New Studies Support Case for Bisphosphonates as Possible Chemopreventive Agent

By Charlie Schmidt

Attendees at the San Antonio Breast Cancer Symposium in December were treated to a remarkable coincidence: two scientists, each unaware of the other’s research, reporting the same findings in back-to-back presentations. Rowan Chlebowski, M.D., Ph.D., from the University of California, Los Angeles, and Gad Rennert, M.D., Ph.D., from the Technion-Israel Institute of Technology, in Haifa, both described evidence to suggest that bisphosphonate treatment for bone loss protects against breast cancer in postmenopausal women.

Chlebowski reviewed case data from the Women’s Health Initiative—an investigation into causes of death and disability in postmenopausal women administered by the National Institutes of Health—and found statistically significantly fewer diagnoses of breast cancer among women who take bisphosphonates than in those who do not. A total of 5,092 invasive breast cancers were diagnosed after 1,163,344 person-years of follow-up (for a rate of 4.38/1,000 person-years). The difference represented a statistically significant 32% reduction in the incidence of invasive breast cancer.

Similarly, Rennert investigated data from the Breast Cancer in Northern Israel study, which he directs, and found that bisphosphonates were associated with a statistically significant 29% drop in relative risk for breast cancer. Specifically, Rennert found that among 2,207 control subjects who did not get breast cancer, 280 used bisphosphonates for more than 1 year. In contrast, among the 1,832 women who did develop breast cancer, 150 used bisphosphonates for more than a year. This difference of 35% dropped to 29% after adjustment for age, diet, family history, and other risk factors.

Both Rennert and Chlebowski are now preparing their results (presented as abstracts in San Antonio) for peer-reviewed publication.

A New Chemoprevention Agent?

Bisphosphonates could make a welcome addition to the current list of breast cancer–preventing drugs, according to Sandhya Pruthi, M.D., director of the breast clinic and assistant professor of medicine at the Mayo Clinic in Rochester, Minn. Pruthi was the Mayo Clinic’s principal investigator on the National Cancer Institute–funded Study of Tamoxifen and Raloxifene (STAR) trial, which concluded in the late 1990s that each drug cuts the risk of invasive breast cancer in postmenopausal women by half. While tamoxifen and raloxifene prevent estrogen receptor (ER)–positive breast cancer, bisphosphonates might also prevent ER-negative cases, which account for up to one-third of all new breast cancer diagnoses, Pruthi said. In Chlebowski’s study, zoledronic acid (Zometa) reduced ER-positive diagnoses by 32% and ER-negative diagnoses by 34%. Unlike the ER-positive data, the latter findings weren’t statistically significant, perhaps owing to fewer patients with ER-negative disease, Chlebowski said. Likewise, Rennert said his results were strongest for ER-positive cases, on account of fewer ER-negative cancers overall. Both tamoxifen and raloxifene inhibit tumor growth by interfering with estrogen activity. Bisphosphonates, on the other hand, kill osteoclasts, which are bone cells that consume skeletal tissue, leading to a loss of bone density and a higher risk of fracture. Millions of women take bisphosphonates.
According to IMS Health, alendronate (Fosamax) is the most widely prescribed bisphosphonate; in 2006, it was the 21st-most-prescribed drug on the market. Used primarily to treat osteoporosis and related conditions, bisphosphonates also affect cancer cells, although how they do so remains unclear.

“The fact that we see similar trends in ER-positive and ER-negative cases argues for mechanisms that aren’t hormonally dependent,” Chlebowski said. “It really supports a role for other pathways in prevention, like angiogenesis inhibition, immune modulation, or an indirect effect on growth factors released by bone.”

Still, bisphosphonates aren’t risk free. Oral use can result in gastrointestinal problems, including esophagitis, Pruthi said. And bisphosphonates given intravenously to a minority of women with osteoporosis—an administration that Pruthi said would be inappropriate for cancer prevention—can sometimes produce osteonecrosis of the jaw after dental procedures. On the other hand, both tamoxifen and raloxifene can produce vaginal dryness and heat flashes in up to 25% of women, if not more, Pruthi added. Moreover, roughly one in every 2,000 women who take tamoxifen develops endometrial cancer.

Confounding by Low Bone Density

The new findings have a caveat, however. Bone loss in postmenopausal women and others at risk of osteoporosis typically results from declines in estrogen, which also protect against breast cancer. It’s therefore possible that women who take bisphosphonates are inherently less vulnerable to the disease, with their underlying hormonal status. Rennert acknowledged that both studies’ descriptive, case-control approaches couldn’t isolate the effects of bisphosphonates from low bone mineral density on cancer risk. Still, his research showed that prevention was apparent only with treatments lasting at least 1 year. “The fact that we see the effect only after that duration signals that it’s probably something to do with the drug, instead of the protective effect of low bone density,” Rennert added that a randomized prevention trial might settle the matter.

Paul Goss, Ph.D., who directs breast cancer research at the Massachusetts General Hospital Cancer Center, in Boston, was ambivalent about the need for such a study. “I’m not sure it’s feasible, given that you’d have to prohibit bisphosphonates in one arm of the trial,” he said. “Too many postmenopausal women use these drugs for osteoporosis; it would be hard to keep the study balanced.”

According to Goss, additional insights into whether the drugs prevent breast cancer might be found in the vast databases generated by bisphosphate approval trials. If those data offer new evidence of prevention, he said, then a randomized, controlled trial to investigate prevention specifically might be warranted. Goss emphasized that the new findings don’t justify using bisphosphonates for primary cancer prevention yet. “There’s too much ambiguity in the results. . . Nonetheless, the findings are credible and compelling, and they need to be confirmed.”

Bisphosphonates ‘killing effect on osteoclasts, helps make skeletal microenvironments hostile to cancer cells, Mundy said. Although scientists largely agree that this is how bisphosphonates lessen the burdens of breast cancer metastases in bone, they’re far less certain about how the drugs might prevent metastases, or even breast cancer itself.

Mundy’s view is that bisphosphonates—being cytotoxic and capable of inducing apoptotic cell death—kill tumor cells directly and lessen the pool of potentially metastatic cells that could leave the breast. Other researchers say the drugs trigger immune reactions that kill cancer cells or antiangiogenic effects that prevent tumors from growing.

The notion that bisphosphonates might kill cells through nonhormonal pathways is intriguing, but according to Goss, it’s also debatable. “I think that all breast cancers have genetic origins in ER-positive cells from...
earlier generations in the family,” he said. “And my evidence for that is even though tamoxifen and raloxifene don’t show reductions in ER-negative cases, premature ovariectomy—the most extreme antiestrogen thing you can do—produces a drop in both types of breast cancer.” Goss is currently investigating the degree to which two classes of drugs—aromatase inhibitors, which also have antitumor properties in ER-positive cells, and Cox-2 inhibitors, which block ER-negative processes—might be useful for breast cancer prevention.

Meanwhile, Rennert plans to compare benign and malignant biopsy samples obtained from women who take bisphosphonates and from those who don’t. If those investigations yield biomarker evidence of cancer prevention, Rennert will make the case for further study in a clinical trial. “And if I see that the preventative effect of bisphosphonates among women with low bone density is much stronger than it is among women who have low bone density and who are not on the drug, then I can separate these two issues,” he said. “I’ll be able to say that we have a drug effect that exceeds that of low bone density with respect to cancer prevention.”

Public Reception
But will the public accept a new chemopreventive drug for cancer? In the November 2009 issue of the journal Breast Cancer Research and Treatment, Angela Fagerlin, Ph.D., from the University of Michigan, reported that even after gaining a full understanding of tamoxifen’s risks and benefits, only 6% of women queried said they would take the drug for breast cancer prevention, even if they were at risk of the disease. Only 1% reported filling a prescription for it.

The lack of public interest in chemoprevention isn’t easy to explain. Some experts cite “omission bias,” which causes some individuals to worry more about low risks from taking a drug than they do about higher risks from not taking it. This phenomenon has been likened to reactions against childhood vaccination.

Chlebowski points out that doctors also play a role, since they’re generally more interested in treating sick patients than otherwise healthy people. Pruthi said patient decisions on chemoprevention depend on how physicians present risks and benefits. “It’s important that you present this so that patients clearly recognize it’s an option,” she said. “More women will take drugs for prevention if they perceive a benefit. And chemoprevention is a much less extreme option than prophylactic mastectomy.”

Still, Pruthi confirmed that necrosis of the jaw after intravenous alendronate treatment has received wide publicity. Patients have filed hundreds of lawsuits against alendronate’s maker, Merck, for this side effect. Pruthi concedes that jaw necrosis could be a public liability with respect to using bisphosphonates for cancer prevention, even though the intravenous route is inapplicable for this use.

Rennert added that in his research, preventative benefits from bisphosphonates were long lasting. The drugs remain in bone for long periods, and breast cancer reductions were observed after treatments given for just 1 year, he said. “Regardless of whether the drugs are anti-inflammatory, antiproliferative, or antiangiogenic, they could be a great value as prevention agents if women only have to take them for a year as opposed to a lifetime,” he said. “We don’t know if that’s the case, but it’s fascinating nonetheless. We have a lot of questions to ask.”

Dr. Chlebowski has reported serving as a consultant and receiving honoraria from AstraZeneca, Novartis, Pfizer, Amgen, and Lilly. Dr. Goss has reported receiving research support and honoraria from Novartis, Pfizer, AstraZeneca, and GlaxoSmithKline.