Endocrine-therapy-related symptoms and breast cancer

Aman Buzdar

The association of a treatment-related adverse effect with treatment success has been reported in various clinical situations. The development of vasomotor or joint symptoms is an indication of therapeutic benefit in women receiving endocrine treatment for hormone-receptor-positive breast cancer.

Advances in the diagnosis and treatment of breast cancer have produced a significant improvement in the prognosis for patients with this disease. Almost three-quarters of women with breast cancer have tumours that express oestrogen or progesterone receptors, and approximately half of these patients are postmenopausal.[1] Endocrine adjuvant therapies are effective in reducing the risk of recurrence in this subgroup of hormone-receptor-positive patients. Receptor-positive breast cancer can be treated with anti-oestrogens (such as tamoxifen) that either block or interfere with oestrogen at the oestrogen-receptor level, or by administering aromatase inhibitors (anastrazole, letrozole, and exemestane) that reduce the endogenous synthesis of oestrogen from the androgens in the peripheral tissues of postmenopausal women.

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was undertaken to compare the efficacy and safety data of the third-generation, oral, non-steroidal aromatase inhibitor anastrozole against tamoxifen for five years as initial adjuvant hormonal treatment in postmenopausal women with hormone-receptor-positive early breast cancer.[2] Aromatase inhibitors have been shown to reduce the risk of breast cancer recurrence if used as initial therapy after two to three years of endocrine therapy with anti-oestrogen therapy, or after completion of five years of adjuvant tamoxifen therapy in high-risk, postmenopausal patients.[3] The adverse effects of aromatase inhibitors are predictable and include hot flushes, arthralgia, myalgia and an increased risk of osteoporosis with a higher risk of bone fractures.[4] Selective aromatase inhibitors have been developed to decrease the adverse effects associated with these agents while maintaining clinical efficacy. The third-generation aromatase inhibitors (for example, anastrozole, letrozole, exemestane) used in adjuvant therapy are more efficacious than anti-oestrogen (tamoxifen) adjuvant therapy in postmenopausal women.[3,5] The availability of oestrogen-receptor testing has helped clinicians identify subsets of patients who might benefit from endocrine therapies, including those in whom the tumour has hormone receptors. Patients with oestrogen-receptor-negative breast cancer do not gain any therapeutic benefit from currently available endocrine agents,

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including aromatase inhibitors.[5]

A major dilemma in the treatment of breast cancer has been our inability to identify the subset of patients who would benefit from a given adjuvant therapy. All therapies are associated with some adverse effects. Anti-oestrogen therapies are associated with an increased risk of thromboembolic events, uterine cancer, and rarely, uterine sarcomas. The hormone-receptor and human epidermal growth factor receptor 2 (HER2) status of the tumour has been shown to identify a subset of women who would benefit from endocrine therapy and anti-HER2 therapy.[6] Another approach has been to determine whether therapy-associated adverse effects can identify the subset of patients who would benefit from that therapy. The association of a particular adverse effect with treatment success has been reported in a few situations; for example, the occurrence of graft-versus-host disease in patients receiving allogeneic transplant,[7] skin toxicity after treatment with EGFR antibodies,[8] and hypertension after anti-angiogenesis therapy.[9]

In the ATAC trial, authors retrospectively analysed the relationship between the incidence of vasomotor or joint symptoms and breast cancer recurrence. These data revealed a lower risk of recurrence in patients who experienced early treatment-related vasomotor symptoms or new joint symptoms.[10] ATAC was a double-blind, randomised, clinical trial in which postmenopausal women with histologically confirmed localised breast cancers were randomly assigned to receive anastrozole (1 mg per day) alone, tamoxifen (20 mg per day) alone, or both for five years as adjuvant treatment. In total, 9,366 women were included in the trial: 3,125 were assigned to receive anastrozole alone, 3,116 were assigned to receive tamoxifen alone, and 3,125 were assigned to receive the combination. At the initial analysis after 33 months of follow-up, the combination treatment was discontinued because no benefit greater than that achieved with tamoxifen alone was observed in terms of efficacy or tolerability. In a retrospective review by Cuzick et al, the investigators evaluated the relationship between treatment-related vasomotor or joint symptoms and subsequent clinical outcome, that is, disease-free survival. Women with hormone-receptor-negative tumours or with unknown hormone-receptor status and those with pre-existing vasomotor or joint symptoms at their entry into the trial were excluded from this analysis.[10]

In the ATAC study, 1,487 of 3,964 (37.5%) patients reported new vasomotor symptoms at the initial three-month follow-up. Patients experiencing these symptoms had a lower risk of recurrence than those without these symptoms (HR 0.84, 95% CI 0.71–1.00, P=0.04). A greater reduction in breast cancer recurrence was observed in 1,245 of 3,964 (31.4%) patients who reported new joint symptoms at their initial three-month follow-up than in those who did not (HR 0.60, 95% CI 0.50–0.72, P=0.0001). Thus, the investigators concluded that the development of new vasomotor symptoms and/or joint symptoms in the initial three months might be a useful indicator of better efficacy of endocrine adjuvant therapy. Improved recurrence-free survival was observed with both anastrozole and tamoxifen adjuvant therapy.[10]

After the diagnosis of breast cancer, any new symptom is of major concern to patients, and their main worry is that it is related to recurrence of their cancer. In addition to discussing the potential adverse effects of endocrine therapy with patients, we should share these additional data, which show that some therapy-related symptoms could actually be an indicator of better outcome from therapy. At present, the potential mechanism underlying this improved outcome from adjuvant endocrine therapy in symptomatic patients is not clear; it might be related to the fact that these women were more compliant with their prescribed medication regimen than were others, or a difference in the metabolism of endocrine therapy might be associated with a pharmacogenomic mechanism.

In conclusion, women treated with aromatase inhibitors experience an increased frequency of joint symptoms, and rather than switch their therapy to another endocrine agent, one should share with the patients the information that these therapy-related adverse effects are actually associated with a lower risk of breast cancer recurrence. Compliance with any oral therapy is an important concern, and this reassurance might help patients cope with their symptoms and potentially enhance their compliance with therapy, ultimately reducing the risk of breast cancer recurrence. If similar supportive evidence becomes available from other prospective AI trials, this would strengthen these unique observations.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Practice point

The onset of new joint symptoms after initiation of adjuvant endocrine therapy is an indicator of increased benefit from treatment, and patients should be encouraged to remain on current therapy.

Author affiliation: Department of Breast Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
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