Clinical management of adverse events in adjuvant therapy for hormone-responsive early breast cancer

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Systemic adjuvant therapy has proven highly effective at reducing recurrences and deaths in patients who have received primary therapy for early breast cancer. However, as with all treatments, adjuvant therapy can cause unwanted side effects, and effective management of these events is essential to ensure that patients comply with, and continue, treatment. Adjuvant endocrine therapy is not associated with the more severe, acute toxicities of chemotherapy, and can therefore be taken for many years. At present, the standard duration of postoperative adjuvant endocrine therapy is 5 years. Prevention and treatment of adverse events associated with long-term endocrine therapy is particularly important in the adjuvant setting, where patients are clinically cancer free. In this situation, the efficacy benefits are not, therefore, obvious to the patient, but side effects may have a negative impact on daily life. Tamoxifen has been the gold standard endocrine therapy for hormone-receptor-positive early breast cancer for many years, and the long-term side effects of this agent are well documented. In recent years, the aromatase inhibitors (AIs) have begun to displace tamoxifen as the adjuvant therapy of choice, owing to greater efficacy and good tolerability. Predictably, the AIs and tamoxifen have partially overlapping side-effect profiles. Both therapies are associated with typical symptoms of estrogen deprivation; however, tamoxifen also has estrogenic activity in some tissues, which can cause either detrimental (genital tract) or beneficial (bone, cardiovascular system, lipids) effects that are not associated with AI use. To reduce treatment discontinuations, it is important that patients are made aware of the possible side effects of adjuvant therapy and the management strategies available to them, prior to starting therapy. The role of physical, alternative and pharmaceutical therapies in the management of adverse events associated with endocrine therapy has been investigated, and strategies are now available to alleviate symptoms and enable patients to benefit from adjuvant endocrine therapy without a significant adverse impact on quality of life.

Key words: adjuvant endocrine therapy, adverse events, breast cancer, hormone-responsive

introduction

For women with early breast cancer, systemic adjuvant therapy, which is given after primary tumor resection, reduces the risk of local and distant disease recurrence, and prolongs overall survival [1]. In hormone-receptor-positive (HR+) disease, endogenous estrogen promotes the growth and survival of the tumor: depriving the tumor cells of estrogen is the rationale for adjuvant endocrine therapy. Tamoxifen, a selective estrogen receptor modulator (SERM), has been the mainstay of adjuvant endocrine therapy for over 30 years, significantly improving outcomes for patients with HR+ breast cancer [1]. Recently, the third-generation aromatase inhibitors (AIs), letrozole, anastrozole and exemestane, have demonstrated superior efficacy to tamoxifen in large, randomized clinical trials, and are now displacing tamoxifen as the postoperative adjuvant treatment of choice for early breast cancer.

For women who have completed primary therapy, accepting long-term adjuvant endocrine therapy depends on the balance between the potential benefits of treatment (i.e. decreased risk of relapse and death) and the possible side effects that they may experience. As adjuvant tamoxifen has been used for many years, abundant, long-term safety data exist, and the side effects are well documented. Although generally well tolerated, serious side effects do become problematic with prolonged tamoxifen use. The increased risk of serious adverse events, together with the lack of clinical benefit seen with longer-term tamoxifen therapy [2], limits the duration of adjuvant tamoxifen to 5 years, outside of a clinical trial. Studies of adjuvant AIs currently have a shorter follow-up than those of tamoxifen and, hence, the long-term toxicities of AIs have yet to be determined. Nonetheless, current data from clinical trials indicate that the AIs are well tolerated, and no major tolerability concerns have been highlighted to date.

Tamoxifen and the AIs have partially overlapping side-effect profiles, reflecting the biological properties of these two classes of drugs: whereas AIs reduce circulating endogenous estrogen levels to almost undetectable levels, tamoxifen acts as an...
estrogen receptor (ER) antagonist or ER agonist, depending on the target tissue. Side effects common to both agents are largely predictable consequences of estrogen deprivation, and, hence, are also natural symptoms of the menopause, such as hot flushes and mood disturbances. Other side effects, for example, gynecological symptoms and thromboembolic disease, are associated more strongly with tamoxifen than the AIs, and these generally reflect tamoxifen’s estrogenic properties, which are absent from the AIs. Conversely, musculoskeletal symptoms, hypercholesterolemia and cardiovascular disease (CVD), have been reported more frequently in patients taking AIs than in those taking tamoxifen, but there is evidence to suggest that at least some of these effects reflect the absence of tamoxifen’s beneficial estrogenic actions on these target tissues rather than a detrimental effect of AIs. The side effects of adjuvant endocrine therapy are discussed in more detail by Professor Perez elsewhere in this supplement.

The choice of adjuvant therapy is affected by patient characteristics, such as age, comorbidity and lifestyle, and disease characteristics, which may influence the risk of relapse or the likelihood of achieving a response to a particular therapeutic agent. The healthcare professional should consider these factors in order to select the most appropriate treatment, based on the medical evidence, before discussing available treatment options with the patient. The clinical evidence regarding relative efficacies, potential side effects and impact on daily life should be presented to the patient in a clear and simple way, and the patient should be given the opportunity to ask questions and voice any concerns they may have regarding the proposed treatment. A joint decision should then be made between the doctor and the patient as to what treatment the patient will receive. It is, therefore, essential that doctors effectively communicate the risks and benefits of a specific treatment to their patients, to enable patients to make an informed decision about their preferred adjuvant therapy.

Adjuvant endocrine therapy is a new phase of treatment after several other interventions, which may include surgery, radiotherapy and chemotherapy, and many patients are, understandably, concerned about the possible side effects of the new treatment. The long-term effects of estrogen deprivation, and how these may affect daily life, can worry patients and also concern the doctor. Effective management of adverse events is essential to maintain a good quality of life (QoL), to ensure that patients continue therapy, and to gain the maximum benefits possible: intolerable side effects are a major reason for non-compliance or discontinuation of adjuvant therapy. Clinical and non-clinical interventions are available, which can alleviate the unwanted side effects of endocrine therapy. Doctors should discuss the potential side effects of treatment and available coping strategies prior to initiation of therapy to avoid discontinuations. The management strategies that are available to help patients cope with the potential side effects of adjuvant endocrine therapy are discussed in this article.

vasomotor instability: hot flushes, night sweats

Vasomotor symptoms are a well-recognized consequence of estrogen deprivation and are one of the most common reasons why women in the Western world seek medical advice at the onset of the menopause. In healthy women, hormone-replacement therapy (HRT) has been shown to alleviate hot flushes [3], but hormonal therapy is contraindicated in women with HR+ breast cancer as estrogen promotes tumor cell growth and may, therefore, increase the risk of disease recurrence. Consequently, alternative treatments for vasomotor symptoms are required for patients with HR+ breast cancer.

Practical, non-pharmacological approaches may help women to cope with uncomfortable hot flushes or night sweats. For example, identification and avoidance of foods or situations that trigger hot flushes, wearing natural fabrics and employing methods of rapid cooling, such as spray mists or moist wipes, can be effective. The ability of complementary therapies that contain isoflavones (naturally occurring compounds that have estrogenic effects) to reduce or prevent hot flushes has been investigated. Such therapies include black cohosh, dong quai, red clover and soy proteins. The potential benefits of vitamin E have also been investigated. However, placebo-controlled clinical trials have failed to demonstrate a significant benefit of any of these agents in either healthy postmenopausal women or women with a history of breast cancer [4–8].

Pharmaceutical treatments have achieved some success in the prevention of hot flushes, but the suitability of these agents for use in women with breast cancer requires confirmation. The centrally acting α-adrenergic agonist, clonidine [9], progestagens [10, 11], and the γ-aminobutyric acid analog, gabapentin [12], have been shown to significantly reduce the frequency of hot flushes compared with placebo in clinical trials of women with a history of breast cancer. Current data from placebo-controlled clinical trials indicate that the selective serotonin reuptake inhibitors (SSRIs; paroxetine, venlafaxine) are the most effective agents available for the prevention of hot flushes [13]. In a randomized, double-blind, cross-over study, paroxetine (10 or 20 mg) significantly reduced the frequency of hot flushes compared with placebo after 4 weeks of treatment (Table 1) in women who could not or did not wish to take HRT [14]. Venlafaxine (37.5–150 mg) has also been shown to significantly reduce hot flushes compared with placebo (Figure 1) in women with a history of breast cancer or women who do not want to take estrogen due to concerns over its association with breast cancer [15]. A small, open-label study has also shown that low-dose venlafaxine (38.5 mg daily for 8 weeks) reduces the number and severity of hot flushes, compared with placebo, in patients with breast cancer [16]. Preliminary data from a randomized, controlled trial suggest that SSRIs may be more effective than other pharmaceutical agents in preventing hot flushes in patients with breast cancer. After 4 weeks of treatment, the reduction in the frequency of hot flushes from baseline was greater in patients taking venlafaxine than in those taking clonidine (56 versus 37%, respectively, \( P = 0.001 \)) [17]. Overall, the SSRIs appear to be effective and tolerable treatments to alleviate hot flushes in women with breast cancer, although studies performed to date have been conducted over short (<9 weeks) treatment periods, and the long-term effects of these agents in patients with breast cancer is currently not known.
gynecological symptoms and sexual functioning

Tamoxifen acts as an ER antagonist or a partial ER agonist, depending on the target tissue. In the breast, for example, tamoxifen blocks the effects of estrogen by competing with estrogen for binding at the ER, thus inhibiting estrogen-dependent tumor growth. In other tissues, such as bone, the uterus and the cardiovascular system, tamoxifen has estrogenic effects that can be beneficial or detrimental, depending on the tissue.

In the genitourinary tract, tamoxifen’s estrogenic activity can cause unwanted side effects, including vaginal discharge and bleeding, and endometrial cancer. Although a rare complication of tamoxifen therapy, endometrial cancer can be fatal, and, therefore, most women who experience gynecological symptoms while on tamoxifen will undergo invasive examinations to rule out endometrial cancer as the cause. Such investigations, which include hysteroscopy associated with endometrial biopsy, can be painful and very distressing to patients, and cause unnecessary anxiety. In randomized, controlled trials comparing adjuvant AIs with tamoxifen, a significant reduction in the frequency of gynecological symptoms was reported in women taking an AI [18–21], reflecting the fact that AIs do not have estrogenic activity. Furthermore, in the BIG (Breast International Group) 1-98 trial, fewer women taking letrozole underwent endometrial biopsies than women taking tamoxifen (2.3 versus 9.1%, respectively, $P < 0.001$) [21], suggesting that many gynecological side effects, invasive examinations, and, consequently, much unnecessary anxiety, could be avoided by prescribing an AI rather than tamoxifen. In the MA.17 trial, the incidence of vaginal bleeding was significantly lower in women taking letrozole than in those on placebo (6 versus 8%, respectively, $P = 0.005$), suggesting that AIs may actually reduce gynecological side effects in postmenopausal women [22]. However, gynecological symptoms are not completely avoided or prevented by AI therapy, and for women who are affected, gynecological problems are unpleasant and can adversely affect QoL. Efforts must therefore be made to alleviate symptoms.

Vaginal dryness occurs as a result of estrogen deprivation, and is commonly reported by women who are going through the menopause and patients receiving adjuvant endocrine therapy. Vaginal dryness can cause pain during intercourse and, subsequently, contributes to loss of libido. Non-hormonal, local lubricants can be used temporarily to alleviate symptoms. Topical vaginal estrogen preparations have been shown to relieve the symptoms of vaginal dryness in healthy, postmenopausal women [23], but may be contraindicated in postmenopausal women taking adjuvant AIs for HR+ breast cancer. A prospective study of seven postmenopausal women taking adjuvant AIs and using topical vaginal estrogen for severe symptoms of atrophic vaginitis reported that the vaginal tablet, Vagifem®, significantly raised systemic serum estradiol levels within 2 weeks of starting use (Table 2) [24]. As the effectiveness of AIs depends on near-complete suppression of estrogen to prevent stimulation of cancer cell growth, even a small increase in systemic estrogen levels may counteract the benefits of AI therapy. Although a large, well-designed, targeted study is required to confirm the effects of vaginal estrogens on circulating estrogen levels, these preliminary findings suggest that topical estrogen use should be avoided in women with breast cancer taking AIs.

musculoskeletal symptoms

arthralgia and myalgia

Bodily pain, including joint pain, is more prevalent in women aged 50–59 years or postmenopausal women than in younger or premenopausal women [25–27], and healthy women taking estrogen replacement therapy report fewer musculoskeletal symptoms than women on placebo [28], suggesting that low estrogen levels may be associated with joint pain. However, the

Table 1. Paroxetine significantly reduces hot flushes compared with placebo [14]

<table>
<thead>
<tr>
<th>Frequency of hot flushes</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(paroxetine versus placebo)</td>
<td></td>
</tr>
<tr>
<td>Paroxetine 10 mg</td>
<td>40.6 versus 13.7%</td>
</tr>
<tr>
<td>Paroxetine 20 mg</td>
<td>51.7 versus 26.6%</td>
</tr>
</tbody>
</table>

Table 2. Topical vaginal estradiol therapy raises serum estradiol levels in postmenopausal women taking AIs (anastrozole, $n = 3$; letrozole, $n = 3$; exemestane, $n = 1$) for early breast cancer [24]

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Median serum estradiol pmol/l (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3 (3–7.4)</td>
</tr>
<tr>
<td>2 weeks</td>
<td>72 (3–232)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>16 (3–40)</td>
</tr>
<tr>
<td>7–10 weeks</td>
<td>17 (3–219)</td>
</tr>
</tbody>
</table>
relationship between estrogen and joint pain and how estrogen deprivation may cause arthralgia has not been well studied, although some indirect evidence exists linking estrogen levels with pain sensitivity [29]. The development of arthralgia may also be related to the effect of decreased estrogen levels on cartilage, a tissue that expresses ERs [30].

In postmenopausal women with early breast cancer, postoperative adjuvant AI therapy, which reduces circulating estrogen levels, has been associated with an increased incidence of arthralgia and myalgia compared with tamoxifen or placebo [18–22]. Although muscular and joint pain are common side effects of AIs, affecting up to 35% of patients [18], and can be troublesome in some individuals, symptoms are rarely severe enough to necessitate treatment discontinuation and usually improve with time. Where necessary, management options are available to help patients to cope with joint and/or muscle pain; for example, physical strategies, such as physiotherapy or massage, can help to relieve symptoms. Pharmacological intervention is limited to analgesics: non-steroidal anti-inflammatory drugs, acetaminophen or cyclo-oxygenase-2 inhibitors are effective in most patients, although stronger analgesics can be prescribed if necessary.

**Bone loss**

Loss of bone mass is a well-recognized consequence of estrogen deprivation. Accelerated bone loss occurs during the menopause, coinciding with naturally decreasing estrogen levels, making postmenopausal women inherently at risk of osteoporosis. In severe cases, bone loss can result in fractures, which cause considerable morbidity, including pain and loss of mobility and independence. Prolonged hospitalization as a result of osteoporotic fractures also contributes to a reduction in QoL [31]; in particular, hip and vertebral fractures can markedly increase morbidity and mortality rates [32, 33]. In addition to natural menopausal bone loss, women with breast cancer are at greater risk of osteoporosis compared with the age-matched, healthy population [34–36], suggesting that an inherent link exists between bone loss and a diagnosis of breast cancer. Furthermore, some anticancer therapies are associated with additional bone loss and, therefore, an increased risk of osteoporosis and fractures [37].

Cancer-treatment-induced bone loss is a well-recognized consequence of some breast cancer treatments, including chemotherapy and AIs. In premenopausal women, chemotherapy can result in ovarian failure, causing premature menopause and accelerated bone loss, associated with decreased circulating estrogen levels [38, 39]. Bone loss is also a predictable side effect of the AIs [18–21], which reduce endogenous circulating estrogen to almost undetectable levels. In contrast, tamoxifen acts as a partial estrogen agonist in bone and protects against bone loss [40]. It is, therefore, essential that bone loss is effectively managed in at-risk patients (such as patients with low bone mass) to prevent fractures and to enable these women to gain the additional efficacy benefits of AI therapy over tamoxifen.

It is important that all patients who are prescribed a treatment that may cause bone loss, such as an AI, receive regular bone health assessments, and that steps are taken to minimize any detrimental effects on bone health, including pharmaceutical intervention when necessary. HRT is the standard treatment for postmenopausal osteoporosis, but is contraindicated in patients with HR+ breast cancer as hormone therapy may promote tumor growth. The American Society of Clinical Oncology (ASCO) has published guidelines for the management of bone loss in women with breast cancer. Bone mineral density (BMD) screening is recommended for patients with breast cancer, including all women aged over 65 years, women aged 60–64 years with risk factors for osteoporosis, postmenopausal women receiving AI therapy, and premenopausal women with cancer-therapy-induced premature menopause. Several methods are available for the measurement of BMD, of which, DEXA (dual-energy X-ray absorptiometry) is a non-invasive technique that can be carried out quickly (scans with modern equipment take less than 15 minutes) and without pain or discomfort to the patient [41]. Following the initial examination, BMD measurements should be repeated annually [42]. Recommendations are made in the ASCO guidelines for the most appropriate intervention when bone loss becomes evident (Figure 2). The recommended treatment depends on the extent of bone loss, and includes reassurance, advice on lifestyle changes to slow or prevent further bone loss, such as increasing weight-bearing physical activity and taking dietary supplements (calcium and vitamin D), and drug therapy, for example with bisphosphonates, for patients experiencing severe bone loss.

Bisphosphonates bind to bone at sites of active metabolism and inhibit osteoclastic bone resorption, and are widely used in the treatment of postmenopausal osteoporosis [43]. Early oral and IV bisphosphonates were associated with considerable gastrotoxicity or long infusion times, respectively, and hence, non-compliance was a common problem. Preliminary results from three ongoing trials suggest that bi-annual 15-minute infusions of the newer, potent bisphosphonate, zoledronic acid, can prevent AI-associated bone loss in women with early breast cancer [44–46]. In the Z-FAST and ZO-FAST trials, postmenopausal women with early breast cancer receiving adjuvant letrozole therapy have been randomized to receive either upfront or delayed zoledronic acid (4 mg IV every 6 months), with delayed treatment being initiated when post-baseline BMD T-scores decreased by at least −2 standard deviations or when a fracture had occurred. Early results from
the Z-FAST and ZO-FAST trials suggest that, after 12 months of letrozole therapy, upfront zoledronic acid can prevent bone loss. In both trials, upfront zoledronic acid resulted in a mean increase in BMD from baseline, whereas a reduction in BMD was seen in patients randomized to delayed therapy, resulting in a significant difference in BMD between the two treatment arms (Table 3) [45–47]. Accelerated bone loss is clearly an important consideration for patients with HR+ early breast cancer taking AIs, and doctors should ensure that regular screening is carried out. Lifestyle changes that can improve or maintain bone health, such as increasing exercise, should be discussed with the patient prior to starting AI therapy in order to prevent bone loss. Preliminary data indicate that, when necessary, bisphosphonate therapy can prevent further bone loss, enabling patients to continue with AI therapy. However, no data are yet available concerning the prevention of late fractures.

### Serum lipids and CVD

In both men and women, the risk of developing CVD increases with age. However, premenopausal women are at significantly lower risk of CVD than men of similar age due to the beneficial effects of estrogen on metabolic risk factors for CVD, including serum lipid and lipoprotein levels, glucose and insulin metabolism, and body fat distribution. Furthermore, in postmenopausal women, who have low estrogen levels, the risk of CVD is substantially increased, suggesting that treatments that reduce estrogen levels may have detrimental effects on the cardiovascular system. There is evidence to suggest that, through its estrogenic activity, tamoxifen protects against CVD and also has lipid-lowering effects; in contrast, the effects of the AIs have not been studied in detail and, consequently, are not fully understood.

The results from a meta-analysis of vascular events in randomized, controlled trials of tamoxifen indicate that tamoxifen protects against CVD. Significantly fewer deaths from myocardial infarction were reported in women taking tamoxifen compared with placebo, based on data from 12 trials involving over 27 000 women [48]. A trend for a lower incidence of myocardial infarction was also associated with exposure to tamoxifen [48]. Data from clinical trials comparing AIs with tamoxifen as adjuvant therapy suggest that AIs may increase the risk of CVD [18, 19, 21], but the number of events was low in both treatment arms, and variation in adverse event reporting between trials makes it difficult to draw any definite conclusions. Furthermore, the use of tamoxifen as the comparator in these studies makes interpretation of the data complicated, as patients in the AI arm did not gain the cardioprotective effects of tamoxifen. It is important to note that, in the MA.17 trial, no increase in cardiovascular events was seen in patients taking letrozole compared with those on placebo [22]. A recently reported meta-analysis of eight adjuvant AI trials, involving over 28 000 patients, suggested that the relative risk of ischemic cardiovascular events with AI therapy compared with tamoxifen was 1.25 (P = 0.001), with no heterogeneity (P = 0.69) [49]. However, this analysis included all trials, regardless of whether they investigated upfront AI therapy, a switching strategy (from tamoxifen to an AI) or extended adjuvant therapy (AI treatment following 5 years of tamoxifen), and did not account for the many other differences between these trials, such as the definition of cardiovascular events, methods of data collection and comparators (tamoxifen or placebo). As the available data do not support an association between AIs and CVD, no special cardiovascular management strategies are required in women taking AIs, but routine health screening, such as blood pressure monitoring, should be continued.

The ATAC (Anastrozole, Tamoxifen Alone or in Combination) and BIG 1-98 trials, comparing tamoxifen with adjuvant anastrozole and letrozole, respectively, suggest that AI use may be associated with an increased incidence of hypercholesterolemia [21, 50], but it is not yet possible to draw definitive conclusions from the available data for several reasons. These two trials report widely differing incidences of hypercholesterolemia in patients taking an AI (43.6% for letrozole; 9% for anastrozole), an observation that is difficult to explain. Furthermore, methodological concerns have been raised regarding data collection methods, suggesting that the reported figures may not reflect the true incidence of hypercholesterolemia in these trials. In ATAC, lipid data were not systematically collected; hypercholesterolemia was not a prespecified adverse event, and was only reported by patients when this condition was diagnosed outside of the trial, either as part of their medical history prior to trial entry or while participating in the trial. In contrast, in BIG 1-98, cholesterol levels were measured and recorded in the case report forms every 6 months. However, over 90% of lipid measurements were carried out in non-fasting patients, and samples were not analyzed centrally; furthermore, approximately 80% of hypercholesterolemic events were grade 1 and did not require specific treatment. Additionally, the lipid-lowering effects of tamoxifen are well documented [51, 52] and, therefore, as for CVD, patients taking AIs are not being compared with a baseline population but with patients gaining the lipid-lowering effects of tamoxifen (~13%). In contrast to tamoxifen-controlled studies, longitudinal and placebo-controlled studies of AIs have found no evidence of a detrimental effect on serum lipids [22, 53–56]. Although further investigation is required, current data indicate that patients taking AIs are not at increased risk of hypercholesterolemia.

Tamoxifen has been shown to have lipid-lowering and cardioprotective effects, but the effects of AIs on lipid metabolism and the cardiovascular system are not fully

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**Table 3.** Upfront zoledronic acid prevents AI-associated bone loss [45, 46]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Letrozole + upfront ZA</th>
<th>Letrozole + delayed ZA</th>
<th>Absolute difference from baseline (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-FAST</td>
<td>Lumbar spine</td>
<td>+ 2.02</td>
<td>−2.61</td>
<td>4.63</td>
</tr>
<tr>
<td></td>
<td>Total hip</td>
<td>+ 1.40</td>
<td>−2.10</td>
<td>3.50</td>
</tr>
<tr>
<td>ZO-FAST</td>
<td>Lumbar spine</td>
<td>+ 2.0</td>
<td>−3.5</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Total hip</td>
<td>+ 1.0</td>
<td>−2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

ZA, zoledronic acid.
understood. However, current data suggest that the effects observed in patients receiving AIs as postoperative adjuvant therapy reflect the absence of tamoxifen’s beneficial effects, rather than a detrimental effect of AIs. However, until the true effects of AIs on these systems are known, patients receiving AI treatment should undergo regular screening for cardiovascular risk factors (blood pressure monitoring, serum cholesterol measurements, etc.) as part of routine health checks, but no specific management strategies are required.

**cognitive function**

The effects of estrogen and estrogen deprivation on cognitive function are poorly understood. ERs are located throughout the brain, particularly in regions associated with learning and memory, including the hippocampus and amygdala [57], and there is evidence to suggest that circulating estrogen levels affect several cognitive functions [58–61]. It has been suggested that the natural decrease in estrogen levels due to the menopause may contribute to progressive cognitive impairment and an increased risk of dementia or Alzheimer’s disease in postmenopausal women [62]. It is reasonable to assume, therefore, that HRT may protect against cognitive decline, but the investigations that have been conducted so far have generated conflicting data. Whereas some observational studies have suggested that HRT may lower the risk of Alzheimer’s disease and preserve cognitive function in postmenopausal women [63–65], other studies have reported an increased risk of dementia associated with estrogen therapy [66, 67].

The relationship between endocrine therapies for early breast cancer and cognitive function has not been thoroughly investigated, and there is currently a lack of clinical data. Studies assessing the effects of SERMs, including tamoxifen, on cognitive function have generated inconsistent results. In a population of elderly women living in a nursing home, tamoxifen therapy was associated with a lower prevalence of Alzheimer’s disease and improved decision-making skills [68]. In contrast, a preliminary assessment of patients with breast cancer suggested that tamoxifen may adversely affect cognitive function [69].

The effects of AIs on cognitive function in women with early breast cancer have not yet been studied in detail. Pilot data from 94 women enrolled in the ATAC trial suggested that verbal memory and processing speed were impaired in patients receiving endocrine treatment (anastrozole, tamoxifen or combined therapy) compared with healthy controls, although measures of working memory, attention and visual memory were similar in the two groups [70]. How exemestane and letrozole affect cognitive function, compared with tamoxifen, has not yet been reported [19, 21], but the QoL substudy in MA.17 reported no adverse effects of extended adjuvant letrozole on mental health or cognitive function, compared with placebo, in women with early breast cancer who had completed 5 years of tamoxifen prior to starting letrozole [71].

It is clear that the effects of adjuvant endocrine treatment on cognitive function require further study. As the prolonged use of such therapies is becoming more widespread, it is increasingly important to determine to what extent, if any, tamoxifen and AIs are associated with impairment of cognitive function, which can have a considerable negative impact on daily life. The ongoing FACE (Femara versus Anastrozole Clinical Evaluation) trial will assess the effects of estrogen deprivation on brain tissue and will hopefully provide insights into this very important potential side effect of endocrine therapy.

**QoL**

An important consideration when choosing adjuvant treatment is the potential impact that therapy will have on a woman’s daily life. Assessment of QoL is essential to provide doctors with a comprehensive assessment of the physical and psychological consequences of treatment on patients’ lives. If the side effects of adjuvant therapy become intolerable, a patient may discontinue treatment and may be unwilling to accept alternative therapy for fear of similar problematic side effects occurring.

The effects of adjuvant endocrine therapies on QoL have been investigated in postmenopausal women with breast cancer. Two trials, which assessed the effect of tamoxifen on QoL in postmenopausal women with early breast cancer, reported that vasomotor symptoms and vaginal discharge were more common in patients on tamoxifen than in patients on placebo, but, overall, tamoxifen did not have a major impact on psychological well-being or sexual functioning [72, 73].

In randomized, controlled trials in patients with HR+ early breast cancer, AIs have been shown to compare favorably with tamoxifen and placebo. In QoL subprotocols, vasomotor or gynecological symptoms were the most commonly reported problems for both AIs and tamoxifen. In the ATAC QoL subprotocol, 2 years of anastrozole or tamoxifen therapy had a similar overall impact on QoL, as assessed by the Functional Assessment of Cancer Therapy-Breast scale plus the endocrine subscale. Endocrine-related symptoms increased between baseline and 3 months and then remained stable for the remainder of the study in both treatment arms [74]. Similarly, in the IES (Intergroup Exemestane Study), QoL did not differ between patients taking exemestane and those taking tamoxifen: some endocrine-related symptoms improved during the study period (vasomotor effects, gynecological and sexual problems), whereas other symptoms persisted (reduced libido and vaginal dryness) [75]. Assessment of QoL in MA.17, using the Short-Form 38-Item Health Survey (SF-36) and the Menopause-Specific Quality of Life Questionnaire (MENQOL), revealed small differences in SF-36 physical functioning ($P < 0.001$), bodily pain ($P = 0.001$) and vitality ($P = 0.005$), and in MENQOL physical domains at 12 months ($P = 0.004$), vasomotor function at 6, 12 and 24 months ($P < 0.001$), and sexual function at 12 and 24 months ($P = 0.02$), but, overall, letrozole did not adversely affect QoL [71]. These studies suggest that the clinical benefits of AI therapy can generally be achieved without a significant negative impact on patients’ lives.

**conclusions**

Patients are naturally concerned about the side effects of any new treatment and how these may affect their daily lives. Before
treatment is started, a comprehensive discussion of the potential risks and benefits of adjuvant therapy should take place between the doctor and the patient, and the patient should be given the opportunity to ask any questions to ensure that they understand why a particular therapy has been chosen. Well-informed patients who understand their treatment are likely to cope better with any adverse events than patients who are not fully aware of the possible effects of treatment. The management of unwanted side effects should also be discussed in detail, both before choosing a treatment and when side effects occur. Long-term adjuvant therapy is more likely to be acceptable if patients understand, before starting treatment, that, should side effects become problematic, effective strategies are available to alleviate symptoms and to help them to cope.

Adjuvant endocrine therapy for HR+ early breast cancer is generally well tolerated and is not associated with the more severe, acute toxicities seen with chemotherapy, enabling patients to take endocrine therapy for several years. Furthermore, as many women who take adjuvant treatment are clinically breast-cancer free, it is important that QoL is maintained so that patients continue to take their medication and gain the long-term benefits, that is, prolonged disease-free and overall survival. Clinical trials indicate that, overall, AIs and tamoxifen are well tolerated and do not adversely affect QoL: to date, no differences between the individual AIs have been identified, and direct comparisons of the AIs are ongoing in the FACE (comparing adjuvant anastrozole and letrozole) and MA.27 (comparing exemestane and anastrozole) trials. Most of the side effects of endocrine therapy are predictable consequences of estrogen deprivation, and are also symptoms of a natural menopause. However, side effects can still be problematic and unpleasant for women who experience them. For many side effects, particularly those associated with AI therapy, effective management options are available to help patients cope with unwanted symptoms. Importantly, when considering treatment options for adjuvant endocrine therapy, the AIs are not associated with the more severe and difficult-to-manage side effects of tamoxifen, namely, thromboembolic disease and endometrial cancer, which can be fatal if not managed correctly. Although some side effects are associated more strongly with the AIs than tamoxifen, such as bone loss and arthralgia, these are generally more preventable or manageable than the side effects associated primarily with tamoxifen. Careful monitoring of patients and the use of management strategies can allow patients to gain the benefits of adjuvant endocrine therapy while minimizing any negative impact on their lives.

disclosures
Dr Monnier has reported that he is a member of the speaker’s bureau of Amgen, Novartis, and Pfizer, and that he is a consultant for Novartis.

references


