Sequential Therapy With Tamoxifen and Aromatase Inhibitors in Early-Stage Postmenopausal Breast Cancer: A Review of the Evidence

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Purpose/Objectives: To review the available evidence for the emerging role of aromatase inhibitors (AIs) in postmenopausal women with hormone-sensitive early-stage breast cancer.

Data Sources: Studies published in journals indexed in PubMed® and abstracts and presentations from international conferences.

Data Synthesis: Switching to an AI improves survival and reduces cancer recurrence in postmenopausal women who have received two or three years of adjuvant tamoxifen treatment but presents challenges with regard to patient selection, cost, and management of treatment-related adverse events such as bone loss and arthralgia.

Conclusions: Third-generation AIs have the potential to significantly improve clinical outcomes in postmenopausal women with early-stage breast cancer, although the optimal treatment regimen for individual patients has yet to be determined.

Implications for Nursing: Oncology nurses play a vital role in identifying patients suitable for AI therapy, educating patients about their treatment, and preventing and managing treatment-related adverse events.

Key Points . . .

- Although tamoxifen has been the standard of care for the adjuvant treatment of early-stage breast cancer in postmenopausal women for many years, the drug is associated with an increased risk of vaginal discharge and bleeding, proliferative endometrial abnormalities, and endometrial cancer, in part because of its partial estrogen-agonist effects. Furthermore, many tumors eventually become resistant to tamoxifen.
- In postmenopausal women, the majority of circulating estrogen is derived peripherally from aromatase-mediated conversion of testosterone. Third-generation aromatase inhibitors (AIs) inhibit peripheral aromatase activity and decrease plasma estrogen levels to less than 20% of pretreatment levels.
- Compared with remaining on tamoxifen, switching from tamoxifen after two or three years to treatment with an AI is associated with improved survival, decreased cancer recurrence, and a decreased incidence of contralateral breast cancer, but it also is associated with an increased incidence of arthralgia, bone loss, and variable effects on lipid metabolism.
- Current clinical treatment guidelines, including those from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the International Consensus Panel on the Treatment of Primary Breast Cancer, recommend that optimal adjuvant hormonal therapy for postmenopausal women with hormone receptor–positive breast cancer should include an AI.

Each year in the United States, approximately 182,460 postmenopausal women are diagnosed with invasive breast cancer (American Cancer Society, 2008). After initial treatment with surgery and radiotherapy, most patients are offered adjuvant endocrine therapy to reduce the risk of recurrent or contralateral breast cancer. Tamoxifen has been the mainstay of adjuvant endocrine therapy for hormone-sensitive early-stage breast cancer since the 1980s. However, the development of newer agents, such as third-generation aromatase inhibitors (AIs), has increased the options available for adjuvant therapy for postmenopausal women with breast cancer (D'Hondt & Piccart, 2004; Grana, 2003; Michaud, 2005; Palmieri & Perez, 2003).

Oncology nurses, in addition to providing clinical care, are an important source of information and guidance, from initial diagnosis through treatment and follow-up, to patients with breast cancer (Halkett, Arbon, Scutter, & Borg, 2006; Harwood, 2004; Rosenzweig, 2006). Patients look to oncology nurses for information about treatment options and guidance regarding the potential impact of treatment on their overall health and quality of life (QOL), as well as for support in dealing with the emotional consequences of treatment (Halkett et al.). Nurses often are the first point of contact in addressing

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symptoms and managing adverse events. Therefore, oncology nurses must have up-to-date information regarding the evolving landscape of adjuvant endocrine therapy, including the risk-benefit profiles of individual AIs and strategies for prevention and management of acute and long-term adverse events associated with their use.

This article reviews available evidence regarding the emerging role of AIs as adjuvant therapy in postmenopausal women with hormone-sensitive early-stage breast cancer, with particular focus on the potential benefits of switching to an AI after two or three years of treatment with tamoxifen. The implications for nursing practice also are discussed.

Tamoxifen: Benefits and Limitations

Approximately 75% of breast tumors are hormone sensitive and therefore targets for antiestrogen therapy (D'Hondt & Piccart, 2004). Tamoxifen is a nonsteroidal selective estrogen receptor (ER) modulator that competes with estradiol for binding sites in malignant breast tissues (AstraZeneca Pharmaceuticals, 2007b). In patients with estrogen receptor (ER)-positive breast cancer, tamoxifen has been shown to significantly reduce the long-term risk of breast cancer recurrence and to increase survival, regardless of lymph node status, age, or menopausal status (Early Breast Cancer Trialists' Collaborative Group, 1998, 2005). As a result, tamoxifen has been the gold standard for adjuvant endocrine therapy following surgery—with or without irradiation—for breast cancer (Grana, 2003; Harwood, 2004; Viale, 2005).

Tamoxifen has tissue-specific estrogen agonist effects that help maintain bone mineral density (BMD) in postmenopausal women (Smith & Dowsett, 2003). However, the estrogen agonist effects of tamoxifen also are believed to be responsible for an increased risk of gynecologic complications (including vaginal discharge and bleeding, proliferative endometrial abnormalities, and endometrial cancer) (American College of Obstetricians and Gynecologists [ACOG], 1996; Early Breast Cancer Trialists' Collaborative Group, 1998; Gradishar, 2005) and an increased risk of thromboembolism and pulmonary embolism (Duggan, Marriott, Edwards, & Cuzick, 2003; Fisher et al., 1998; Gradishar; McCaskill-Stevens et al., 2004).

Optimal benefit from tamoxifen is achieved with five years of treatment, with no additional benefit beyond five years in women with ER-positive breast cancer and negative lymph nodes (Fisher, Dignam, Bryant, & Wolmark, 2001). Furthermore, patients who receive tamoxifen therapy beyond five years are almost twice as likely to develop endometrial cancer compared with patients who discontinue tamoxifen (Fisher et al., 2007). Therefore, current clinical guidelines recommend that tamoxifen treatment be limited to five years or less (NCCN, 2007; Winer et al., 2005).

Tamoxifen's clinical utility also is limited by resistance, which can develop as early as 12–18 months after initiation of therapy (Morandi et al., 2004). Approximately 40% of patients treated with adjuvant tamoxifen eventually relapse and die from breast cancer (Ring & Dowsett, 2004); in tamoxifen-resistant patients, continued treatment may serve to stimulate malignant cells (Morandi et al.). Although the mechanisms of tamoxifen resistance have yet to be fully defined, several hypotheses have been proposed, including the development of pharmacologic tolerance, mutations or alterations in the expression and function of ER genes, acquired hypersensitivity of the ER in response to low levels of circulating estrogens, and ER activation via the mixed estrogen antagonist/agonist effects of tamoxifen (Ali & Coombes, 2002; Jansen et al., 2005; Mamounas, 2001; Ring & Dowsett).

The Emerging Role of Aromatase Inhibitors as Adjuvant Therapy in Postmenopausal Women

Recognition of tamoxifen's clinical limitations has prompted a search for other agents that can suppress the activity of estrogen. In postmenopausal women, circulating estrogen is derived primarily from aromatase-mediated conversion of androgens to estrogens in peripheral tissues (Miller, 2004; Smith & Dowsett, 2003). By inhibiting or inactivating aromatase, AIs interrupt the final enzymatic step in estrogen synthesis, leading to a corresponding drop in plasma estrogen levels (Miller, 2004) (see Figure 1). Because AIs do not have the estrogen agonist effects of tamoxifen (Smith & Dowsett), they almost completely inhibit peripheral aromatase activity (Lonning, Pfister, Martoni, & Zamagni, 2003; Miller, 2003) and cause a reduction in plasma estrogen levels to less than 20% of postmenopausal levels (Lake & Hudis, 2002; Morandi et al., 2004).

Three third-generation AIs currently are approved in the United States for adjuvant therapy of early-stage breast cancer: the nonsteroidal inhibitors anastrozole (Arimidex®, AstraZeneca Pharmaceuticals LP) and letrozole (Femara®, Novartis Pharmaceuticals) and the steroidal inactivator exemestane (Aromasin®, Pfizer Inc.) (see Table 1). Nonsteroidal AIs inhibit aromatase activity by binding reversibly to the cytochrome p450 portion of the aromatase molecule (Campos, 2004; Miller & Dixon, 2000). In contrast, the steroidal agent exemestane inactivates aromatase by binding irreversibly to the aromatase substrate-binding site, so that production of new estrogens requires biosynthesis of new molecules of the aromatase enzyme (Dixon, 2004). Studies have indicated no

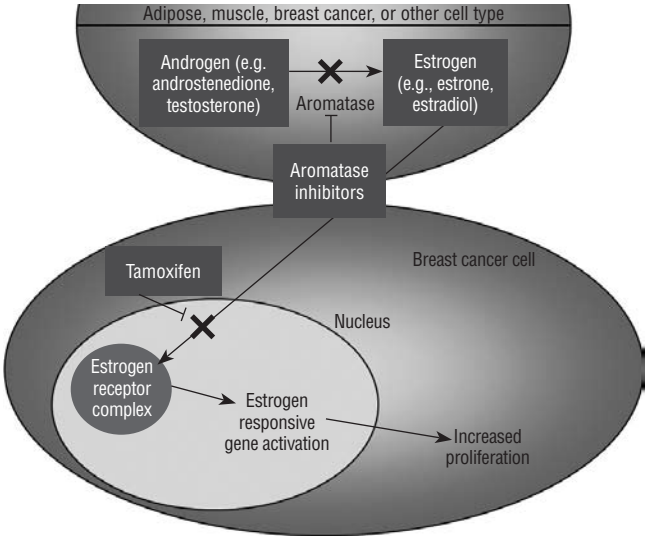

Figure 1. Mechanism of Action of Aromatase Inhibitors and Tamoxifen

Table 1. Comparison of Currently Available Aromatase Inhibitors

Aromatase Inhibitor	Indication(s) (United States)	Recommended Oral Dosage (mg per day)	Inhibition of Whole-Body Aromatization (%)	Suppression of Plasma Estrogens (%)
Anastrozole	Adjuvant treatment of postmenopausal women with hormone receptor–positive early-stage breast cancer First-line treatment of postmenopausal women with hormone receptor–positive or hormone receptor–unknown locally advanced or metastatic breast cancer Treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy	1.0	96.0	81–85
Letrozole	Adjuvant treatment of postmenopausal women with hormone receptor–positive early-stage breast cancer First-line treatment of postmenopausal women with hormone receptor–positive or hormone receptor–unknown locally advanced or metastatic breast cancer Extended adjuvant treatment of early-stage breast cancer in postmenopausal women who have received five years of adjuvant tamoxifen therapy Treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy	2.5	98.9	84–88
Exemestane	Adjuvant treatment of postmenopausal women with estrogen receptor–positive early-stage breast cancer who have received two or three years of tamoxifen and are switched to exemestane for completion of a total of five consecutive years of adjuvant hormonal therapy Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy	25.0	97.9	85–95

Note. Based on information from AstraZeneca Pharmaceuticals, 2007a; Brueggemeier, 2002; Brueggemeier et al., 2005; Novartis Pharmaceuticals, 2007.

cross-resistance between the steroidal and nonsteroidal AIs (Campos; Lonning, 2002; Lonning et al., 2003).

Current adjuvant therapy guidelines present several options for the use of AIs in the treatment of postmenopausal women with early-stage breast cancer (NCCN, 2007; Winer et al., 2005), including early adjuvant therapy up front (initial therapy after surgery), extended adjuvant therapy after five years of tamoxifen, and sequential (switch) therapy after two or three years of tamoxifen treatment.

The efficacy and safety of up-front and extended adjuvant AI therapy in postmenopausal women with early-stage breast cancer were established in two pivotal clinical trials: the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and the National Cancer Institute of Canada Clinical Trials Group MA.17 Study (MA.17). In the ATAC trial, up-front anastrozole significantly prolonged disease-free survival and time to recurrence and reduced the risk of contralateral breast cancer compared with up-front tamoxifen after a median follow-up of 68 months (ATAC Trialists' Group, 2002; Howell et al., 2005). In the MA.17 study, which evaluated extended adjuvant therapy with letrozole or placebo for five years in patients who already had received tamoxifen for approximately five years (Goss, 2006; Goss et al., 2003), letrozole significantly improved disease-free survival rates and decreased the risk of recurrence after a median follow-up of 2.5 years (Goss).

Because tamoxifen resistance may develop well before five years of adjuvant therapy have been completed (Morandi et al., 2004), considerable interest exists in the potential benefits of an early switch from tamoxifen to an AI. To date, several trials have evaluated the efficacy and safety of switching to an AI after two or three years of tamoxifen treatment, notably the Intergroup Exemestane Study (IES), the German Arimidex-Nolvadex (ARNO)-95 and Austrian Breast Cancer Study Group (ABCSG)-8 trials, and the Italian Tamoxifen Anastrozole (ITA) trial. The trials have consistently shown that an early switch to AI therapy improves clinical outcomes when compared with continued treatment with tamoxifen for postmenopausal women with hormone-sensitive early-stage breast cancer (Boccardo et al., 2005; Coombes et al., 2004, 2007; Jakesz et al., 2005; Kaufmann et al., 2006). A recent pooled analysis of five published trials of sequential therapy (including IES, ITA, and ABCSG-8/ARNO-95) recently confirmed the benefits of an early switch from tamoxifen to an AI. Bria et al. (2006) analyzed data from 8,794 postmenopausal patients and found that an early switch reduced the risk of relapse, secondary breast cancer, and death from any cause by 23% and also significantly improved overall survival. To date, a significant improvement in overall survival has not been reported with other adjuvant AI regimens. However, given the different study populations and durations of treatment, comparisons across clinical trials are difficult.

Current clinical guidelines, including those from the American Society of Clinical Oncology (ASCO), the NCCN, and the International Consensus Panel on the Treatment of Primary Breast Cancer (St. Gallen), recommend that optimal adjuvant hormonal therapy for postmenopausal women with hormone receptor–positive breast cancer should include an AI (Goldhirsch et al., 2005; NCCN, 2007; Winer et al., 2005). Questions remain about the optimal use of the agents, including appropriate patient selection, the optimal regimen for an individual patient, and the prevention and management of AI-related adverse events.

Acute and Long-Term Side Effects of Aromatase Inhibitors

Bone Metabolism

Estrogen plays a key role in bone metabolism and bone health. After menopause, all women experience ongoing bone loss as a result of aging and estrogen deficiency (Shapiro, 2005). The risk of developing osteoporosis and associated fractures increases significantly after menopause, making bone health an important consideration during selection of medication for postmenopausal women (Eastell et al., 2006). In contrast to the estrogen-agonist effects of tamoxifen, which have been shown to contribute to bone preservation (Shapiro, 2005), AIs increase the rate of bone loss in postmenopausal women (Coleman et al., 2005; Eastell et al.; Lonning et al., 2005; Perez et al., 2006).

In a substudy of the MA.17 trial, after a median follow-up of 24 months, letrozole-treated patients experienced significant decreases in BMD at the hip and spine compared with placebo-treated patients (Perez et al., 2006). Similarly, in the IES, levels of bone turnover markers increased significantly in the exemestane-treated group compared with the tamoxifen group (Coleman et al., 2005). More recently, a two-year, randomized, placebo-controlled trial of exemestane in postmenopausal women with surgically resected early-stage breast cancer found that patients treated with exemestane experienced a significantly greater mean annual rate of bone loss in the femoral neck compared with placebo-treated patients (–2.72% versus –1.48%; $p = 0.024$) (Lonning et al., 2005). However, no patients with normal BMD at baseline developed osteoporosis while receiving exemestane.

Clinical studies also have evaluated fracture risk. The IES found a nonsignificant increase in fracture rates in patients switched to exemestane compared with those who remained on tamoxifen after a median follow-up of 31 months (3.1% versus 2.3%, respectively) (Coombes et al., 2004). However, after 58 months, the exemestane group had experienced a significantly higher incidence of all fractures ($p = 0.003$) (Coombes et al., 2006). Similarly, the ATAC trial found a significant increase in the incidence of lumbar spine fractures in the anastrozole group compared with the tamoxifen group after a median follow-up of 68 months (1.5% versus 0.9%; $p = 0.03$) (Howell et al., 2005).

Fracture rates may be lower for women who have received tamoxifen previously because of its bone-sparing effects; however, given the different populations in the studies and the different durations of AI therapy, comparing fracture rates across clinical trials is difficult (Winer et al., 2005). Long-term follow-up data from some of the ongoing studies may help researchers further evaluate the long-term fracture risk associated with AIs and the different adjuvant regimens.

In the clinical setting, healthcare professionals must evaluate patients for evidence of bone loss as well as risk factors for osteoporosis at the start of and during treatment. Current ASCO guidelines recommend that all high-risk patients have a baseline BMD evaluation before starting an AI and be monitored periodically during treatment (Winer et al., 2005). Healthcare professionals and patients can prevent osteoporotic fractures by maximizing peak skeletal mass, avoiding or slowing rates of bone loss, and preventing falls. Fundamental ways to maintain bone health include adequate calcium intake (1,200 mg per day), adequate vitamin D intake (300–800 IU per day), weight-bearing exercise, and avoidance of smoking (Hillner et al., 2003).

Administration of an IV or oral bisphosphonate may help prevent or treat bone loss in patients receiving AIs (Winer et al., 2005). In the Zometa-Femara Adjuvant Synergy Trial, coadministration of letrozole and the bisphosphonate zoledronic acid resulted in a 2.02% increase in lumbar spine BMD after 12 months, whereas treatment with letrozole alone resulted in a 2.61% decrease in BMD (Brufsky et al., 2004).

Lipid Metabolism

Adjuvant therapy with tamoxifen has been shown to have generally favorable effects on serum lipids (Atalay et al., 2004). In contrast, third-generation AIs appear to have variable effects on lipid metabolism (see Table 2). Although some studies indicate that exemestane has no significant impact on total cholesterol, high-density lipoprotein (HDL) cholesterol, apolipoprotein A1, apolipoprotein B, or lipoprotein (a) levels (Atalay et al.), a recent study found that exemestane treatment resulted in modest reductions in HDL and apolipoproteins (Lonning et al., 2005). The findings suggest that all patients should undergo careful monitoring of lipid levels and evaluation of other risk factors for heart disease before and during adjuvant hormonal treatment.

Endometrial and Other Effects of Estrogen Deprivation

As previously discussed, the estrogen-agonist effects of tamoxifen increase the risk of gynecologic complications, such as vaginal discharge and bleeding, proliferative endometrial abnormalities, and endometrial cancer (ACOG, 1996). In contrast, treatment with AIs is associated with an increase in symptoms related to estrogen deprivation, including vaginal dryness, pain or discomfort with intercourse, and loss of libido (Fallowfield et al., 2004). In a subgroup of 179 patients enrolled in the IES with similar baseline endometrial measurements, the exemestane group showed significantly less endometrial thickening and a decreased risk of endometrial cancer compared with the tamoxifen-treated group (Coombes et al., 2007). Improved communication between patients and caregivers can lead to better symptom management through education about vaginal lubrications and moisturizers and may introduce the option of antidepressants. Treating these side effects with estrogen-replacement therapies, including localized therapies such as vaginal rings and vaginal estradiol tablets, likely is contraindicated

Table 2. Effects of Endocrine Therapy on Plasma Lipid Levels

Agent	Low-Density Lipoprotein Cholesterol	High-Density Lipoprotein Cholesterol	Total Cholesterol	Triglycerides	Total: High-Density Lipoprotein Cholesterol	Lipoprotein (a)	Apolipoprotein B
Tamoxifen	Decreases	No change	Decreases	No data	No data	Decreases	Decreases
Anastrozole	Increases or no change	Increases or no change	Increases or no change	No change	No change	Increases or no change	Increases or no change
Letrozole	Increases or no change	No change	Increases or no change	No change	Increases or no change	No data	Increases or no change
Exemestane	Decreases or no change	Decreases or no change	Decreases or no change	Decreases	No data	No change	No change

Note. From "The Effects of Aromatase Inhibitors on Lipids and Thrombosis," by N.J. Bundred, 2005, *British Journal of Cancer, 93*(Suppl. 1), p. S24. Copyright 2005 by MacMillan Publishers Ltd. Adapted with permission.

for postmenopausal women (Kendall, Dowsett, Folkerd, & Smith, 2006).

Arthralgia and Myalgia

AI-induced estrogen deprivation also may be responsible for the increased incidence of arthralgia and myalgia reported in patients receiving AIs (Coombes et al., 2004; Whelan et al., 2005; Winters, Habin, & Gallagher, 2007). Although the effects have not been regarded as significant toxicities, anecdotal reports indicate that, in some patients, arthralgia can be a debilitating and treatment-limiting side effect (Donnellan, Douglas, Cameron, & Leonard, 2001). However, a study by Crew et al. (2007) found that of 94 patients receiving AI therapy, 47% reported having AI-related joint pain: 47 (24%) had new-onset joint pain, and 47 (24%) had worsening of prior joint pain after starting adjuvant AI therapy.

In a study of 12 patients with breast cancer who reported severe musculoskeletal pain while receiving an AI, symptoms were found to be associated with enhancement and thickening of the tendon sheath and symptoms were not relieved with administration of nonsteroidal anti-inflammatory drugs (NSAIDs) (Morales et al., 2006). Because the exact mechanism of AI-related arthralgia remains unclear, little literature supports the treatment of such side effects. In Crew et al.'s (2007) study, women reported using NSAIDs, acetaminophen, opiates, and oral supplements such as glucosamine, chondroitin, and omega fish oils. Among the patients who used oral medications to relieve their AI-related arthralgia, 78% reported moderate to complete relief of their joint symptoms. In addition, 49 women (46%) used nonpharmacologic interventions, mainly exercise, to relieve their joint symptoms. Further research is needed to evaluate the pathophysiology of the effects and to determine appropriate strategies for prevention and treatment.

Quality of Life

Early detection and improved treatment protocols have extended the life expectancy for many patients with breast cancer, making long-term QOL an important issue when healthcare professionals are counseling and treating patients.

QOL outcomes were evaluated in subprotocols of the ATAC and IES trials (Cella et al., 2006; Fallowfield et al., 2006). In the IES substudy, mean scores on the Functional Assessment of Cancer Therapy–Endocrine Symptoms (FACT-ES) scale increased over time in the tamoxifen and exemestane groups, indicating an overall improvement in endocrine symptoms. In addition, no significant differences were found between groups or from baseline in the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy–Breast (FACT-B) scale at 3 through 24 months (Fallowfield et al., 2006). Similar findings were seen in the ATAC substudy comparing up-front anastrozole with tamoxifen; no statistically significant between-group differences were observed in either the TOI or FACT-ES. Of note, both groups showed steady improvement in the TOI of the FACT-B over five years of follow-up (Cella et al.).

Nursing Implications and Outstanding Questions

As a result of the emerging evidence of the clinical benefits of AIs in the adjuvant endocrine setting, current clinical guidelines recommend the use of AIs in the adjuvant treatment of postmenopausal women with early-stage breast cancer (Goldhirsch et al., 2005; NCCN, 2007; Winer et al., 2005). Although the agents offer potentially significant benefits compared with tamoxifen, questions remain concerning patient selection and the optimal regimen for individual patients.

Residual ovarian function is an absolute contraindication to the administration of AIs because AI-induced suppression of peripheral estrogen synthesis can lead to increased ovarian production of estrogen and stimulation of estrogen-dependent tumor cells (Smith et al., 2006). However, assessment of anovulatory status can be complicated in patients who were pre- or perimenopausal at diagnosis and who have undergone treatment that induces a potentially reversible anovulatory state. The criteria for being "postmenopausal" have varied across trials (Burstein et al., 2006), and no consensus exists on what constitutes menopause in such patients. As a result, care must be taken when healthcare professionals are considering a switch to AI therapy in patients who were not clearly postmenopausal at diagnosis.

Patients with ER-positive/progesterone receptor (PR)-negative or node-negative tumors may derive less clinical benefit from AI therapy than patients with hormone-responsive, node-positive disease. For example, in the MA.17 trial, patients with

ER-positive/PR-positive tumors showed a significant increase in disease-free survival with letrozole, whereas those with ER-positive/PR-negative tumors did not (Goss, Ingle, Palmer, Shepherd, & Tu, 2005). New technologies, such as gene expression profiling, eventually may aid in the selection of patients who are most likely to benefit from the agents (Jansen et al., 2005).

AIs are known to increase the rate of bone loss with a concomitant increase in fracture risk, which must be taken into account when healthcare professionals are counseling patients about the risks and benefits of AIs. Many women with breast cancer will be long-term survivors and must be educated to take adequate calcium and vitamin D, abstain from smoking, and participate in weight-bearing exercise. As mentioned earlier, routine screening using BMD tests is vital to early detection.

Despite a generally acceptable toxicity profile, AIs are associated with sexual effects related to estrogen depletion that have the potential to significantly disrupt patients' lives. To enhance long-term compliance, healthcare professionals should educate patients about the effects and provide them with strategies for dealing with symptoms such as vaginal dryness and diminished libido. In addition, all patients, particularly those with known cardiovascular risk factors, must be screened carefully before initiation of AI therapy and during treatment to monitor for changes in lipid levels. At-risk patients should be counseled regarding dietary and lifestyle changes to maintain healthy lipid levels.

Finally, the financial costs associated with AI treatment should be considered. AI therapy is much more expensive than tamoxifen therapy, and the costs are substantially higher when a patient receives five years of tamoxifen followed by an AI, compared with tamoxifen alone (Lonning, 2006; Viale, 2005). A cost/utility comparison by Lonning (2006) found that tamoxifen treatment for two to three years followed by an AI for two to three years (five years of total therapy) provided the lowest cost- and quality-adjusted life years estimates. Considering the costs and benefits of the various hormonal adjuvant therapies, choosing a treatment protocol that is clinically and economically appropriate for an individual patient is an ongoing challenge for patients and all members of the oncology treatment team.

Conclusions

Third-generation AIs have the potential to significantly improve clinical outcomes in postmenopausal women with early-stage breast cancer, although the optimal treatment regimen for individual patients has yet to be determined. Switching to an AI is an effective option for postmenopausal women who have received two or three years of adjuvant tamoxifen treatment, but it presents challenges with regard to patient selection, cost, and management of treatment-related side effects such as bone loss and arthralgias. The fracture risk associated with long-term therapy and concerns regarding lipid metabolism also are limitations to AI use. Gene expression profiling may be a useful tool in the future for the selection of patients who are most likely to benefit from AI treatment.

Oncology nurses will continue to play a vital role in identifying patients suitable for AI therapy following tamoxifen, educating patients about the treatment, and preventing and managing treatment-related side effects. To date, much of the management of AI-related side effects has focused on symptom relief. However, recommendations on the management and treatment of bone loss related to AIs are beginning to emerge. In addition, nurses have opportunities to educate patients about preventive measures to reduce the impact and severity of arthralgia and bone loss. Continuous monitoring for side effects associated with AI therapy, particularly bone loss, arthralgia, and myalgia, and increased serum lipid levels can provide valuable information when healthcare professionals are deciding whether to maintain AI therapy or resume tamoxifen. Oncology nurses are well positioned to generate further much-needed nursing research on the acute and long-term side effects of AI therapy. Practicing evidence-based nursing enables oncology nurses to provide the highest quality of care in addressing the needs of patients and their families.

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