Vitamin D regimen is effective in resolving bone pain related to aromatase-inhibitor therapy

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How do you ensure that your patients with breast cancer adhere to their aromatase inhibitor regimen despite its painful side effects? The solution may be a high-dose vitamin D supplement, according to a recently published paper by Antonella L. Rastelli, MD, assistant professor of medicine at Washington University School of Medicine in St. Louis, Missouri, and colleagues.[1] The researchers found that high-dose vitamin D relieves joint and muscle aches for many breast cancer patients taking estrogen-lowering drugs.[1]

IMPACT OF SIDE EFFECTS

Although the side effects of adjuvant aromatase-inhibitor therapy are different from those associated with chemotherapy, approximately half of patients on these medications experience severe musculoskeletal pain and stiffness in the hands, wrists, knees, hips, lower back, shoulders, and feet. Symptoms can often be so intolerable that some patients choose to discontinue therapy. Rastelli's colleague, Marie E. Taylor, MD, assistant professor of radiation oncology at Washington University School of Medicine, was the first in the group to realize that patients on aromatase inhibitors who experienced this discomfort obtained some relief from high doses of vitamin D.

Aromatase inhibitors also cause bone loss. Rastelli manages a survivorship clinic for patients with breast cancer; therefore, she concentrates on bone health to lessen bone loss. Aromatase inhibitors have the opposite effect on bone mass preservation than does tamoxifen. "With aromatase inhibitors we see bone loss and fractures, and it is very important to take care of this problem early on," Rastelli explained.

TREAT THE SYMPTOMS

Patients were coming to the clinic with complaints of pain similar to the pain of osteomalacia, a condition characterized by extremely low vitamin D levels—usually less than 10 ng/mL. "These patients would tell us they hurt all over, cannot climb stairs well, and have pain in every part of their body. We did not believe these patients had overt osteomalacia, but because cancer patients often have low levels of vitamin D, we checked and found their vitamin D levels were very low," she said.

> Some participants reported feeling better on a weekly regimen.

Rastelli and her colleagues decided to treat the patients who were in pain with high doses of vitamin D. Many of them reported their aches were more tolerable or completely resolved. Some said their energy level improved as well. Rastelli's group decided to design a double-blind, placebo-controlled trial to confirm that their patients' results were more than a placebo effect.

They enrolled 60 patients who had pain and discomfort associated with anastrozole (Arimidex, generics), one of three FDA-approved aromatase inhibitors. (The other FDA-approved aromatase inhibitors, letrozole [Femara, generics] and exemestane [Aromasin, generic], also cause musculoskeletal symptoms.) In addition to pain, all study participants also had low vitamin D levels. Half of them were randomly assigned to receive the recommended daily dose of vitamin D3 (400 IU) plus a 50,000-unit vitamin D2 capsule once a week. The other half received the recommended daily dose of 400 IU of vitamin D3 plus a weekly placebo capsule. All of the participants took 1,000 mg of calcium daily throughout the study.

The high-dose vitamin D formula used was the plant-derived D2. Although the D2 dose was prescription-strength, the researchers stressed its safety due to its rapid elimination. D2 is usually eliminated 7 to 10 days after ingestion. Vitamin D3, which is animal-derived, stays in the system longer (more than 15 days) and can build up, especially at

high doses. The researchers also noted that some study participants returned to the clinic after being switched from a weekly regimen to a monthly regimen, reporting they felt better on the weekly regimen than they did on the monthly regimen. Apparently, this finding was the result of how rapidly vitamin D2 is metabolized: in order for the effect to persist the patient must take it weekly.

LONGER-TERM TREATMENT IS BETTER

Patients were allowed to continue taking NSAIDs or acetaminophen during the study, if they chose; however, those patients who did experienced minimal benefit. Of course, these analgesics cannot be taken safely for a long time. Rastelli emphasized, "We have to consider this regimen long term. Patients have to stay on the aromatase inhibitors for at least 5 years, if not longer."

Many oncologists now believe that if patients tolerate the drug fairly well and are not having tremendous bone loss, they should continue therapy for a longer period. Some studies suggest that patients who develop joint aches and arthralgia symptoms may be the ones who benefit the most from the medication, and they may even have fewer recurrences of breast cancer. Therefore, it is very important to keep these patients more comfortable and capable of continuing aromatase inhibitor therapy.

ADDITIONAL BENEFITS

The researchers measured bone density as a secondary end point. They obtained bone densities at the beginning and also 6 months into the study, to see if there was any difference between the patients who received placebo and those who received vitamin D2. Although the number of patients was limited, the researchers were surprised to see the bone density maintenance trended to significance in the patients on vitamin D versus placebo. This might be because of its role in calcium absorption.

"Vitamin D deficiency/insufficiency, common in breast cancer patients, is a risk factor for bone loss through the development of secondary hyperparathyroidism, a condition characterized by low vitamin D, above normal i-PTH and normal calcium levels.[2] Increased bone turnover in this condition represents an appropriate physiologic response to maintain homeostatic levels of serum calcium, but at the expense of cortical bone resorption and accelerated bone loss.[3-5] Secondary hyperparathyroidism is relatively common in breast cancer patients with low vitamin D levels," reported Rastelli.[1]

She noted that patients who are not taking vitamin D are at multiple risk of bone loss if they are treated with aromatase inhibitors and have profound estrogen deprivation in addition to secondary hyperparathyroidism. They also feel better, making it easier for them to adhere to their exercise and medication regimens.

"Patients who get the vitamin D weekly feel better because their pain is reduced and sometimes goes away completely. High-dose vitamin D seems to be really effective in reducing the musculoskeletal pain caused by aromatase inhibitors," Rastelli said. "Given the similar side effects, patients on all three of these drugs may derive benefit from high-dose vitamin D. This makes the medication much more tolerable. Millions of women worldwide take aromatase inhibitor therapy. We may have another tool to help them remain on it longer." ■

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