Teaching Lecture

E12. Managing toxicity of aromatase inhibitors in early breast cancer

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Introduction

Third-generation aromatase inhibitors (AIs) are our current hormone therapy of choice in postmenopausal women with hormone-receptor-positive breast cancer. They are given either upfront over 5 years or as sequential therapy for 2–3 years before or after 2–3 years of tamoxifen. Their use for another 5 years after the standard 5 years of adjuvant endocrine therapy in the extended setting or as a primary preventive therapy among women at high risk for breast cancer is currently being investigated [1]. While, when compared with 5 years of tamoxifen, treatment schedules containing an AI further reduce the risk of breast cancer events (recurrence or new breast cancer) or breast-cancer-related death in postmenopausal women, these drugs are also associated with important side-effects. Although predictive biomarkers for benefit from an AI-containing schedule over 5 years of tamoxifen do exist, most postmenopausal women in the Western world do get an AI and are exposed to these side-effects.

AIs substantially suppress the low remaining circulating oestrogen levels in postmenopausal breast cancer patients. These women are therefore confronted with exacerbating menopause-related side-effects such as hot flashes and night sweats, musculoskeletal problems, sexual dysfunction, cognitive deterioration, and changes in lipid metabolism and bone mineral density (BMD). Acute menopausal symptoms contribute to suboptimal adherence and premature discontinuation, which are likely to affect treatment efficacy. In clinical practice, discontinuation rates for an initial started AI go up to 50% at 3 years of follow-up, in contrast with the better compliance reported in clinical trials, probably attributable to close monitoring of motivated trial patients [2]. The long-term toxicities such as AI-induced bone loss have been well studied and are treatable. However, the cardiovascular consequences of changes in lipid metabolism need to be further monitored in adjuvant trials – such as the MINDACT (Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy) and SOLE (Study Of Letrozole Extension) trials – using AIs for over 5 years.

Short-term and especially long-term side-effects need to be balanced against the net benefit from AI therapy over tamoxifen; as breast cancers are increasingly being diagnosed at an early stage, thanks to screening programmes, the patients will be more and more likely die from non-breast-cancer-related causes. We here focus on musculoskeletal discomfort and bone health but will also discuss the management of other AI-related toxicities.

Musculoskeletal discomfort

The further decline in oestrogen levels during AI therapy is associated with arthralgia and myalgia [3], also known as the AI-induced musculoskeletal syndrome (AIMSS), a term which also embraces morning stiffness, paraesthesia and carpal tunnel syndrome (CTS). AIMSS is reported in up to 50% of AI-treated patients [4].

The underlying aetiology remains to be unravelled, and further research to better treat this syndrome is keenly awaited. Just as for the natural menopause, previous studies have failed to reveal any systemic inflammatory processes in AIMSS patients. We demonstrated fluid retention in peripheral joints, probably resulting from localised inflammation in tendons [5]; this has been confirmed by others using different imaging techniques [6,7]. Spontaneous resolution of symptoms within 6–18 months after starting treatment with AI has been reported, implying no permanent changes in joints. In our experience, however, intra-articular fluid and tenosynovial changes, observed on magnetic resonance imaging (MRI) already during the first 6 months, were still present after 2 years of treatment in most of the patients [8]. This observation emphasises the need for proper treatment of these persistent symptoms. Since AIs induce changes in insulin-like growth factor 1 (IGF-1) levels, we hypothesise, and are now studying, the involvement of the growth hormone (GH)/IGF-I axis in AIMSS development. This net change in the GH/IGF-1 axis may be more pronounced in women with low baseline IGF-1 levels, which is more often seen in very lean and obese women than in those with a normal BMI. In addition, in these patients with extremes in BMI we observed a larger AI-induced decrease in grip strength.

As no causal relationship has yet been established, and because systemic oestrogens are strictly contraindicated, treatment of AIMSS remains mainly symptomatic. First, patients should be encouraged to change their lifestyle when necessary. Tobacco cessation, alcohol and caffeine moderation, exercise and weight control should be promoted. In case these adaptations do not relieve

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musculoskeletal pain, non-steroidal anti-inflammatory drugs, acetaminophen and cyclo-oxygenase-2 inhibitors may offer some relief, but adverse effects should be closely monitored. Drug holidays or switching to another AI or tamoxifen can also be options. Patients suffering from CTS or arthritis should be referred to a specialist for proper diagnosis and therapy. Education of patients, as well as their relatives, is crucial before initiating treatment. Furthermore, other musculoskeletal disorders should be detected prior to and observed during AI-treatment.

New treatment modalities under investigation include glucosamine, diuretics, duloxetine, probiotics, vitamin D, and capsaicin. In addition, studies have suggested beneficial effects of acupuncture and yoga [11].

Bone health

Menopause is associated with bone loss reflected in decreased BMD and leading to increased risk of fractures [12]. AIs potentially exacerbate this deleterious effect on skeletal health. Several placebo-controlled trials with AIs have demonstrated accelerated BMD loss; when AIs were compared to tamoxifen, they were associated with an increased risk of fractures during treatment. However, the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial substudy on bone showed that, after anastrozole cessation, bone loss and concomitant fracture risk can resolve [13].

Expert recommendations regarding bone health management in postmenopausal breast cancer patients have been published. They advocate measurement of BMD at baseline before treatment and annually thereafter in those at high risk. Life-style interventions, calcium with vitamin D supplements and bisphosphonates for those with a T-score below –2.0 are also recommended. Some authors have suggested that bone loss itself could contribute to arthralgia, so that concomitant administration of bisphosphonates and/or vitamin D might reduce BMD loss and development of arthralgia as well. However, the ZO-FAST (Zometa-Femara Adjuvant Synergy Trial) could not confirm this hypothesis [11]. A number of drugs, such as RANK-L antibodies, are currently under investigation and may be even more effective than bisphosphonates, but this needs further research.

Conclusion

As the number of breast cancer survivors will continue to increase, managing these frequently encountered AI toxicities has become of great importance not only to improve quality of life for the patients but also to ensure maximum benefits from the drug. Further research investigating aetiology of AIMSS, predictors of toxicity, and improved interventions are clearly needed. Furthermore, the continuing search for predictive biomarkers showing a clear benefit of 5 or even more years of an AI over a tamoxifen-containing treatment schedule therefore remains a priority.

Conflict of interest statement

The authors have no conflicts of interest or study funding to be reported.

References

[1] Khan QJ, O'Dea AP, Sharma P. Musculoskeletal adverse events associated with adjuvant aromatase inhibitors. *J Oncol* 2010.

[2] Huiart L, Dell'Aniello S, Suissa S. Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. *Br J Cancer* 2011; 104: 1558–1563.

[3] Dugan SA, Powell LH, Kravitz HM, et al. Musculoskeletal pain and menopausal status. *Clin J Pain* 2006; 22: 325–331.

[4] Henry N, Giles J, Stearns V. Aromatase inhibitor-associated musculoskeletal symptoms: etiology and strategies for management. *Oncology* 2008; 22: 1401–1408.

[5] Morales L, Pans S, Verschueren K, et al. Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. *J Clin Oncol* 2008; 26: 3147–3152.

[6] Dizdar O, Ozçakar L, Malas F, et al. Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia. *J Clin Oncol* 2009; 27: 4955–4960.

[7] Henry N, Jacobson J, Banerjee M, et al. A prospective study of aromatase inhibitor-associated musculoskeletal symptoms and abnormalities on serial high-resolution wrist ultrasonography. *Cancer* 2010. 116(18): 4360–4367.

[8] Lintermans A, Van Calster B, Laenen A, et al. Prospective study to assess fluid accumulation and tenosynovial changes in the aromatase inhibitor-induced musculoskeletal syndrome – 2 year follow-up data. In St. Gallen International Breast Cancer Conference. St. Gallen: 2011.

[9] Ingle JN, Schaid DJ, Goss PE, et al. Genome-wide associations and functional genomic studies of musculoskeletal adverse events in women receiving aromatase inhibitors. *J Clin Oncol* 2010; 28: 4674–4682.

[10] Mao JJ, Su HI, Feng R, et al. Association of functional polymorphisms in CYP19A1 with aromatase inhibitor associated arthralgia in breast cancer survivors. *Breast Cancer Res* 2011; 13: R8.

[11] Lintermans A, Neven P. Pharmacology of arthralgia with estrogen deprivation. *Steroids* 2011; 76: 781–785.

[12] McCloskey E. Effects of third-generation aromatase inhibitors on bone. *Eur J Cancer* 2006; 42: 1044–1051.

[13] Eastell R, Adams J, Clack G, et al. Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. *Ann Oncol* 2011; 22: 857–862.