Risk vs. Benefit: Bisphosphonates in Breast Cancer

These common drugs can curb bone metastasis and may even keep DCIS in check, but side effects make education and awareness crucial.

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Bisphosphonates are popular bone-targeting drugs. Older people take them to prevent and treat osteoporosis. Breast cancer patients, particularly those with metastatic disease, take them to prevent and treat bone lesions or “mets.” These bone agents are also given to people with lung, prostate, multiple myeloma and other cancers.

Proven to prevent fractures and keep metastatic bone disease at bay, these drugs might also have broader benefits. A new analysis by scientists at Fred Hutchinson Cancer Research Center in Seattle suggests the drugs might keep people diagnosed with DCIS — the very earliest form of breast cancer — from developing invasive disease.

But bisphosphonates and other bone-modifying agents, or BMAs, can also come with short- and long-term side effects. And that last includes heart disease, kidney toxicity and a rare but troubling condition known as osteonecrosis of the jaw, or ONJ, in which small portions of the jaw become exposed and don’t heal. Bizarrely, while bone drugs markedly reduce overall fractures, they can also, in rare cases, cause fractures.

What’s the story with BMAs in breast cancer? Do the benefits outweigh the risks? How prevalent are side effects like ONJ? Can you prevent it? What about cost? And access? We talked with patients, cancer researchers and clinicians to get their takes on bisphosphonates — and a chemical cousin, denosumab — and how these drugs currently fit into our oncology armamentarium.

A drug with many uses

Previous trials have shown bisphosphonates might help lower the risk of developing breast cancer in postmenopausal women and reduce recurrence and death in early stage breast cancer patients.

New research out from epidemiologist Chris Li, MD, PhD, and others at the Hutch now suggests bisphosphonates may also keep women with ductal carcinoma in situ, or DCIS, from developing invasive disease.

“Twenty percent of all breast cancers (in the U.S.) are DCIS,” said Li, lead author of the study published last month in the journal Cancer Research. “DCIS has a very high survival rate, but women with a history of DCIS have an elevated risk of developing a subsequent invasive breast cancer. This study suggests that bisphosphonates may lower this risk.”

As this is the first study to report on this relationship, the results will need to be confirmed, Li said; it won’t change clinical practice any time soon.

But it does reflect a growing interest in expanding the use of these drugs into another cancer population. And raises important questions about the tradeoffs, the risks vs. benefits, which researchers continue to investigate.

‘A proven therapy’

Breast cancer treatment — especially anti-estrogen therapy — is hard on the bones. It accelerates the aging process, throwing many patients into early menopause (either surgically or chemically) and that can trigger bone loss, osteoporosis and fractures. Cancer wreaks similar havoc. Metastatic bone disease can cause a cascade of collateral damage — from deep, difficult-to-treat pain to debilitating fractures and worse.

That’s where BMAs come in. Rigorously studied for decades, they’ve become a cornerstone of treatment in breast cancer, with their use recommended in both early and advanced breast cancer patients by the American Society of Clinical Oncology, or ASCO, and the National Cancer Comprehensive Network, which develops guidelines for cancer treatment.

“In breast cancer, drugs that block bone breakdown are a proven therapy when bone metastases are present, reducing fractures, pain and the requirement for surgery and radiation,” said Dr. Julie Gralow, new chief medical officer for ASCO. A former Hutch clinical researcher and head of breast oncology at Seattle Cancer Care Alliance, Gralow has studied BMAs extensively through the SWOG Cancer Research Network.

She recently investigated the efficacy and side effect profile of three BMAs (IV-infused zoledronic acid and two oral agents) in a Phase 3 randomized trial. All three agents effectively fended off bone mets, but the researchers saw a bit more osteonecrosis of the jaw with zoledronic acid.

“These drugs do have some side effects including kidney toxicity, a first-infusion flu-like effect and ONJ,” Gralow said. “But these risks are far lower than the benefits in the metastatic setting.”

‘A fine balance’

Poorni Manohar, MD, a physician-researcher with the Hutch and SCCA, is selective about using the drugs. In the early-stage setting, she said she’d recommend it to someone whose DEXA scan shows osteopenia, or low bone mineral density, “especially if they’re going on an aromatase inhibitor (or AI) which further reduces the bone density.”

In the metastatic setting, she uses them “routinely,” but said it’s imperative to “balance the side

effects against the benefits."

"With metastatic breast cancer, we are trying to preserve their quality of life," she said. "If someone has just one site of disease, I might not strongly push it. It's a fine balance to achieve. Women with metastatic disease will be on this drug indefinitely."

Gralow said in early-stage post-menopausal women (including those who've had ovary suppression), BMAs can reduce risk of bone mets but "since many are at low risk of recurrence even if they don't use it, we weigh the risks and benefits differently than in the metastatic setting when the risk of a bone fracture and bone pain from the met is high."

"We're much more cautious about using them when the risk of breast cancer recurrence is low and the risk of ONJ, for example, is elevated, as in smokers and those with poor dental health," she said.

Cancer patients usually get higher doses of BMAs than those who take them for osteoporosis. Manohar said patients should also be aware the drugs "stay in your body for a very long time." And with some, it's essential to taper off, not stop suddenly. Side effects like ONJ and atypical femur fractures are "associated with more long-term use," Manohar said, but again stressed these adverse effects are rare.

"We're pretty good at screening before we start," she said. "If someone has dental procedures coming up, that's a clue to hold off or not give it."

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