

LE Magazine January 1999

## On The COVER

### Battling Back Against Cancer-Induced Bone Metastasis and Pain

By William Faloon

A European therapy is showing remarkable success in treating a host of diseases, including multiple myeloma, osteoporosis and breast cancer.

It usually is detected as a small lump in the breast. A biopsy then determines if it's cancer. In the next 12 months, 180,000 women will find out that they do, indeed, have breast cancer and 46,000 will die from the disease. Since breasts are not essential to sustain life, breast cancer cells inflict their lethal effects when they metastasize to the lung, liver, brain, bone and other organs.

As this metastatic process progresses, patients may face excruciating bone pain at the same time their internal organs are failing. Pneumonia and liver failure are common, direct causes of death from breast cancer cell metastasis, while bone fractures are the most frequent cause of disability as tumor cells infiltrate into the bone and cause calcium to be displaced into the blood. As bone is broken down by tumor cells, growth factors are released from the bone matrix that promote cancer cell proliferation. In addition to fractures, complications of bone metastasis include spinal cord compression and hypercalcemia, or too much calcium in the blood. Bone metastasis develops in about 75% of those women who eventually die from breast cancer.

However, for at least 15 years, a therapy has been available that is known to reduce the incidence of bone metastasis, relieve bone pain, prevent fractures and reverse hypercalcemia. In a study published in the Aug. 6, 1998, *New England Journal of Medicine*, women who received the drug clodronate showed a 50% reduction in both bone and visceral (lung, liver) metastasis, compared with placebo. The most stunning statistic showed that over a 36-month period, those in the placebo group were 366% more likely to die, compared with those receiving the clodronate therapy. Despite these facts, clodronate is not approved by the FDA.

#### The 'New' Cancer Drug

Breast and prostate cancer cells frequently metastasize to the bone where they cause severe degradation of bone tissue. Multiple myeloma is a primary cancer that degrades bone. Arrayed against this action are bisphosphonates, a class of drug that protects against the degradation of bone primarily by inhibiting excess activity of osteoclasts, bone cells that absorb and remove bone tissue so that the bone-producing *osteoblasts* can bring together the minerals calcium, magnesium and phosphorous to form new healthy bone. When osteoclasts become overactive, they break down too much bone, which can result in a pathological reduction of bone density.

Clodronate, one of the most investigated of the bisphosphonate class of drugs, has been clinically used for more than 15 years in treating malignant diseases. It is the most-used, most-effective and safest drug in the treatment of hypercalcemia. It inhibits bone destruction, prevents bone fractures, relieves bone pain and prevents the development of new bone lesions. Clodronate may even reduce mortality. Large-scale studies in humans with breast cancer indicate the benefits of prolonged administration of clodronate to reduce the frequency of pathological skeletal events, and reduce as well the need for radiation therapy.

*The New England Journal of Medicine* study confirmed many previous studies showing that breast cancer patients receiving clodronate experienced about half the number of metastatic lesions to the bone, compared with the placebo group.

Another study conducted in Finland showed improved survival when breast-cancer patients were treated with clodronate or placebo. Bone pain, extension of bone metastasis and formation of new bony metastatic lesions were reduced by clodronate, and development of severe hypercalcemia was prevented during the first 12-month period. The patients were then withdrawn from clodronate treatment and followed for at least 12 months, during which time there were fewer fractures and less hypercalcemia in the patients previously treated with clodronate than in the placebo group. The survival rate was higher in the clodronate group compared with the placebo group, and no side effects were observed in either group.

While clodronate has been investigated as a therapy for advanced metastatic bone cancer in dozens of human studies, only two

studies show that clodronate improved breast cancer patient survival. However, it would appear that if clodronate were administered earlier in the disease state, it could significantly prolong survival, as was demonstrated in *The New England Journal of Medicine* study.

## Hypercalcemia

As noted, tumor-induced hypercalcemia is essentially due to an increase in osteoclast-induced breakdown of the bone into the blood. During this process of bone destruction, substances such as growth factors are released that promote tumor cell growth. Since the bisphosphonates are potent inhibitors of osteoclast activity, they represent an effective method of safely treating hypercalcemic events that frequently occur in patients with breast cancer and other diseases.

In a double-blind multicenter study, the effect of intravenous clodronate-plus-hydration was compared with placebo-plus-hydration in the treatment of hypercalcemia in breast cancer patients with bone metastases. A significant difference in favor of clodronate was observed in the time taken to return to normal blood calcium. A total of 17 of 21 patients on clodronate achieved normal blood levels of calcium, compared with only four of 19 patients on placebo. The only adverse event associated with clodronate was symptomatic hypocalcemia (too little calcium in the blood) in one patient.

In 1991, Italian scientists reviewed 126 publications on clinical studies concerning the use of clodronate in the therapy of bone disease, finding that clodronate therapy does not have any clinically significant side effects, and is tolerable and safe. However, it is still advisable to have a blood test within 10 days of beginning clodronate therapy to make sure clodronate is not removing too much calcium from the blood.

## Bone Pain

The acute pain-relieving effect of bisphosphonate drugs like clodronate occurs within days or a week. In fact, in a controlled trial using clodronate in patients with metastatic bone disease and pain, more than twice as many patients chose clodronate for pain than placebo.

In another study of tumor patients with bone metastases or related hypercalcemia, 71.4% indicated an improvement in quality of life. And in yet another trial, three-quarters of postmenopausal women with skeletal metastases from breast cancer treated with clodronate and tamoxifen, a standard hormonal therapy, experienced pain relief. Serum bone marker levels indicated stabilization of skeletal metastatic lesions.

As far as calcium in the blood is concerned, another trial produced a 47 percent reduction among breast cancer patients with bone metastasis, compared with placebo. Vertebral fractures were reduced by one-third. Vertebral deformity was also reduced, as was bone pain. In patients who receive clodronate before developing bone metastasis, the results are even more dramatic, showing consistent 50% reductions in skeletal metastasis and fractures.

An inevitable conclusion may be that all breast cancer patients should consider supplementing with 800 milligrams of clodronate twice a day for metastatic prevention purposes.

## Protecting Bone

Women with primary breast cancer who receive chemotherapy may experience ovarian failure or early menopause, leading to a loss of bone-mineral density. However, clodronate reduced bone density loss in one study of women with breast cancer, compared with placebo. Another study, with post-menopausal breast cancer patients without skeletal metastases who were being treated with clodronate and tamoxifen, confirms this result. There were no significant changes in patients given anti-estrogen drugs only. (Doctors often advise cancer patients using clodronate to take plenty of calcium, magnesium and even phosphorous to enable bones to regenerate.)

Yet another study in two oncology centers in the United Kingdom and Canada on breast cancer victims who had not experienced skeletal metastases showed that the incidence of skeletal metastases was significantly lower with clodronate treatment than with placebo.

The molecular mechanisms by which tumor cells degrade bone involve tumor cell adhesion to bone as well as the release of toxic chemicals from tumor cells that stimulate osteoclast-induced bone degradation. Bisphosphonates inhibit both cancer-cell adhesion to the bone matrix and (as noted) osteoclast activity. By preventing tumor cell adhesion, bisphosphonates are useful agents for the prophylactic treatment of patients with cancer that is known to preferentially metastasize to bone.

There is evidence that growth factors such as insulin-like growth factor and transforming growth factor are released when the bone matrix is degraded. These growth factors could stimulate tumor cell proliferation throughout the body, which may be a reason that

early use of clodronate has significantly improved survival.

A large number of clinical studies indicate that clodronate is a safe and efficacious drug.

### Prostate Cancer

The majority of patients with advanced prostate carcinoma have painful skeletal metastases. Some studies show that clodronate can enable patients to be maintained free of bone pain, even up to eventual death. Other studies show that clodronate is only moderately effective in the long-term alleviation of prostate cancer bone pain.

However, it may be instrumental in causing other treatments to be more effective. For example, estramustine phosphate is generally used as a second-line treatment in patients with advanced prostate cancer, and in Europe, clodronate is often used as an adjunct to treat bone metastases, and relieve the attendant bone pain. Therefore, the interaction of clodronate and estramustine phosphate and their bioavailability were studied in 12 patients with prostate carcinoma and bone metastases. The serum concentrations of estramustine phosphate were elevated by about 80% when the drug was given together with clodronate. The urinary excretion of estrone, a major metabolite of estramustine phosphate, also was significantly higher after the admission with clodronate, all suggesting that clodronate increases the oral bioavailability, and thus effectiveness, of beneficial estramustine phosphate treatment.

Nevertheless, the majority of studies show that clodronate is more effective in preventing and treating breast cancer metastasis than it is in treating prostate cancer metastasis to bone.

### Multiple Myeloma

Myeloma is a bone-destroying primary tumor. It may develop at the same time in many sites and cause large areas of patch destruction of the bone. Multiple myeloma is a bone marrow cancer that also destroys bone tissue. A review of the literature shows the prominent place of clodronate in the treatment of multiple myeloma.

In one study, 15 newly diagnosed and untreated patients with multiple myeloma received chemotherapy and clodronate for six months. Treatment response was compared with chemotherapy administered in the historical group of patients. The results showed that the proportion of patients with progressive bone lesions was twice as high in the group not getting clodronate. Clodronate helped reduce the incidence of severe pain by nearly three-fourths. Needless to say, the changes led to radical improvements in the patients' reported quality of life.

The objective of another study was to evaluate the effect of clodronate on the development of bone density in patients with multiple myeloma. A total of 22 patients who were treated for more than 12 months with clodronate were evaluated. The patients were given clodronate in intravenous infusions (five infusions of 600 mg) in three-month intervals. At the onset of the investigation, three patients had a decline in blood calcium values, but as soon as regular administration of calcium supplements was started, blood calcium levels returned to normal. Clodronate was shown to stabilize the amount of bone mass, reduce pain and also improve the quality of the patients' lives.

As for clodronate taken orally, another study treating multiple myeloma showed that after treatment, there was a higher bone response in the clodronate group (13%) when compared with the control group (6%). Hypercalcemia was observed more often in the control group. The number of progressive sites was 26% lower in the clodronate group compared with placebo. The bone resorption index was significantly reduced in the clodronate group, but not in the control group. A reduction of pain and analgesic consumption was observed under clodronate treatment.

Other multiple myeloma studies demonstrated that progression of skeletal disease occurred 31% less often in patients who received clodronate, and survival was longer. Finnish and English studies have demonstrated that clodronate delayed the progression of bone lesions, and the English study showed lessened pain and a slight reduction in the progression of vertebral fractures.

In another British study, scientists explained how the increase in osteoclast activity is caused by osteoclast-activating factors secreted by myeloma cells. These bony lesions do not respond well to standard chemotherapy. It was noted that clodronate is a potent inhibitor of osteoclast activity and does not impair bone mineralization. In a long-term (18 months) placebo-controlled study, these scientists showed that clodronate, given orally at a daily dose of 1,600 mg can decrease both the incidence of the pathological fractures and the activity of osteoclasts. These results, along with those from other studies suggest that clodronate may inhibit the progression of malignant lesions in multiple myeloma.

While the Food and Drug Administration was keeping Americans from accessing clodronate, the agency did approve an expensive bisphosphonate drug in 1996 called pamidronate and sold under the trade name Aredia. Treatment with Aredia costs more than

\$2,000 a month and must be administered in a medical setting via a 4- to 24-hour intravenous infusion.

The high cost of Aredia has caused hmo's and other insurance companies to refuse to pay for it. Insurance companies also can avoid covering Aredia treatment in early stage breast cancer because the FDA has approved it for the treatment of "moderate to severe hypercalcemia associated with malignancy." Women with metastatic breast cancer, however, often do not manifest serious hypercalcemia until the disease has significantly progressed. The FDA has thus restricted the use even of Aredia in a way that makes it more of a palliative therapy in advanced disease, rather than a potential life-saving therapy used early in the disease state.

The FDA also has approved Aredia for treating multiple myeloma and Paget's disease, but here again, insurance companies can insist that the patient be treated with old-line FDA-approved biphosphonates that are not as effective as Aredia or clodronate.

A review of the published literature provides conflicting results as to whether clodronate or Aredia is the better drug. Proponents of Aredia state it provides a longer period of remission from hypercalcemia. One study compared single infusions of either Aredia or clodronate at the highest doses commonly used. A total of 100% of patients in the Aredia group achieved normal serum calcium following Aredia, compared with 80% receiving clodronate. The median time to achieve normal serum calcium was four days for Aredia and three days with clodronate. The median duration of normalized serum calcium was 28 days after Aredia and 14 days after clodronate. Two patients who failed to respond to clodronate were successfully treated with Aredia. Two patients experienced fever after Aredia but no significant toxicity was observed with either treatment. The doctors concluded, "Both agents are effective in the management of hypercalcemia of malignancy. At the doses studied, the effects of Aredia are more complete and longer-lasting than those of clodronate."

What the above study did not mention is that clodronate can be taken orally every day, while Aredia administration is restricted to intravenous infusion. The fact that the calcium normalizing effects of a single dose of Aredia lasted twice as long as a single dose of clodronate does not reveal much, since it was already known that clodronate should be taken every day by mouth to maintain its effects. The major unpleasant side effect to Aredia is a transient fever, sometimes accompanied by flu-like symptoms such as myalgia and lymphopenia. Clodronate, on the other hand, appears to be free of unpleasant side effects, other than the very rare case of causing too little calcium in the blood (hypocalcemia).

Further, there is no evidence to show that Aredia increases survival or prevents the development of metastasis in breast cancer. Two studies show clodronate can improve survival. The greatest concern to cancer patients, however, may be that Aredia has been consistently shown to significantly elevate blood levels of the tumor necrosis factor and interleukin-6 (il-6), which have differing effects on various cancer cell lines. Clodronate does not increase these cytokines.

Here is another worry: One study comparing the effects of Aredia and clodronate on cancer patients showed a significant decrease in lymphocyte and leukocyte count in the Aredia group. In the same group, seven patients (24%) showed a transient increase of body temperature. These changes were not found in the patients treated with clodronate. Plasma il-6 and serum tumor necrosis factor (tnf) levels increased significantly after Aredia treatment, whereas no change was seen after clodronate infusion.

Why is this worrisome? Breast cancer patients already have elevated levels of tnf and il-6. Elevation of these two cytokines reflects an advanced disease state and impending death. High serum level of il-6 also is regarded as a predictor of poor prognosis in multiple myeloma, and a more advanced disease. Clodronate does not boost toxic il-6.

In addition, patients with elevated serum tnf levels have a significantly higher mortality rate than those with undetectable serum tnf levels. These findings suggest that tnf may be one of the factors contributing to wasting syndrome in patients with prostate cancer. tnf also is involved in inducing autoimmune inflammatory disease. A study evaluated the possible anti-inflammatory action of Aredia and clodronate and found that low concentrations of Aredia induced il-6

### A Needless Suppression

The Food and Drug Administration's suppression of clodronate may have caused the premature or needless death of about 30,000 American women each year, based on the Aug. 6, 1998, *New England Journal of Medicine* study. Since clodronate could have been made available 15 years ago, about 517,000 American breast cancer victims were forced to suffer agonizing bone metastasis, and a total of 450,000 women probably died prematurely because the FDA aggressively denied this drug to cancer patients.

It is difficult for people to comprehend how many Americans suffer and die because of the FDA's failure to approve safe medications fast enough. Clodronate is non-toxic and its efficacy has been proven in hundreds of scientific studies, yet the FDA has sent agents to other countries in order to shut down companies that ship this therapy to American cancer patients.

Clodronate is a stark example of the FDA's willingness to let Americans suffer and die in order to protect the enormous profits of the pharmaceutical industry. The worst part about this is that so many Americans know the FDA is incompetent and corrupt, yet

sit back and do nothing, while watching those they care about suffer and die needlessly. Can we draw medical analogies from other countries to show how governments cause their citizens to die in order to further political ideologies? An extreme example is occurring in Afghanistan right now. The fundamentalist Taliban government has decreed that women are not allowed to practice medicine and that male doctors are not allowed to touch or see the bodies of female patients. Thus, health care for women effectively has been eliminated. Women and children are dying needlessly from illnesses that are left untreated. How are the Afghans coping with this problem? In some cases, a male relative will go to a doctor and point to places on his own body where the female patient feels pain. The doctor then prescribes medication for the male relative to procure for her.

If the medical situation in Afghanistan sounds barbaric, it is. But so is the FDA's position when it denies American breast cancer patients a proven therapy that has safely been used in Europe and other countries for almost 20 years. The fact that clodronate is non-toxic, is not terribly expensive, and has been shown to improve survival would make it the drug of choice in a free market.

#### In use against . . . Hyperparathyroidism

European doctors have found that clodronate is effective in restoring normal calcium levels in both primary and secondary hyperparathyroidism, thus avoiding the need for surgery in many people. In one study, clodronate was given by mouth for two to 32 weeks (1.0-3.2 grams daily) to nine patients with primary hyperparathyroidism. In all patients, blood markers of parathyroid disease were restored to normal with the most important marker being the serum calcium concentration. All patients, of course, had too much calcium in their blood before treatment. After treatment, serum calcium levels fell to the upper end of the normal range in all patients. Hypercalcemia (too much blood calcium) and hypercalciuria (too much calcium in the urine) recurred when treatment was stopped. These results suggest that clodronate may be of use in the medical management of primary hyperparathyroidism, particularly in patients in whom suppression of bone disease is desirable before surgery or in whom surgery is contraindicated.

In the case of secondary hyperparathyroidism, studies indicate that clodronate (800 mg taken twice a day) along with 2,500 mg of calcium and 1,000 international units of vitamin D3 a day, could restore proper metabolic balance and thus stop the parathyroid glands from secreting too much PTH. When treating secondary parathyroidism, clodronate may be needed only for two to eight weeks, but the calcium and vitamin D3 supplementation should continue.

#### How to Obtain, Use Clodronate

For a free directory of offshore companies that ship some unapproved medications, such as clodronate, to Americans, write to: International Society for Free Choice, 9 Dubnoc Street, 64368 Tel Aviv, Israel. The standard dose for treating cancer is 800 mg of clodronate, taken twice a day. In some studies, twice this dose has been safely used. It should be noted that biphosphonate drugs like clodronate are considered adjuvant cancer therapies because conventional therapies (such as cytotoxic chemotherapy) are almost always used with clodronate. In other words, clodronate does not directly kill cancer cells, but it does prevent metastasis.

Breast cancer patients may want to consider a three-to-five year regimen of clodronate therapy. Blood tests to measure serum calcium levels and kidney function should be done 10 days after initiating clodronate therapy and every one to two months thereafter. The concern for a small minority of people is that clodronate will cause too much calcium to be pulled from the blood to the bone. Regular blood testing will detect a serum calcium deficit. One study warns those suffering from severe renal insufficiency against taking clodronate. The kidneys normally remove excess clodronate, and dialysis may not efficiently remove clodronate from the blood. Another study encourages clodronate to be used in renal disease when hypercalcemia is present. Regular blood tests can detect kidney problems early, though clodronate dose not appear to cause kidney disease.

Do not use clodronate if you are pregnant because it could adversely effect calcium metabolism to the fetus.

[Back to the Magazine Forum](#)

treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.