Endocrine Therapy Toxicity: Management Options

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OVERVIEW

Treatment with adjuvant endocrine therapy, including tamoxifen and the aromatase inhibitors, has resulted in notable improvements in disease-free and overall survival for patients with hormone receptor-positive breast cancer. Despite their proven benefit, however, adherence to and persistence with the medications is poor in part because of bothersome side effects that can negatively affect quality of life. Retrospective analyses have identified possible predictors of development of toxicity. Reports have also suggested that development of toxicity may be a biomarker of better response to therapy. In addition, there has been considerable research investment into the management of these side effects, which may lead to improved adherence and persistence with therapy. However, although notable advances have been made, much more remains to be done to provide patients with truly personalized therapy for hormone receptor-positive breast cancer.

The use of adjuvant endocrine therapy, including tamoxifen and the aromatase inhibitors (AI), for treatment of early-stage, hormone receptor (HR)-positive breast cancer has resulted in noteworthy improvements in disease-free and overall survival. Recent data support the use of tamoxifen for up to 10 years in women with HR-positive breast cancer without contraindications to therapy.1 In addition, American Society of Clinical Oncology (ASCO) guidelines recommend use of an AI for at least a portion of adjuvant endocrine therapy for postmenopausal women with HR-positive breast cancer.2 Treatment with adjuvant endocrine therapy for 5 to 10 years is therefore now standard of care for the vast majority of patients with stage I-III HR-positive breast cancer. However, despite the clear benefits from treatment, adherence and persistence with therapy are poor.3

SIDE EFFECTS OF ADJUVANT ENDOCRINE THERAPY

The initial large randomized clinical trials of tamoxifen and the AIs did not report high treatment discontinuation rates for study participants. However, studies of endocrine therapy usage in real-world settings, including interrogation of insurance records and observational studies in academic- and community-based practices, have revealed much higher rates of treatment discontinuation.4-5 Factors associated with noncompliance with chronic oral medications include toxicity, cost, patient age, poor patient-provider communication, multiple comorbidities, and beliefs about both medications and disease recurrence.4 For adjuvant endocrine therapy for breast cancer, development of intolerable side effects has been identified as the primary reason for poor persistence with therapy.6,7 Increased knowledge about the side-effect profiles of these medications and potential management options by both physicians and patients may lead to improved adherence and persistence with these important anticancer treatments.

Tamoxifen

Tamoxifen is a selective estrogen-receptor modulator that decreases the risk of breast cancer recurrence by 41% and death from breast cancer by 34% when taken for 5 years.8 However, it is associated with numerous bothersome side effects and rare but serious toxicities.9 Patients most commonly report menopausal symptoms including hot flashes and gynecologic complications, which can have a substantial negative effect on quality of life. Rare but serious toxicities include increased risks of endometrial cancer and thromboembolism (VTE). Obesity and prior estrogen replacement therapy are associated with an increased risk of endometrial cancer with tamoxifen therapy, and risk increases with longer duration of therapy.1,10 In the ATLAS trial, the cumulative risk of developing endometrial cancer in years 5 to 14 of therapy was 3.1% for tamoxifen-treated women versus 1.6% for placebo-treated women.1 VTE risk is increased in patients who use tobacco and who have a personal and family history of VTE, and may be increased in patients who are carriers of the Factor V Leiden mutation, although no association with prothrombin gene mutations was identified.11 In ATLAS, the relative risk of developing a pulmonary embolus was 1.87.1

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Although both endometrial cancer and VTE are serious, the incidence is very low even with extended tamoxifen therapy.

**Aromatase Inhibitors**

There are three third-generation AI medications (anastrozole, exemestane, and letrozole) in routine clinical use. AIs block aromatase, which is the enzyme responsible for the conversion of androgens to estrogens in postmenopausal women, resulting in notably lowered circulating concentrations of estrogens. Estrogen depletion is thought to be a primary cause of AI toxicity. Rare but serious risks of AI therapy include decreased bone mineral density and concomitant increased risk of fracture. In addition, although all AIs have the same mechanism of action and side-effects, some patients who are treated with more than one of the individual AI medications experience a different effect profile, some patients who are treated with more than one of the individual AI medications experience a different constellation of side effects from the different drugs. As with tamoxifen, these side effects can negatively affect quality of life and have been shown to lead to treatment discontinuation.

**IS THERE A BENEFIT FROM EXPERIENCING SIDE EFFECTS?**

Large randomized clinical trials have demonstrated an improvement in breast cancer outcomes for patients treated with adjuvant endocrine therapy. However, it remains difficult to determine the benefit from a specific treatment for an individual patient. Because the side effects may be related to suppression of estrogen production or the degree of estrogen-receptor blockade, some have questioned whether the development of side effects is indicative of a benefit from endocrine therapy. A number of unplanned retrospective analyses have been performed to investigate this question (Table 1).

The majority of analyses have evaluated associations between symptoms and endocrine therapy in general, rather than tamoxifen or the AIs in particular. Most but not all analyses have identified an association between development of musculoskeletal toxicity and improved disease free and overall survival (Table 1). A subset also identified associations between development of vasomotor symptoms and improved breast cancer outcomes.

There are some limitations, however, that make it difficult to determine how to incorporate these findings into routine patient care. Importantly, the large randomized clinical trials collected physician-graded adverse events as opposed to patient-reported outcomes, which has been shown to result in under-reporting of symptoms. In addition, there was no consistent definition for musculoskeletal symptoms across studies. Finally, standardized data collection forms were not used in most trials.

This symptom-reporting limitation has direct implications for the analysis of the data. Most studies either excluded symptomatic patients at baseline from the analysis or did not capture baseline symptoms, which makes it difficult to interpret these findings for patients with pre-existing symptoms. In addition, the analyses investigated presence or absence of symptoms without accounting for severity, so it is unknown whether patients who experience the most severe toxicity are also the ones who obtain the most benefit from therapy.

At present, clinicians are unable to use these results to guide individual patient treatment decisions. Is a patient who remains asymptomatic obtaining no benefit from the medication, and should she be switched to a different one? What about a woman who only experiences worsening of pre-existing symptoms rather than entirely new symptoms? Finally, if the toxicity resolves spontaneously, does that imply that she is no longer receiving benefit from the therapy? Analysis of patient-reported outcomes is important for increasing the understanding the effect of new therapies on both disease outcome and quality of life.

**KEY POINTS**

- One of the most common reasons for poor adherence and persistence with adjuvant endocrine therapy is treatment-related toxicity.
- Some retrospective analyses have identified associations between development of musculoskeletal toxicity and vasomotor symptoms and improved breast cancer outcomes, although the analyses have important limitations.
- The most common side effects associated with aromatase inhibitors are musculoskeletal in nature, including arthralgia, myalgia, and carpal tunnel syndrome. Multiple studies have identified predictors of developing this toxicity, and the most commonly reported factor is prior chemotherapy.
- Numerous nonhormonal options have been identified for treating vasomotor symptoms, including antidepressants and anticonvulsants.
- Few effective treatments have been identified for managing aromatase inhibitor-associated musculoskeletal symptoms, although numerous randomized clinical trials are currently underway.

**PREDICTORS OF DEVELOPING TOXICITY**

In addition to being able to predict the benefit from a medication for an individual patient, it would also be useful to be able to predict which side effects a patient is likely to experience. This information could help guide treatment decision-making for a patient with multiple equivalent treatment options or could allow patients and physicians to be more proactive about management of toxicity, which might improve compliance and persistence with therapy.
Numerous retrospective analyses have been performed to identify predictors of development of toxicity, especially for the AIs.6,12 In the ATAC trial, prior chemotherapy and prior estrogen replacement therapy were associated with increased risk of developing AI-associated musculoskeletal symptoms. Similarly, in a cross-sectional study conducted by investigators at Columbia University, development of joint pain and stiffness was associated with having prior taxane-based chemotherapy and was inversely associated with prior tamoxifen therapy. The association between the development of symptoms and body mass index remains uncertain.

In addition to clinical and demographic factors, associations between symptoms present at the time of AI treatment initiation and early treatment discontinuation have been identified in two retrospective analyses. An exploratory analysis from the MA.27 trial, which compared adjuvant exemestane and anastrozole, demonstrated an association between bother from side effects from prior treatment and early AI therapy discontinuation.16 More recently, a similar analysis in the Exemestane and Letrozole Pharmacogenomics study revealed an association between poor sleep quality, tired feeling, and forgetfulness and nonpersistence with AI therapy.17 In addition, the more symptoms a patient reported before AI initiation, the greater her likelihood of discontinuing AI therapy because of toxicity.

Despite the identification of clinical, demographic, and patient-reported factors that are associated with nonpersistence with AI therapy because of toxicity, it remains difficult to prospectively identify individual patients who will have difficulty tolerating therapy. Future studies should focus on this high-risk population so that interventions can be developed to prevent or lessen the development of side effects, which may increase adherence and persistence with AI therapy. In addition, this may lead to improvements in both the quality of life of breast cancer survivors and breast cancer outcomes.

**MANAGING TOXICITY**

As noted above, endocrine therapies for breast cancer are associated with a number of bothersome side effects, most of which can be managed. Strategies for treating the most common toxicities, hot flashes and arthralgias, are outlined below.

**Hot Flashes**

Vasomotor symptoms are common side effects of both tamoxifen and the AIs and can negatively affect quality of life. The neuroendocrine mechanisms underlying development of hot flashes remain poorly defined, although estrogen withdrawal at the time of menopause appears to play a role. The North American Menopause Society recommends lifestyle changes, such as avoiding triggers and keeping the core body temperature cool, as the first-line therapy for mild hot flashes. However, additional measures are generally needed for treatment of more severe vasomotor symptoms. Hormonal therapies are effective, but their use in women with a history of breast cancer is controversial because of safety concerns. For those women receiving AIs, supplemental estrogenic agents are contraindicated. Therefore, extensive research has been conducted to identify nonhormonal medications or nonpharmacologic options for symptom management (Table 2). The most commonly studied and used agents are antidepressants such as selective serotonin-norepinephrine reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI).18 Anticonvulsants, antihypertensives, natural health products, and nonpharmacologic interventions have also been studied.18

**Antidepressants.** Multiple trials of breast cancer survivors have demonstrated decreases in hot flashes with many but not all of the antidepressants compared to placebo.18 For example, doses of venlafaxine ranging from 37.5 mg to 150.0 mg decreased median hot flash score by 37% to 61%

**TABLE 1. Associations between Endocrine Therapy Toxicity and Breast Cancer Outcomes**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Analyzed Treatment Arms</th>
<th>Landmark Analysis</th>
<th>Endpoint</th>
<th>Vasomotor Symptoms</th>
<th>Musculoskeletal Symptoms</th>
<th>Vulvo-Yaginal Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>tamoxifen + anastrozole</td>
<td>3 mo</td>
<td>Recurrence</td>
<td>0.84 (0.71-1.00), p = 0.04</td>
<td>0.60 (0.50-0.72), p &lt; 0.0001</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>tamoxifen</td>
<td>3 mo</td>
<td>Recurrence</td>
<td>0.81 (0.65-1.01), p = 0.06</td>
<td>0.58 (0.45-0.74), p &lt; 0.0001</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>anastrozole</td>
<td>3 mo</td>
<td>Recurrence</td>
<td>0.85 (0.65-1.11), p = 0.3</td>
<td>0.65 (0.50-0.85), p = 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>tamoxifen + letrozole</td>
<td>3 mo</td>
<td>DFS</td>
<td>0.86 (0.73-1.02), p = 0.084</td>
<td>0.52 (0.32-0.86), p = 0.011</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mo</td>
<td>DFS</td>
<td>0.82 (0.70-0.96), 0.014</td>
<td>0.65 (0.49-0.87), p = 0.0031</td>
<td>N/A</td>
</tr>
<tr>
<td>MA.27</td>
<td>anastrozole + exemestane</td>
<td>3 mo</td>
<td>RFS</td>
<td>N/A</td>
<td>0.85 (0.51-1.44), p = 0.55</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade 3/4/0.62 (0.33-1.18), p = 0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAM</td>
<td>tamoxifen + exemestane</td>
<td>12 mo</td>
<td>DFS</td>
<td>0.73 (0.62-0.87), p &lt; 0.001</td>
<td>0.83 (0.69-0.98), p = 0.030</td>
<td>0.77 (0.59-1.01), p = 0.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mo</td>
<td>OS</td>
<td>0.58 (0.42-0.80), p = 0.001</td>
<td>0.81 (0.65-1.01), p = 0.055</td>
<td>0.57 (0.39-0.83), p = 0.003</td>
</tr>
<tr>
<td>TEAM</td>
<td>exemestane</td>
<td>6 mo</td>
<td>RFS</td>
<td>0.39 (0.19-0.81), p = 0.012</td>
<td>0.68 (0.39-1.17), p = 0.16</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
<td>0.65 (0.40-1.03), p = 0.068</td>
<td>0.65 (0.37-1.13), p = 0.12</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: DFS, disease-free survival; N/A, not available; OS, overall survival; RFS, recurrence-free survival.
over 4 weeks, compared to a 27% decrease with placebo. Similar beneficial efficacy has been reported in placebo-controlled trials of other SSRIs and SNRIs, including paroxetine, citalopram, and desvenlafaxine. In contrast, fluoxetine and sertraline appear less effective. Of note, paroxetine 7.5 mg daily was approved by the U.S. Food and Drug Administration in 2013 as a nonhormonal treatment for moderate to severe hot flashes. Some studies have raised concerns that the concomitant use of tamoxifen and CYP2D6 inhibitors, including paroxetine, will decrease efficacy of tamoxifen, and this remains unresolved.

**Anticonvulsants.** Anticonvulsant medications have also been tested for management of hot flashes in women with breast cancer. Gabapentin 900 mg daily was shown to be more effective than placebo for decreasing hot flash severity score after 12 weeks of treatment (45% vs. 29% reduction, respectively). Similar findings have been noted for pregabalin. Gabapentin and venlafaxine were compared in a randomized cross-over trial. Although both drugs reduced hot flash scores by 66%, more participants expressed a preference for treatment with venlafaxine.

**Antihypertensives.** Clonidine is a centrally acting alpha-adrenergic agonist that may act by reducing norepinephrine release. A meta-analysis of 10 trials found that half of trials reported a decrease in hot flashes with clonidine therapy, whereas the others reported no benefit. In addition, the side effects of clonidine limit its tolerability. For these reasons, clonidine is not routinely used, although it can be considered for selected patients.

**Other.** Numerous complementary and alternative therapies have also been tested for management of hot flashes. Thus far, randomized, placebo-controlled trials of phytoestrogens, including soy phytoestrogens, red clover, and flaxseed, have not supported their use for hot flash management. Similarly, there is no evidence to support use of black cohosh, vitamin E, evening primrose oil, dong quai, or ginseng for treating hot flashes. Some behavioral interventions such as relaxation training and hypnosis have shown promise in small studies, although larger randomized trials are needed.

Overall, much progress has been made in the past decade to identify effective management options for hot flashes. However, some patients do not obtain benefit from these treatment options, and others have considerable side effects from the hot flash treatments themselves. Therefore, research is ongoing to identify management options for vasomotor symptoms that have a more optimal benefit/risk ratio.

**Arthralgias**

Musculoskeletal symptoms have emerged as a treatment-limiting toxicity of AI therapy. A number of studies have identified musculoskeletal toxicity as the most frequent cause for treatment discontinuation. Since standard analgesics are often ineffective, considerable research is being conducted to identify effective management options for arthralgias (Table 2).

**Crossover.** An option for some patients is switching from one endocrine therapy to another. For example, patients can potentially switch from an AI to tamoxifen or from one AI to another. Although the AIs all act via the same mechanism and have similar side-effect profiles, some patients are able to tolerate a second AI even though they discontinued the first AI because of intolerable side effects. The two studies that evaluated this option allowed for a brief washout period of about 1 month following discontinuation of the first AI medication before starting the second one. In the ATOLL trial,
patients who had discontinued treatment with anastrozole because of musculoskeletal toxicity were subsequently treated with letrozole. At the 6 month time point, 71.5% of patients were still taking letrozole, although the majority still reported some degree of musculoskeletal symptoms. Therefore switching from one endocrine therapy to another is a feasible option for some patients.

Pharmacologic treatments. Identification of new symptom management options is essential to improve persistence with adjuvant AI therapy. No randomized, placebo-controlled trials of pharmacologic agents for treatment of AIMSS have yet been reported. SWOG S0927 investigated the effect of omega 3 fatty acids versus placebo on AIMSS; the trial is fully accrued and we await the results. In a pilot study of the SNRI duloxetine, pain decreased by at least 30.0% in 72.0% of enrolled patients, and average pain decreased by a mean of 60.9%. This approach is now being tested in an ongoing placebo-controlled, randomized clinical trial, SWOG S1202 (NCT01598298). The Alliance is also conducting a randomized, placebo-controlled trial of subcutaneous testosterone versus placebo for treatment of AIMSS (NCT01573442).

Nonpharmacologic therapies. Nonpharmacologic approaches including acupuncture and exercise have also been investigated. Acupuncture has been shown to improve AI-associated arthralgias compared to sham acupuncture in a single-institution randomized controlled trial. True acupuncture resulted in an approximately 50% improvement in worst pain and pain severity at 6 weeks, whereas sham acupuncture did not improve either pain measure. A follow-up study that includes multiple institutions, SWOG S1200, is now being conducted to confirm these results (NCT01535066). Recently a year-long exercise intervention versus usual care was also presented. The Hormones and Physical Exercise (HOPE) intervention resulted in an improvement of approximately 30% in worst pain, as compared to a slight increase in pain for patients managed with usual care.

Prevention. In contrast to trials investigating treatment of AIMSS, other studies have studied interventions designed to prevent the symptoms from developing. In the VITAL trial, women with low-serum vitamin D concentrations who were starting letrozole were randomly assigned to high-dose (30,000 international units [IU]) versus low dose (600 IU) vitamin D daily for 6 months. At 6 months, there was a statistically noteworthy reduction in the incidence of the musculoskeletal toxicity for the patients in the high-dose cohort (38% vs. 61%). Therefore, ensuring that patients are not vitamin D deficient during AI therapy may decrease the incidence of AIMSS, although a subset of patients will still develop symptoms.

CONCLUSION
Adjuvant endocrine therapy has substantial, potentially life-saving benefits for patients with HR-positive, early-stage breast cancer. Treatments are associated with side effects, however, including serious but rare toxicities as well as bothersome side effects that negatively affect adherence and persistence with therapy. Personalization of endocrine therapy, taking into account both effectiveness and tolerability of the medication, has the potential to result in improved breast cancer outcomes and quality of life for breast cancer survivors. Noteworthy advances have been made in identifying predictors of response to therapy as well as effective options for managing side effects, but much work remains to be done.

Disclosures of Potential Conflicts of Interest
The author(s) indicated no potential conflicts of interest.

References


