Aromatase Inhibitor-Related Joint Pain

Aromatase inhibitors (AIs) are a common therapy for post-menopausal women with hormone positive breast cancer. After menopause, estrogen is mainly produced by converting androgens (sex hormones produced by the adrenal glands) into estrogens, which occurs in fat cells (as opposed to in the ovaries before menopause). An enzyme called aromatase is responsible for this conversion. AIs block this conversion, leading to less estrogen in the body.

While AIs are an effective therapy in reducing the risk of breast cancer recurrence, they increase the risk of developing osteoporosis and commonly cause joint (or muscle) aches and pains. These joint symptoms, often called arthralgias, can interfere with quality of life and are often the cause of a woman stopping therapy early.

Studies have found joint symptoms most often develop within the first 3 months on therapy, though some cases continue to develop after 3 months. In studies of AI-related joint symptoms, anywhere from 20-50% of women on therapy reported the side effect. Symptoms typically affect the fingers, hands, wrists, elbows, shoulders, knees and ankles. Carpal tunnel syndrome is a common diagnosis in women with AI-related joint symptoms. Other diagnoses include osteoarthritis, tendonitis and bursitis.

What causes AI-related joint symptoms?
The actual cause of AI-related joint symptoms is not well understood. One common theory is that the rapid drop in estrogen levels may be responsible for joint pain for two reasons:

- This drop may actually lower the pain threshold, allowing the brain to better "detect" joint symptoms that already exist.
- The drop in estrogen causes cytokines (proteins released by the body's cells) to be released in high levels, which may hasten bone loss and aging, leading to pain.

Unfortunately, a poor understanding of the cause makes it difficult to prevent this side effect. In turn, the goal is to treat the symptoms to allow women to have good quality of life while completing their prescribed therapy in full.

Who is at risk for developing this side effect?
It would be helpful for healthcare providers to have a way of predicting who is at greatest risk for developing AI-related joint symptoms. Unfortunately studies have not found consistent predictors. Some studies have shown that having received prior chemotherapy, prior hormone replacement therapy, prior taxane chemotherapy (paclitaxel, taxotere) and having had their last menstrual period within 5 years may predict increased risk. On the flip side, taking tamoxifen before an AI may reduce the likelihood of developing joint symptoms. There may also be an increased risk for those with pre-existing joint symptoms, such as rheumatoid arthritis. Research continues to identify factors that could help better predict each woman's risk.

Managing Joint Symptoms
First and foremost, patients should talk with their oncology team if they develop joint symptoms. The oncology team is there to support each patient to complete their prescribed therapy and will help identify ways to manage this side effect. To derive the full benefit from AI therapy, it is important to take the medication daily, for as long as it is prescribed. It is important to communicate with your team if your side effects are making it difficult for you to take your medications as directed.

Medications for Symptom Management
A significant component of the joint symptoms experienced with AIs is swelling of the joints. Therefore, a medication that decreases this swelling, such as non-steroidal anti-inflammatory drugs (NSAIDS, such as ibuprofen) or a coxib (such as celecoxib, or Celebrex), may help with pain relief. However, these medications are not without side effects of their own, so each
patient should discuss his/her health history with the team before starting these medications. Additional pain relieving medications, including acetaminophen and opioids, can be added for those patients who do not get relief with an anti-inflammatory alone or for those who cannot tolerate the anti-inflammatory medications.

**Switching AIs**

While there are no studies to confirm the effectiveness of changing to another drug, some practitioners will switch to another AI or tamoxifen when symptoms are unmanageable and may lead to the patient stopping therapy altogether. Prior to switching, it may be beneficial to stop therapy for 6 to 8 weeks to be sure that the AI is the cause of the symptoms.

**Supplements and Other Therapies**

There has been recent interest in the possibility that vitamin D supplementation may help to decrease AI-related arthralgia, although this has not been proven in clinical trials. Some studies have suggested that calcium and bisphosphonate therapy (used to prevent/treat osteoporosis) may also prevent AI-related joint symptoms.

Small studies have found a benefit to acupuncture and exercise. Acupuncture was shown to reduce pain from joint symptoms and improve functioning and well-being. Gentle stretching and exercise may also be helpful in reducing symptoms.

**Conclusion**

Al-related joint symptoms can cause significant pain and interfere with functioning and quality of life. Researchers continue to seek ways to identify women at highest risk for developing this side effect and to find effective therapies to treat it. Women should be advised about this side effect when starting an AI, and encouraged to report these symptoms to the healthcare team. The management of joint symptoms is of utmost importance to helping patients complete their prescribed therapy in full.

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