

## FEATURE STORY

# Good to the Bone

BY PAUL ENGSTROM

*Proactive strategy has patients taking preventive steps to protect their bones during therapy.*

Bone health was on Karen Tappin's radar screen long before she underwent a bilateral mastectomy in early 2001. Her mother had suffered fractures of the hip, femur, fibula, knee cap, and wrist possibly due to osteoporosis, severe bone loss that carries a higher-than-normal fracture risk and has a strong genetic link. And for years Tappin, of Healdsburg, California, has been troubled by osteopenia—thinning of bone mass that can lead to osteoporosis.

But bone health became an even greater concern for Tappin after her breast cancer surgery because, as she learned, some chemotherapies, like the Cytosan (cyclophosphamide) she received along with Adriamycin (doxorubicin), may directly affect bone metabolism independent of their effect on hormones. To counter that potential threat and the greater risk of fracture, the 64-year-old retired coordinator of special school programs takes Fosamax (alendronate)—a drug for treating or preventing osteoporosis in postmenopausal women—as well as calcium and vitamin D supplements.

Tappin's case highlights the balancing act some clinicians and their cancer patients must perform: Treating the disease effectively but preventing collateral bone damage and the higher fracture risk associated with it. The types of fracture most often related to bone loss occur in the hip, vertebra, and wrist, and can result in permanent disability in some patients.



Karen Tappin's family history coupled with certain cancer therapies led her to develop a plan to protect her bones. Photo by Jason Ballard

When most patients start cancer treatment, bone health is “very low on their priority list,” says Julie Gralow, MD, a medical oncologist at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, whose specialty is breast cancer. “They’re more worried about getting a good regimen that will give them the best chance of reducing their risk of [cancer] recurrence. They’re not thinking about their long-term health until after treatment is done in the [post-surgery] setting.”

Experts note, however, that as better therapies improve patients' longevity, early diagnosis and prevention of osteoporosis are critical because fractures can have a

severe impact on quality of life and mortality of long-term cancer survivors. According to one study, 352 recently diagnosed breast cancer patients had a 2.72 percent annual incidence of vertebral fractures compared with 0.53 percent annual incidence in a control group of 776 women.

The Women's Health Initiative looked at the incidence of self-reported fractures among women with and without a history of breast cancer (average follow-up was five years). For hip fractures, the cumulative fracture incidence was similar between both groups, but postmenopausal breast cancer survivors suffered a significantly greater incidence of wrist and lower arm fracture, and of total fractures.

## A Common Culprit

Although anyone receiving chemotherapy can experience bone loss, it occurs most commonly in those who undergo hormone-modifying treatments. These comprise aromatase inhibitors, such as Arimidex (anastrozole), Femara (letrozole), and Aromasin (exemestane), for postmenopausal women; removing or shutting down the ovaries in premenopausal women; and androgen deprivation therapy, which involves removing the testicles or treatment with luteinizing hormone-releasing hormone (LHRH) analogs and LHRH antagonists, for men with prostate cancer. Estrogen in men and women and androgens (including testosterone) in men play key roles in maintaining a healthy balance between bone-building osteoblasts and bone-eating osteoclasts.

Regarding prostate cancer patients, results from several prospective studies revealed that all forms of androgen deprivation therapy caused annual bone mineral density decreases of up to 9.6 percent, thus increasing the risk of fracture. This was much greater than the decrease associated with postmenopausal women taking the aromatase inhibitor Aromasin, who lost bone mineral density at a mean annual rate of 2.7 percent, according to research reported recently in the *Journal of Clinical Oncology*.

Aromatase inhibitors for postmenopausal women block the conversion of androgens to estrogen by the enzyme aromatase. In effect, they deprive tumors of growth signals from estrogen. Ovarian ablative therapies for premenopausal women—removal of the ovaries, chemotherapy to shut down the ovaries, and radiation—also can lead to bone loss because they halt the production of hormones.

For prostate cancer, patterns of care have changed dramatically in recent decades, says Matthew Smith, MD, PhD, director of research in the genitourinary medical oncology unit at Massachusetts General Hospital Cancer Center. "Androgen deprivation therapy is used much more broadly and earlier in the course of the disease," Dr. Smith says. "In many cases, hormones have improved outcomes in a variety of settings. But because we treat early and often in asymptomatic men, there's been an increased [bone loss] burden on cancer survivors."

Patients with other common cancers, such as lung and colorectal, aren't particularly at risk for bone loss because therapies for those tumors don't involve

hormone deprivation. A cancer where the tumor itself poses a bone health hazard is multiple myeloma, which originates in bone marrow. The body's immune system depends in part on healthy plasma cells in the blood, and when these cells become cancerous, they eat away portions of bone and can secrete substances that increase loss of bone calcium, thus increasing the risk of fracture.

View Illustration: Rebuilding the Bone

## Key Predictors

Patients and their doctors can do a number of things to prevent osteoporosis, whether it's a result of cancer treatment or other factors. Determining if someone has a family history of osteoporosis, a personal history of fracture, or symptoms such as bone pain are important indicators of changes in bone structure, says Susan Slovin, MD, PhD, a genitourinary oncologist at Memorial Sloan-Kettering Cancer Center in New York.

For people at risk of osteoporosis, experts recommend daily supplements of calcium, a building block in bone formation, and vitamin D, which maximizes the body's absorption of calcium. The skin manufactures enough vitamin D after 10 to 15 minutes of direct sun exposure, but a variety of factors can affect an individual's ability to produce vitamin D. Fortified or soy milk, fortified orange juice and cereal, yogurt, egg yolks, saltwater fish, and liver are good sources of natural vitamin D.

Not smoking, avoiding excessive alcohol, and regular weight-bearing exercise, such as climbing stairs, jumping rope, walking, and dancing, also promote bone health. Exercise stimulates the production of cells that cause bone formation and builds stronger muscles that provide more stability while walking, thus lowering the risk of fracture due to a fall.

"The majority of my patients know that good physical activity, maintaining good body weight, and eating a healthy diet all matter," says Dr. Gralow. "But I don't know that we, as oncologists in the medical community, enforce these strategies enough."

Experts believe clinical follow-up of patients with bone loss caused by cancer treatment and regular assessment of bone health are inadequate, partly because the responsibility for follow-up may not be clearly delineated among a patient's often numerous caregivers. Karen Tappin says she became a strong self-advocate of her own bone health to avoid this pitfall—a strategy clinicians endorse.

"I'm not passive," Tappin says. "I go in to see the doctor with questions like, 'Should I be doing this? What do you think about that?' And I'm always checking the latest research."

## Halting Bone Breakdown

The majority of osteoporosis drugs slow the destructive resorption, or breakdown, of bone, making it more resistant to fracture. Among these compounds are bisphosphonates, selective estrogen receptor modulators

(SERMs), calcitonin, and receptor activator of NF- $\kappa$ B ligand (RANKL) blockers. The only Food and Drug Administration-approved agent that prevents bone loss and dramatically reduces risk of fracture is Forteo (teriparatide), a recombinant human parathyroid hormone treatment that patients self-inject daily. Since long-term safety and effectiveness data are unclear, the maximum recommended treatment period of parathyroid hormone therapy is about two years.

Bisphosphonates, the most effective treatment for cancer-related bone loss and the only agents (other than estrogen replacement therapy) known to lower the incidence of hip and vertebral fractures, attach to the surface of bone and inhibit bone resorption, thereby promoting an increase in bone mineral density. Depending on the specific agent, they are available in daily, weekly, and monthly oral and intravenous formulations, including Zometa (zoledronic acid), Fosamax, Aredia (pamidronate), Actonel (risedronate), and Boniva (ibandronate).

In August 2007, the FDA approved a form of zoledronic acid called Reclast for postmenopausal osteoporosis that patients receive just once a year by infusion. And preliminary results from a five-year study known as Z-FAST suggest that in postmenopausal women with early-stage breast cancer, a combination of Zometa and Femara effectively suppresses bone loss.

Although bisphosphonates are generally well tolerated, they can cause stomach or esophagus irritation, nausea, and heartburn. They also may alter kidney function or, in rare cases, damage jaw bone when patients take high intravenous doses over a long period.

Given these risks, 84-year-old David Michener, MD, a retired physician in Point Richmond, California, has avoided bisphosphonates since he was diagnosed with prostate cancer in 1992 and had his testicles removed. Despite replacement testosterone, calcium and vitamin D supplements, and daily weight-bearing exercise, which he describes as an “annoying interference, but tolerable,” a DEXA scan last May showed the bone mineral density in his left hip had declined by more than 16 percent since early 2001.

“It’s likely in the next few months we will need to consider bisphosphonates,” Dr. Michener says.

In postmenopausal women who lack sufficient estrogen, SERMs tamoxifen and Evista (raloxifene) can promote absorption of calcium by bone. Although tamoxifen mimics estrogen’s effect on the bone, the drug blocks estrogen’s effect on breast tissue, which is why clinicians use it to treat metastatic breast cancer or to prevent breast cancer recurrence. Evista is the only FDA-approved SERM for preventing and treating osteoporosis. (Evista was approved in September 2007 for reducing breast cancer risk.) Side effects of SERMs include leg cramps, hot flashes, and blood clots.

Another option for patients is Miacalcin (calcitonin), which inhibits the formation and activity of bone-eating osteoclasts. Although clinical trials of its effectiveness in patients with bone loss resulting from cancer therapy have not been conducted, Miacalcin has proven effective in treating postmenopausal osteoporosis. Side effects of Miacalcin include flushing and upset stomach.

Among the most promising investigational agents to promote bone health in cancer patients are RANKL blockers and synthetic osteoprotegerin, a naturally

occurring protein in the body that reduces osteoclast production. Researchers are developing monoclonal antibodies to block RANKL, a pathway that controls the activation, differentiation, proliferation, and survival of osteoclasts.

Researchers say denosumab, a RANKL antibody, could be an effective treatment for osteoporosis based on preliminary results from a clinical trial involving 412 postmenopausal women with low bone mass that suggests denosumab significantly increases bone mineral density and reduces bone resorption.

Experts view such results to be among the most positive findings from research on new therapies. Such strides will surely complement the greater attention good bone health in cancer survivors is receiving among both patients and clinicians.