70 percent of those with prostate cancer who previously had elevated NTX levels. (Almost all the patients who had normal levels of NTX at the beginning of the clinical trial maintained those levels.)

Regardless of the tumor type, the return to normal NTX levels was associated with a reduced risk of a first-time bone-related

complication and death, compared with NTX levels that did not return to normal.

Infection in Older People With Cancer

RISK OF CHEMOTHERAPY-RELATED INFECTION

Doctors may now be able to determine which older people with cancer are likely to develop a complication from chemotherapy called **neutropenia**, a low white blood cell count that can increase their risk of infection. With this information, doctors can then treat those at increased risk with the right drugs to prevent this problem.

Researchers from the University of Rochester, in New York, collected data on nearly 1,400 older people with cancer, all of whom were at least 65. The patients were being treated at more than 100 randomly selected centers for lung, breast, colorectal, ovarian, or blood cancers.

The researchers found that certain factors put patients at risk for neutropenia during the first cycle of chemotherapy. The factors include the use of drugs called **anthracyclines**, increased levels of bilirubin (a yellowish fluid found in the liver and blood), and reduced kidney function. Using these risk factors as a guide, doctors may be able to select which older people with cancer who are having chemotherapy are at increased risk of neutropenia and could benefit from using myeloid growth factors—drugs that help reduce the risk.

Follow-Up Care

A MUST FOR CHILDHOOD CANCER SURVIVORS

Survivors of childhood cancer may be at high risk for health problems later in life as a result of their cancer or its treatment. Over time, approximately two-thirds of childhood cancer survivors will develop at least one medical condition such as

another cancer, heart problems, lung disease, stroke, or early menopause. Even though these people require regular follow-up medical care because of their cancer history, the results of a new study show that very few are getting it. Much can be learned from this study to help educate cancer patients and their family doctors about the importance of continued health care.

The Childhood Cancer Survivor Study (CCSS) sponsored by the National Cancer Institute, follows people who survived at least five years after being diagnosed with cancer between 1970 and 1986. More than 8,000 members completed a questionnaire about the health care they received within the past two years. More than two-thirds of those surveyed had received general medical care, but less than half had received cancer-related care. For instance, just about half of survivors at risk for breast cancer reported having a mammogram (X-ray of the breast). Such a test can help diagnose breast cancer early, when treatment has the best chance of success.

Researchers encourage all survivors of childhood cancer to be aware of their risk of later health problems and to receive regular follow-up medical care. Survivors should tell their doctors that they have been treated for cancer and, if possible, give their doctors a record of the drugs and doses of chemotherapy and radiation used.

Please note: Although the treatments discussed in this chapter are showing promise, most are still in clinical trials—some in earlier phases of research—and may not be available yet to the general public. Your doctor can help guide you as to which new medications could be right for you and whether you are eligible to take part in the clinical trials of these new treatments.

