Aromatase Inhibitor Agents in Breast Cancer: Evolving Practices in Hormonal Therapy Treatment

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Purpose/Objectives: To review the role of aromatase inhibitor agents with regard to current treatment strategies with hormonal therapy for women with breast cancer.

Data Sources: Published articles and books.

Data Synthesis: Hormonal therapy is an essential component of the treatment of most women with breast cancer. Aromatase inhibitor agents are becoming an integral part of treatment for women with metastatic breast cancer and recently have become much more prominent in the treatment of women with early-stage breast cancer. The exact role of these agents in adjuvant therapy of breast cancer, either sequentially with the "gold standard" tamoxifen or for the duration of therapy, has yet to be determined.

Conclusions: Recent studies with aromatase inhibitor agents are intriguing and suggest an improved side-effect profile and efficacy. The approval of these agents for the adjuvant treatment of breast cancer has led to a significant change in practice.

Implications for Nursing: Breast cancer is an extremely common cancer in women, and oncology nurses take care of large numbers of patients with this disease. Oncology nurses need the most recent information so they can discuss aromatase inhibitor agents and therapy with their patients.

Key Points . . .

- ➤ Breast cancer is a very common cancer in women, and hormonal therapy is an essential part of treatment for many patients.
- ➤ Aromatase inhibitor agents are showing prominence in the treatment of women with breast cancer in the metastatic and adjuvant settings.
- ➤ Recent clinical trial results are intriguing and suggest that aromatase inhibitor agents may be useful in sequential settings with tamoxifen in the adjuvant setting, possibly helping patients who develop tamoxifen resistance.
- ➤ Therapy with aromatase inhibitor agents is expensive; further studies need to be performed to determine the exact role of aromatase inhibitor agents in early-stage breast cancer.

Goal for CE Enrollees:

To enhance nurses' knowledge about the role of aromatase inhibitors in hormonal treatment for women with breast cancer.

Objectives for CE Enrollees:

1. Discuss the history of hormonal therapy in the treatment of breast cancer.
2. Outline the current evidence related to the use of aromatase inhibitors in the treatment of breast cancer.
3. Describe the nursing role in caring for patients undergoing hormonal therapy for breast cancer.

Breast cancer will affect approximately 211,240 women in 2005 (American Cancer Society, 2005). This makes the disease the most common cancer in women, and it is the second leading cause of cancer mortality in the United States (Banerjee, George, Song, Roy, & Hryniuk, 2004). This cancer may be treated with surgery, radiation therapy, chemotherapy, or hormonal therapy. Hormone receptor status is an important prognostic factor in women with breast cancer because it helps to determine whether hormone therapy will be useful. Approximately 50% of women with breast cancer have estrogen receptor-positive (ER-positive) tumors at diagnosis (Major, 2003). The implementation of hormonal therapy in these patients traditionally has been based on the identification of hormone receptor status and subsequent administration of tamoxifen therapy; however, U.S. Food and Drug Administration (FDA) approval (FDA, 2004) of the agent letrozole (Femara®, Novartis Pharmaceuticals, East Hanover, NJ) following tamoxifen therapy as an adjuvant treatment has provided an exciting change in practice for patients with hormone-responsive breast cancer. Several trials now have looked at other agents to block estrogen and tumor growth. Hormonal therapy now includes tamoxifen as the "gold standard" as well as the aromatase inhibitor agents, inactivators, and pure antiestrogens.

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How best to give these agents, particularly in the adjuvant setting, remains an unanswered question at this time; however, this class of agents clearly has an important role in early-stage hormone receptor-positive breast cancer.

History of Hormonal Therapy in Breast Cancer

The nature of breast cancer includes estrogen; it is involved in the normal biology of the breast (Mouridsen, Rose, Brodie, & Smith, 2003). Because the presence of estrogen stimulates tumor growth, blocking its effects is desirable. The first manipulation of hormones in the treatment of women with breast cancer occurred in the early 1900s. Beatson attempted to treat advanced breast cancer in women by oophorectomy and achieved a 37% response rate in 46 postmenopausal women (Clemons & Goss, 2001). Once specific hormone receptors were identified in the 1960s, the search began for medications that could be taken to block or inhibit estrogen, thus avoiding surgery (Ingle, 2003). Tamoxifen use originally began in the 1970s for the induction of ovulation; subsequently, the drug was found to block the growth of ER-positive cancer cells. Tamoxifen actually is not a true estrogen antagonist but rather a selective estrogen receptor modulator (SERM) (Hayes, 2004; Mouridsen et al., 2003).

Tamoxifen first was approved as a treatment for advanced breast cancer in postmenopausal women in 1977, and its use was expanded to adjuvant therapy with chemotherapy in postmenopausal, node-positive women in 1985 (Grana, 2003). It now has a role in adjuvant therapy alone in postmenopausal, node-positive women; premenopausal women with ER-positive disease; adjuvant therapy in node-negative, ER-positive, pre- and postmenopausal women; and male breast cancer (Grana; Palmieri & Perez, 2003). For patients with early, hormone receptor-positive breast cancer, the current recommendation has been to use adjuvant chemotherapy with or without an antiestrogen agent for five years following primary surgery. This is often the course for women with unknown receptor status as well. Continuing treatment with tamoxifen therapy longer than five years has not improved recurrence-free or overall survival; researchers do not know whether doing so may be disadvantageous as well (Burstein, 2003; Fisher, Dignam, Bryant, & Wolmark, 2001).

The effectiveness of tamoxifen in the treatment of women with breast cancer has been determined with multiple trials; if given adjuvantly for five years after primary therapy, the incidence of contralateral breast cancer is reduced by 47% (Hortobagyi, 1998). Tamoxifen also has been shown to be instrumental in reducing the risk of breast cancer in women at high risk for the disease (Serrano, Perego, Costa, & Decensi, 2004). However, other agents have been identified as having a role in the hormonal therapy treatment of patients with breast cancer; side-effect profiles in these agents differ as well. Because some women become resistant to the effectiveness of tamoxifen, healthcare providers have been interested in additional therapies to block or inhibit estrogen.

Hormonal Therapy Options in the Treatment of Patients With Early-Stage Breast Cancer

Endocrine treatment is an essential part of treating patients with breast cancer, whether surgically by oophorectomy or medically by blocking estrogen with medications. Although tamoxifen was the mainstay of treatment for patients with breast cancer after primary therapy with surgery and chemotherapy or radiation therapy, identification of the enzyme aromatase has changed the way hormonal therapy is administered to these patients. Aromatase is present in high levels in the placenta and granulose cells of ovarian follicles; it exists in lower levels in nonglandular tissues, including subcutaneous fat, muscle, liver, brain, normal breast, and breast cancer tissue (Smith & Dowsett, 2003). Aromatase is essential in the conversion of androgen to estrogen in postmenopausal women, and aromatase inhibitors prevent the conversion by inhibiting the enzyme needed to perform the function (Versea & Rosenzweig, 2003). Aromatase inhibitors may be given after breast cancer recurs following tamoxifen therapy, and researchers are studying whether these agents should compete with or replace tamoxifen as first-line therapy for postmenopausal women with ER-positive breast cancer. Current research results have led to the recent approval of letrozole for treatment of patients in the extended adjuvant setting after tamoxifen therapy, and the American Society of Clinical Oncology (ASCO) technology update of 2004 has established a role for aromatase inhibitor therapy in the adjuvant setting (Winer et al., 2004)

The FDA approval of letrozole in the adjuvant setting and corresponding interest presently in the prolongation or alteration in sequencing of hormonal therapy for patients with early-stage breast cancer without documented recurrence after tamoxifen therapy are based on two recent trials, MA-17 and Intergroup Exemestane Study (Coombes et al., 2004; Goss et al., 2003). Neoadjuvant administration of the inhibitors is being studied as well (Lake & Hudis, 2002). The nonsteroidal aromatase inhibitors are anastrozole (Arimidex®, AstraZeneca Pharmaceuticals, LP, Wilmington, DE) and letrozole. Additionally, SERMs such as tamoxifen, toremifene, and raloxifene have had a role in the inhibition of estrogen by binding competitively to the receptor. The steroidal antiestrogens also play a role in reducing estrogen (Goss & Strasser, 2001) and include exemestane (Aromasin®, Pfizer Oncology, New York, NY). Fulvestrant (Faslodex®, AstraZeneca Pharmaceuticals, LP) is the first drug of the pure estrogen antagonist class to be approved in metastatic breast cancer (Lynn, 2002; Versea & Rosenzweig, 2003).

These agents are appropriate only for postmenopausal women; if used in premenopausal women, the agents may increase gonadotropins and estradiol levels because of the reduced feedback of estrogen to the hypothalamus and pituitary, thus benefiting tumor growth (Smith & Dowsett, 2003). If used in premenopausal women, ovarian function first must be suppressed completely by using a luteinizing hormone-releasing hormone agonist agent (Versea & Rosenzweig, 2003).

Several large, multicenter, randomized trials are looking at the role of aromatase inhibitor agents compared to tamoxifen in postmenopausal women (see Table 1). ASCO updated its technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer in November 2004. The technology assessment looked at data from multiple large, randomized trials and concluded that although the optimal timing and duration of aromatase inhibitor therapy could not be established, the treatment options for postmenopausal women should include five years of aromatase inhibitor treatment or sequential therapy with tamoxifen (for two to three years or five years in total)

Table 1. Selected Studies With Aromatase Inhibitors Versus Tamoxifen in Breast Cancer

Study	Design	End Points	Results	Adverse Events	Reference
Tamoxifen versus anastrozole in postmenopausal women with advanced breast cancer (ABC)	668 postmenopausal women randomized to 1 mg anastrozole or tamoxifen 20 mg daily (estrogen receptor positive [ER+] or unknown)	Time to progression (TTP), objective response (OR), and tolerability	Median TTP (anastrozole versus tamoxifen, 8.2 versus 8.3 months), OR (32.9% anastrozole versus 32.6% in CR or PR), and clinical benefit for anastrozole (56.2% versus 55.5% tamoxifen) were similar.	Incidence of thromboembolic events (4.8% and 7.3%) and vaginal bleeding (1.2% and 2.4%) were reported in fewer patients taking anastrozole than tamoxifen, respectively.	Bonneterre et al., 2000
Tamoxifen versus anastrozole in postmenopausal women with ABC	353 postmenopausal women randomized to anastrozole 1 mg or tamoxifen 20 mg daily (ER+ or status unknown)	OR, complete response (CR), or partial response (PR), TTP, and tolerability	Anastrozole was equivalent to tamoxifen in OR with clinical benefit in 59% of patients on anastrozole and 46% on tamoxifen; anastrozole was significantly better than tamoxifen in TTP (11.1 versus 5.6 months).	Thromboembolic events and vaginal bleeding were reported in fewer patients in the anastrozole group.	Nabholtz et al., 2000
Tamoxifen for three years followed by either further tamoxifen or aminoglutethimide in postmenopausal women	380 ER+ postmenopausal women randomized to three years of tamoxifen 20 mg followed by additional two years of tamoxifen or aminoglutethimide 250 mg	Event-free survival (EFS) treatment failures at distant sites, disease-free survival (DFS), breast cancer-specific survival	Patients switched from tamoxifen to aminoglutethimide showed comparable EFS but longer overall survival in the aminoglutethimide group (p = 0.005).	Treatment-related side effects were more common in theaminoglutethimide group; however, more serious adverse events occurred in the tamoxifen group.	Boccardo et al., 2001
Tamoxifen versus letrozole in postmenopausal women with ABC	907 postmenopausal women randomized to letrozole 2.5 mg or tamoxifen 20 mg daily (ER+ or receptor unknown)	Primary was TTP; secondary was overall OR rate, rate and duration of clinical benefit, time to treatment failure, and tolerability	Letrozole was superior to tamoxifen in TTP (41 versus 26 weeks), time to treatment failure (40 versus 25 weeks), OR rate (30% versus 20%), and clinical benefit (49% versus 38%)	The number of adverse events for both groups was similar; safety and tolerability also were similar.	Mouridsen et al., 2001
Tamoxifen versus tamoxifen combined with anastrozole versus anastrozole alone	9,366 (84% hormone receptor positive) postmenopausal women randomized to anastrozole 1 mg, tamoxifen 20 mg, or combination of both	DFS, TTP, and incidence of contralateral breast cancer, tolerability at 47 months follow-up period	DFS at four years was more favorable for anastrozole (86.9%) than tamoxifen (84.%); TTP was significantly better for anastrozole than tamoxifen (p = 0.015); reduction in contralateral breast cancer occurred more with anastrozole than tamoxifen (0.5% versus 1.1%); additional benefit was seen throughout the hormone receptor-positive groups.	Endometrial cancer, vaginal bleeding, and cerebrovascular or venous thromboembolic events were less frequent in the anastrozole group, but musculoskeletal disorders and fractures were less frequent in the tamoxifen group.	Baum et al., 2003
Tamoxifen alone versus tamoxifen followed by letrozole therapy in postmenopausal women with early-stage breast cancer	5,187 postmenopausal women (ER+ or receptor unknown) randomized to letrozole 2.5 mg or placebo orally daily for five years after five years of adjuvant tamoxifen therapy	Primary end point was DFS or development of new primary cancer in the contralateral breast. Secondary end point was overall survival quality of life and long-term safety.	Median follow-up was 2.4 years (study terminated early because of interim results). At interim analysis, 207 local or metastatic recurrences of breast cancer or new primary cancers in contralateral breast existed (75 letrozole versus 132 placebo), and DFS of 93% letrozole versus 87% placebo group ($p \leq 0.001$). Overall survival was 42 deaths with placebo versus 31 with letrozole (p = 0.25).	The letrozole group had more low-grade hot flashes, arthritis, arthralgias, and myalgia, but vaginal bleeding was less common. 5.8% of the women in the letrozole group had osteoporosis versus 4.5% in the placebo group; rates of fractures were similar.	Goss et al., 2003
Tamoxifen for two or three years followed by exemestane therapy versus tamoxifen alone in postmenopausal women	4,742 postmenopausal women (ER+ or receptor unknown) randomized to switch to exemestane 25 mg after two or three years of tamoxifen 20 mg versus tamoxifen 20 mg alone for five years total treatment	Primary end point was DFS; secondary was overall survival, incidence of contralateral breast cancer, and long-term tolerability.	After a median follow-up of 30.6 months, 449 first events (recurrence, contralateral breast cancer, death) were reported (183 in exemestane group versus 266 in the tamoxifen group, $p < 0.001$). Overall survival was not significantly different. Contralateral breast cancer occurred in 20 patients in the tamoxifen group versus 9 in the exemestane group (p = 0.04).	Exemestane had higher incidence of arthralgia and diarrhea than tamoxifen, but gynecologic symptoms, vaginal bleeding, and muscle cramps were more common with tamoxifen. Fractures were reported more frequently for the exemestane group (not statistically significant) (72 versus 53 patients). More thromboembolic events occurred in the tamoxifen group than the exemestane group (55 patients versus 30 patients).	Coombes et al., 2004

followed by aromatase inhibitor therapy (Winer et al., 2004). This represents a significant change in practice. The data that led to the changes included several key trials reported in 2003 and 2004 that will be reviewed in this article.

The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial also reported that anastrozole, an aromatase inhibitor, was slightly better than tamoxifen for women in reducing their risk of breast cancer recurrence (Buzdar, 2003a, 2004a; Wilkinson, 2004). Additionally, for women who have a risk factor such as history of thromboembolism, initial therapy choices should include aromatase inhibitor agents to reduce the risk of blood clots associated with tamoxifen therapy (Buzdar, 2003b).

Treatment of ER-positive and progesterone receptor-positive (PR-positive) breast cancer includes tamoxifen and anastrozole for adjuvant treatment of postmenopausal women with early-stage breast cancer (Wilkinson, 2004). In the metastatic setting, postmenopausal patients may be treated during the first and second line with anastrozole and letrozole, and fulvestrant is approved as second-line therapy for metastatic breast cancer (Buzdar, 2003b, 2004b). Exemestane is approved for second-line use in the metastatic setting. However, the role of aromatase inhibitor agents following tamoxifen therapy in postmenopausal women with early-stage breast cancer without recurrent disease was less defined until recent trial results prompted the ASCO technology update and subsequent approval of letrozole as post-tamoxifen therapy as an adjuvant therapy (Winer et al., 2004).

Current Trial Results With Aromatase Inhibitor Agents Following Tamoxifen Therapy in Early-Stage Breast Cancer

Two articles were released in 2003 that looked at the role of aromatase inhibitor agents after tamoxifen therapy in women with ER-positive breast cancer. The approval of letrozole following tamoxifen therapy in the adjuvant setting was based, in part, on this research. These reports also have generated controversy in hormonal treatment and management of this patient population.

Goss et al. (2003) reported a randomized trial of 5,187 postmenopausal women with early-stage breast cancer. These women had received five years of tamoxifen therapy (i.e., standard therapy) and were enrolled in a double-blind, placebo-controlled trial to test the effectiveness of an additional five years of letrozole therapy after completion of five years of tamoxifen therapy. The primary end point of the trial was disease-free survival. The median follow-up time was 2.4 years, and, at an interim analysis, 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast had occurred. Seventy-five of these occurred in the patients receiving letrozole versus 132 in the placebo group ($p \geq 0.001$), and the estimated four-year disease-free survival rates were 93% versus 87%. Overall survival was not statistically significant ($p = 0.25$), with 42 of the women in the placebo group dying versus 31 in the letrozole group. As expected, side effects (myalgias, hot flashes) and cases of osteoporosis occurred in the letrozole group; however, vaginal bleeding occurred less frequently. The rates of fracture were similar between the two groups (Goss et al.).

Because of the interim analysis, the data and safety monitoring committee recommended that the trial be terminated and the participants informed of the results. All women who had been placed in the placebo group were given the option to cross over to the letrozole group. Subsequently, the data gleaned from the study are not as significant as they could have been had the study continued to its original five-year mark (Bryant & Wolmark, 2003). The original intent of the study was not met because the women did not receive five years of letrozole therapy following tamoxifen. All ongoing follow-up of the study will be somewhat compromised because the women were allowed to cross over to letrozole therapy (Bryant & Wolmark). Because of this, a recommendation to follow five years of tamoxifen with five years of letrozole cannot be made and the FDA indication does not recommend five years of therapy; instead, individual healthcare providers should make the decision for treatment length.

In clinical practice, providers have looked favorably at the data and decided on extension of hormone blockade with letrozole therapy before the FDA approval; the subsequent approval and changes recommended by ASCO now have validated this practice. Additionally, because of the attention generated in the lay literature and media, many patients with breast cancer may be influenced to seek counsel with their healthcare providers about therapy options. Because breast cancer is common in women, this decision could affect large numbers of patients.

Coombes et al. (2004) reported on a randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. The double-blind trial studied 4,742 patients: 2,362 were randomly switched to exemestane after two or three years of tamoxifen, and 2,380 continued to receive tamoxifen for the entire trial. The primary endpoint was disease-free survival, and, after a median follow-up of 30.6 months, 449 events of local or metastatic recurrence, contralateral breast cancer, or death occurred in the two groups. The exemestane group had 183 events versus 266 events in the tamoxifen group ($p \leq 0.001$). Although overall survival was not statistically different in the two groups studied, the conclusion was that exemestane therapy did significantly improve disease-free survival compared to the tamoxifen treatment group. The data and safety committee recommended the early release of results based on the planned interim analysis (Coombes et al.). Researchers hoped that the trial would be able to meet its long-term assessment of survival benefits. The challenges of this particular study included the fact that the tamoxifen groups did not receive the standard five years of therapy and the optimal time or pattern of treatment with these agents is not fully established. For this reason, the 2004 update of ASCO's technology assessment recommended two to three years of tamoxifen therapy followed by aromatase inhibitor therapy equaling a total treatment time of five years of therapy (Winer et al., 2004). However, several small studies reported by Italian researchers have used aminoglutethimide and anastrozole after tamoxifen therapy, with patients having similar results.

The first of these small Italian studies looked at 380 postmenopausal patients with breast cancer receiving tamoxifen treatment for three years who were randomized to either continue tamoxifen for two additional years or switch to low-dose aminoglutethimide for two years (Boccardo et al., 2001). Aminoglutethimide was chosen as the aromatase inhibitor drug in this trial because it was available to the study group

and had been tested in the adjuvant setting and found safe for patients with breast cancer, having been used as a therapeutic option for patients with metastatic disease not responding to tamoxifen (Boccardo et al., 2001). No differences in disease-free survival were noted, but a trend in the aminoglutethimide group in overall survival ($p = 0.005$) and breast cancer-specific survival ($p = 0.06$) was noted. The researchers recommended that larger studies were needed; however, the results were intriguing and revealed that sequencing tamoxifen with an aromatase inhibitor agent could become a preferred alternative to tamoxifen alone in early-stage breast cancer (Boccardo et al., 2001).

Another Italian study looked at 426 ER-positive patients who were on tamoxifen for two or more years and then randomly assigned to tamoxifen alone until five years elapsed or switched to anastrozole until completion of five years of therapy. This group also showed that switching to aromatase inhibitor therapy, specifically anastrozole in this trial, was favorable for women with breast cancer and appeared to decrease their risk of relapse and death (Boccardo et al., 2003). Reasons for the positive results may be related to breast cancer possibly becoming resistant to tamoxifen prior to the total of five years of therapy; thus, switching to another therapy becomes beneficial for some patients.

The results of these studies have challenged clinicians regarding appropriate hormonal therapy treatment, including whether five years of tamoxifen should be the standard followed by additional therapy or whether the pattern should be changed altogether. Although the exact pattern and duration of hormonal therapy use with aromatase inhibitors and tamoxifen cannot be stated, the evidence was compelling enough to induce the changes recommended by the ASCO 2004 technology assessment group and for the October 2004 FDA approval (FDA, 2004) of letrozole following five years of tamoxifen therapy. Letrozole currently is approved after tamoxifen therapy in the adjuvant setting in breast cancer, as well as anastrozole, as initial aromatase inhibitor therapy in some patients. Because the trials were reported at the median follow-up of 30 months, allowing for an appropriate risk-benefit analysis is inadequate and researchers have difficulty making standardized treatment decisions for all patients (Piccart-Gebhart, 2004).

The ATAC trial also revealed its first results prior to the participants completing their originally assigned therapy. The ATAC trial first published early results in 2001, showing anastrozole to be an effective hormonal therapy option for postmenopausal patients who had been diagnosed with ER-positive early breast cancer (Baum et al., 2002). This large study of 9,366 patients randomly assigned 3,125 women to anastrozole, 3,116 to tamoxifen, and 3,125 to the combination group. The bulk of the women (84%) had tumors that were ER or PR positive. Median follow-up was 33.3 months, and disease-free survival at three years for the anastrozole group was 89% versus 87% for tamoxifen; the combination group showed a result similar to the tamoxifen-alone group. Furthermore, the improvement in the anastrozole group for disease-free survival was seen primarily in patients with ER- or PR-positive tumors. Patients also reported tolerating the anastrozole therapy better than tamoxifen (Baum et al., 2002).

In December 2002, the ATAC update (Winer et al., 2002) confirmed what the earlier reported data had shown. The anastrozole group continued to show a disease-free survival advantage (94% versus 92%) over the tamoxifen group and that the use of anastrozole alone versus a tamoxifen and anastrozole combination was more advantageous. At 47 months, the results continued to show anastrozole to be more effective and better tolerated than tamoxifen (Buzdar, 2004a). However, because the data are not yet complete and long-term survival data have not yet been established, replacement of tamoxifen therapy with alternatives cannot be recommended for all patients. National Comprehensive Cancer Network (2005) guidelines have endorsed the use of letrozole and anastrozole in specific situations. ASCO produced a working group update in 2003 that noted that the updated results from the ATAC trial continued to show statistically significant improvement in disease-free survival for anastrozole versus tamoxifen; however, the consensus reported that the original recommendations should continue to be followed (Winer et al., 2003). The original status report of 2002 considered the ATAC trial and supporting data to be very favorable (Winer et al., 2002); the 2004 update now recommends adjuvant therapy for postmenopausal women with ER- or PR-positive breast cancer with an aromatase inhibitor, although optimal treatment pattern, duration, or sequence is not yet known (Winer et al., 2004). Patients should be given the opportunity to discuss the data and all treatment options with their clinicians.

Side Effects Associated With Hormonal Therapy Agents and Nursing Implications

The side effects of tamoxifen therapy are well known (see Table 2). Patients receiving tamoxifen therapy may experience significant deleterious effects, including an increased risk for endometrial cancer and thromboembolic events, hot flashes, and irregular menses (Bernstein et al., 1999; Grana, 2003). Vaginal discharge and cataracts also may occur (Chung & Carlson, 2003). The increased risk for endometrial cancer and thromboembolic events may be related to the effect of tamoxifen as an estrogen agonist on these tissues, occurring while its antiestrogen effects are noted in the breast (Mouridsen et al., 2003).

Aromatase inhibitor agents have been noted to have an improved side-effect profile compared to tamoxifen. The lack of agonist effects in the endometrium and reduced thromboembolic risk are significant (Grana, 2003). Weight gain is less of a problem than with other therapies such as megestrol acetate (Campos, 2004). However, this therapy is not without side effects and may cause osteoporosis and osteoporotic fractures, hot flashes, night sweats, nausea, myalgias, and effects on sexual function (Burstein, 2003; Campos). The ATAC trial showed that tamoxifen was superior to anastrozole for musculoskeletal disorders and fractures ($p < 0.0001$) (Buzdar, 2004a).

Oncology nurses may be exposed to many patients with breast cancer who are concerned about current trial results and further options in therapy. Developing a standardized approach, including patient education regarding trial results and end points, can assist nurses with patient choices in alteration or prolongation of therapy. The ASCO guidelines formally have endorsed aromatase inhibitor therapy in postmenopausal patients with hormone-responsive tumors, and patients should

Table 2. Selected Hormonal Therapy Agents and Nursing Implications

Agent	Approved Use	Side Effects	Nursing Implications
Tamoxifen (Nolvadex®; also available as generic) Antiestrogen Dose: 20 mg daily for five years	Adjuvant treatment of axillary node-negative or node-positive breast cancer in women or metastatic breast cancer; reduces risk of invasive breast cancer following breast surgery and radiation in women with ductal carcinoma in situ; reduces incidence of breast cancer in high-risk women and advanced metastatic breast cancer in men	Nausea, diarrhea, peripheral edema, superficial phlebitis, thromboembolism, pulmonary embolism or thrombus when combined with other chemotherapy, hepatic changes, vaginal bleeding, hot flashes, menstrual irregularities, endometrial cancer, corneal changes and cataracts, and other effects, including bone or tumor pain and weight gain	Nurses should be aware of side effects of therapy and discuss potential effects with patients. Patient teaching must include importance of reporting vaginal bleeding and regular gynecologic examinations. Incidence of thromboembolism should be reviewed and reporting any unilateral edema or pain in extremities stressed. In postmenopausal patients, tamoxifen may have a protective bone effect and increase bone density.
Anastrozole (Arimidex®) Nonsteroidal aromatase inhibitor Dose: 1 mg daily	First-line treatment of postmenopausal women with advanced or locally advanced breast cancer that is receptor positive or receptor unknown; advanced breast cancer in postmenopausal women with progression of breast cancer after tamoxifen and adjuvant therapy of postmenopausal early breast cancer that is receptor positive	Nausea, joint pain, pathologic fracture, hot flashes, vaginal dryness, peripheral edema, and weight gain	Nurses should be aware of side effects of therapy and discuss potential effects with patients. Patients receiving anastrozole reportedly have a higher incidence of osteoporosis; bone density examinations with bisphosphonate therapy and/or calcium and vitamin D supplementation may be considered.
Letrozole (Femara®) Non-steroidal aromatase inhibitor Dose: 2.5 mg daily	First-line treatment of advanced or metastatic breast cancer in postmenopausal women who have hormone receptor-positive or hormone receptor-unknown disease; also approved with progression of disease following antiestrogen therapy as well as in the extended adjuvant setting after tamoxifen	Bone pain, back pain, nausea, dyspnea, arthralgias, fracture, and hot flashes	Nurses should be aware of side effects of therapy and discuss potential effects with patients. Patients receiving anastrozole reportedly have a higher incidence of osteoporosis; bone density examinations with bisphosphonate therapy and/or calcium and vitamin D supplementation may be considered.
Exemestane (Aromasin®) Steroidal aromatase inactivator Dose: 25 mg daily	Treatment of advanced breast cancer in postmenopausal women where the disease has progressed following tamoxifen therapy	Nausea, anorexia, edema, weakness, sweating, hot flashes, pathologic fractures, and pain at tumor site	Nurses should be aware of side effects of therapy and discuss potential effects with patients. Patients receiving exemestane have shown a higher incidence of osteoporosis in clinical trials; however, this is not statistically significant.
Fulvestrant (Faslodex®) Pure estrogen antagonist Dose: 250 mg every 28 days intramuscularly	Second-line hormonal treatment in postmenopausal women with metastatic breast cancer	Vaginal dryness, arthralgias, gastrointestinal disturbances, and injection-site reactions	Nurses should be aware of side effects of therapy and discuss potential effects with patients. The drug is contraindicated in patients who are receiving coumadin or have other hematologic problems that may prohibit an intramuscular injection.

Note. Based on information from Spratto & Woods, 2004; Versea & Rosenzweig, 2003; Wilkinson, 2004.

be counseled on possible treatment benefits and reasons for aromatase inhibitor therapy. Additionally, the National Comprehensive Cancer Network (2005) guidelines address aromatase inhibitor therapy in suitable patients and can be used as a resource. With appropriate discussion, patients can be helped to understand the latest research results, including problems with data obtained from current studies, to make better-informed decisions

Changing to or Adding Aromatase Inhibitor Agents: Costs and Effect

Tamoxifen, as the gold standard of treatment for adjuvant therapy of ER- or PR-positive breast cancer, is less expensive than the newer aromatase inhibitor agents. Thus, when changes in practice occur, hospital formularies and pharmacy budgets need to take into account the subsequent increase in costs when switching to aromatase inhibitor agents. Additionally, if aromatase inhibitor agents are prescribed after five years of tamoxifen therapy, then the cost of aromatase inhibitor therapy must be added to the initial standard therapy.

Tamoxifen has been available commercially since the 1970s. Tamoxifen is used to treat early- and advanced-stage breast cancer and to reduce the risk for recurrence. It is arguably the most widely prescribed treatment for breast cancer and may be the single most-prescribed drug in the world for the treatment of any type of cancer (Lieff Cabraser Heimann & Bernstein, LLP, n.d.). Several manufacturers produce generic tamoxifen; these companies report an average wholesale price (AWP) close to $113.10 dollars for a package of 60 10 mg tablets ($1.885 per 10 mg tablet or approximately $3.77 per day). Because breast cancer is one of the leading causes of death in women, and more than 1.2 million will be diagnosed with breast cancer this year worldwide, the potential numbers of prescriptions written for treatment of breast cancer are astounding. The American Cancer Society (2005) estimated that in 2005, approximately 211,240 women in the United States will be diagnosed with invasive breast cancer.

Tamoxifen is ineffective in approximately 50% of patients with ER-positive tumors, and the patients who do respond initially may subsequently develop resistance to the drug (Schiff et al., 2004). Tamoxifen resistance is becoming recognized as

a potential problem for some patients with breast cancer and can be influenced by cellular stress, growth factors, or other pathways that may signal ER and its regulators, which can mediate resistance (Piccart-Gebhart, 2004). This process can change tamoxifen's effect from an antagonist to an agonist effect (Schiff et al.). Obviously, this is not a desired effect in the treatment of patients with breast cancer. Other concerns are the side-effect profile of the drug, including its effect on endometrial tissue and the potential for increase in thromboembolic risk. Positive effects are the increase in bone mineral density for postmenopausal patients and the drug's effects on lipids (Piccart-Gebhart).

The economic impact of the aromatase inhibitor agents cannot be underemphasized (see Table 3). These are expensive agents, and treatment is lengthy. If patients with breast cancer receive five years of tamoxifen followed by an additional five years of letrozole therapy, the total cost would be significantly more than tamoxifen alone. If patients receive three years of tamoxifen and switch to two years of exemestane, the cost also would be increased.

Despite the costs of therapy with aromatase inhibitor agents, the potential benefit to patients is considerable. Potent reasons exist to explore the continuation of estrogen blockade in these patients, as well as to define the appropriate pattern of drug usage. However, these are not the only costs associated with the use of aromatase inhibitor agents. If these drugs are used in this population of patients, the side-effect profile is uniquely different than the favorable increase in bone mineral density associated with postmenopausal women on tamoxifen and switches to an increase in osteoporosis and fracture risk as seen in the ATAC trial and others. Thus, many patients on aromatase inhibitors are considered to be candidates for bisphosphonate therapy to increase bone mineral density and reduce fracture risk.

When the cost of bisphosphonate therapy is added to the total treatment costs, the increase is significant. Oral bisphosphonates are known to be difficult to take, primarily because of the gastrointestinal irritation, the adequate hydration required with the dose, and the need to stay upright for 30 minutes after the dose (Viale & Yamamoto, 2003). The AWP of alendronate (Fosamax®, Merck & Co., Inc., Whitehouse Station, NJ) is approximately $17.60 for a 70 mg dose. The drug is taken weekly to prevent osteoporosis. If oral therapy with alendronate or other oral bisphosphonates is not tolerated, an option may be to administer the bisphosphonate via IV because this form is more potent, is better tolerated, and has improved absorption. Although no FDA-approved indication exists for the use of IV agents in this setting, some clinicians may begin to use this type of therapy as an alternative to oral bisphosphonates; however, the cost of switching is significant (Maxwell & Viale, in press). Patients receiving aromatase inhibitor agents also should consider vitamin D and calcium supplementation as well as the importance of weight-bearing and resistance exercises to help strengthen bone density. Baseline dual energy x-ray absorptiometry scanning should be considered to determine bone density levels at the start of therapy (Maxwell & Viale).

Table 3. Average Wholesale Price (AWP) of Selected Aromatase Inhibitor Agents (Daily Therapy Prices)

Drug	AWP ($)
Anastrozole (Arimidex®), 1 mg	7.50
Exemestane (Aromasin®), 25 mg	8.08
Letrozole (Femara®), 2.5 mg	7.89
Fulvestrant (Faslodex®) (approved in the metastatic setting; price is for monthly injection), 250 mg	944.32

Example. Total therapy cost for postmenopausal woman recommended to take five years of tamoxifen therapy followed by five years of letrozole therapy
Tamoxifen $3.77 per day x five years = $6,880.25
Letrozole $7.89 per day x five years = $14,399.25
Consider adding alendronate $17.60 weekly x five years = $4,224.00.

Note. Actual therapy costs may differ significantly for patients because of pharmacy purchasing plans, insurance plans, or other pharmaceutical benefit plans.

Note. Based on information from Fleming, 2004.

Summary

Breast cancer continues to be a very common cancer in women, and healthcare providers can expect to continue to see large numbers of patients with breast cancer who will need treatment with hormonal therapy. Current trials have challenged the previously established clinical opinions on the very best way to treat patients with early-stage breast cancer with hormonal therapy. These research results have led to the new ASCO technology update recommendations that call for aromatase inhibitor therapy to reduce the risk of tumor recurrence in adjuvant therapy of hormone receptor-positive breast cancer in postmenopausal women. Oncology nurses will take care of patients who will have questions regarding the best therapy choices for their treatment and should be prepared to discuss the results of current trials and the pros and cons of aromatase therapy as an option for treatment. Helping patients decipher the information needed to decide on appropriate therapy choices is an important role for oncology nurses. Exploring patient medication assistance programs also can help certain patients with the associated costs of therapy with aromatase inhibitor agents.

Tamoxifen is currently the gold standard in the treatment of women with hormone-positive breast cancer, although the development of tamoxifen resistance is gaining awareness. Aromatase inhibitor therapy has been shown to be equivalent and, in some trials, superior to the gold standard treatment; clinicians need to be aware of therapy options. The 2004 ASCO technology update recommendations call for adjuvant therapy for postmenopausal women with ER- or PR-positive breast cancer to include an aromatase inhibitor (Winer et al., 2004). The exact pattern or sequence of aromatase inhibitors with tamoxifen has yet to be determined, and the role of tamoxifen is becoming less clear. Interim results from the BIG 1-98 Collaborative Group (2005) study (8,028 postmenopausal women randomized to tamoxifen for five years, letrozole for five years or two years of tamoxifen followed by three years of letrozole versus two years of letrozole, followed by three years of tamoxifen) indicated that letrozole further reduced the risk of cancer recurrence by 19% beyond the benefit of tamoxifen alone in postmenopausal women with ER-positive breast cancer. Further recommendations by ASCO will almost certainly take these new data into account when more mature data become available. The aromatase inhibitor agents are associated with osteoporosis; therefore, women receiving these

agents should be protected with bisphosphonate therapy and counseled about lifestyle modifications, including the need for weight-bearing and endurance exercises and the intake of vitamin D and calcium. The optimal treatment of early-stage breast cancer is evolving, yet significant changes are occurring in practice involving aromatase inhibitor therapy which may improve patient outcomes. Oncology nurses should understand that the ideal position for hormonal therapy agents in the treatment of breast cancer is still under study and that further research is needed.

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