Advances in Endocrine Therapy for Breast Cancer: Considering Efficacy, Safety, and Quality of Life

Kerry V. Harwood, RN, MSN

Breast cancer is the most common cancer found in women in the United States. Endocrine therapy is the standard of care for most women with hormone receptor-positive tumors in adjuvant and metastatic settings. The selective estrogen response modifier tamoxifen has been the standard treatment for postmenopausal patients for many years. Numerous new endocrine therapy agents provide women with novel treatment options, including the non-steroidal aromatase inhibitors anastrozole and letrozole, the steroidal aromatase inhibitor exemestane, and the estrogen receptor antagonist fulvestrant. Clinical trials have begun to define the role of these agents and their unique side-effect profiles. Nurses are vital in supporting patients in the decision-making process, managing side effects of treatment, and making observations to enhance understanding of the patient experience with new treatments. This article will assist nurses in educating patients about endocrine therapy options and their associated potential short- and long-term side effects, as well as treatment demands.

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incidence of endometrial cancer (Bergman et al., 2000; Bissett, Davis, & George, 1994), hot flashes, vaginal discharge, vaginal bleeding, and thromboembolic events (Meier & Jick, 1998).

Tamoxifen has been shown to reduce the occurrence of breast cancer in high-risk women (Fisher, Powles, & Pritchard, 2000), but the toxicity profile of tamoxifen has limited its use in the preventive setting (Gail, 2001). Another SERM, raloxifene, is approved for use as an osteoporosis prevention agent and currently is being evaluated as a potential breast cancer prevention agent (ClinicalTrials.gov, 2004).

Aromatase Inhibitors

The main source of estrogen in a premenopausal woman is the ovaries. When a woman experiences menopause, her ovaries cease production of estrogen, but her estrogen levels do not decline to zero. Androgens secreted at low levels by the adrenal glands circulate through a woman’s body and can be converted into estrogens through the action of the enzyme aromatase, which is present in many tissues, such as muscle, fat, and even breast tumors. Aromatase inhibitors (AIs) inhibit the synthesis of estrogens by inhibiting aromatase (see Figure 1C). The AIs are effective in postmenopausal women whose ovarian function has ceased; however, AIs are not effective in premenopausal women because they are unable to fully suppress estrogen production in the ovaries (Buzdar, Robertson, Eiermann, & Nabholz, 2002). In addition, attempts to lower estrogen synthesis cause the ovaries to compensate and increase estrogen synthesis via a feedback loop through the pituitary gland.

AIs have no intrinsic estrogen agonist effects (Buzdar et al., 2002), although exemestane may have partial androgenic effects (Clemett & Lamb, 2000). They present alternative treatment options to tamoxifen in postmenopausal women with advanced, hormone receptor-positive breast cancer (Buzdar et al., 2002) and early-stage breast cancer (Baum et al., 2002, 2003).

The first highly selective, nonsteroidal AI, anastrozole, was introduced in 1996 for the treatment of advanced breast cancer (Bonne Terre et al., 2000, 2001; Buzdar et al., 1996, 1998; Nabholz et al., 2000). This was followed by letrozole (Lamb & Adkins, 1998) and exemestane (Clemett & Lamb, 2000).

Estrogen Receptor Antagonists

The estrogen receptor antagonist fulvestrant, like tamoxifen, acts by binding to the estrogen receptor. In contrast to tamoxifen, fulvestrant appears to completely block activation of the estrogen receptor and cause rapid loss of estrogen receptor protein, as well as reduction in progesterone receptor levels (Curran & Wiseman, 2001; Howell et al., 2002) (see Figure 1D). Unlike the effect of the SERMs, the estrogen receptor is destroyed with fulvestrant rather than simply blocked, and unlike tamoxifen, fulvestrant has no known estrogenic activity. In contrast to the previously described endocrine therapies, which all are taken orally, fulvestrant is administered as a monthly intramuscular injection. Fulvestrant is indicated for second-line hormonal treatment in postmenopausal women with metastatic breast cancer.

Progestins

Progestins such as megestrol acetate and medroxyprogesterone act similarly to the hormone progesterone. Their mechanism of action in breast cancer has not been fully elucidated. These agents are administered orally on a daily basis. Until the AIs became available in the mid-1990s, the progestins were considered standard second-line therapy for advanced breast cancer in postmenopausal patients. Now, megestrol acetate generally is used as a third- or fourth-line therapy (Lundgren, 1992).
Factors Influencing Choice of Therapy

Given the widening range of treatment options, factors such as efficacy, safety, tolerability, and quality of life (QOL) should be considered when making treatment decisions. This is particularly relevant for post-menopausal patients who may have the full range of options available to them. In some situations, treatment recommendations and decisions can be based on clear direction from clinical trials. In coming years, clinical trial data may assist in choosing a sequence of agents and provide more complete information on long-term side effects. Treatment choices likely will be based on individualized risk-benefit assessments.

Efficacy

The effectiveness of a drug in controlling a disease is of primary importance when choosing appropriate therapy. Efficacy endpoints reported in clinical trials vary with the stage of disease. For early-stage breast cancer, these endpoints typically include time to recurrence, disease-free survival (DFS), and, secondarily, incidence of contralateral breast cancer; eventually, overall survival is reported. For advanced breast cancer, primary endpoints may include complete response, partial response, stable disease, and time to progression. With multiple endocrine treatment options available, an important factor is lack of cross resistance (i.e., the ability of a new hormonal agent to produce a response after the failure of other hormonal agents). This is a concern in the advanced disease setting.

Early-stage disease adjuvant therapy: The only published data that currently are available about primary adjuvant treatment of early-stage breast cancer with an AI are from a study of anastrozole (Baum et al., 2002, 2003). The Arimidex@ (AstraZeneca Pharmaceuticals LP, Wilmington, DE), Tamoxifen, Alone or in Combination (ATAC) trial is a large, randomized clinical study that recruited 9,366 patients from 381 centers in 21 countries (Baum et al., 2002). The first results, at a median follow-up of 33.3 months, showed that anastrozole significantly prolonged DFS and time to recurrence (TTR) compared with tamoxifen (Baum et al., 2002). The estimated DFS at three years was 89.4% for anastrozole and 87.4% for tamoxifen. Significantly fewer contralateral breast cancers were found as a first event in the anastrozole (14 of 3,125; 0.5%) versus the tamoxifen (33 of 3,116; 1.1%) group, corresponding to a 58% reduction in the risk of developing contralateral breast cancer for women in the anastrozole group.

An efficacy update at a median follow-up of 47 months confirmed the benefits in DFS, TTR, and the reduction in contralateral breast cancer (Baum et al., 2003). In this updated analysis, anastrozole was associated with estimated risk reductions of 14% for DFS, 17% for TTR, and 38% for contralateral breast cancer. Long-term survival data are not yet mature for analysis. However, based on DFS and recurrence data (see Figure 2), anastrozole has greater efficacy than tamoxifen in hormone-responsive patients (Baum et al., 2003).

Extended adjuvant therapy: Letrozole has been evaluated for its efficacy after primary tamoxifen adjuvant therapy. In a multicenter, randomized, placebo-controlled clinical trial, 5,187 women were recruited to compare treatment with letrozole versus placebo in patients who already received five years of tamoxifen as adjuvant therapy for early-stage breast cancer (Goss et al., 2003). After a median follow-up of 2.4 years, a significant difference was found in DFS, with 75 recurrences (local or metastatic) or new primary contralateral breast cancers in the letrozole group (n = 2,575) compared with 132 in the placebo group (n = 2,582). Because of the highly significant efficacy result versus placebo (p < 0.0001), the trial was terminated early. Therefore, data on long-term risks and benefits as well as overall survival will not result from this trial. In addition, early termination of the trial may indicate that long-term adverse events are underestimated (Bryant & Wolmark, 2003).

Switching adjuvant therapy: The BIG 97-02 switching trial assessed whether, after two to three years of tamoxifen treatment, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the five-year treatment (Coombes et al., 2004). In total, 4,742 patients who already completed two to three years of tamoxifen treatment were enrolled. Of these, 2,362 were assigned to switch to exemestane and 2,380 were assigned to continue tamoxifen. Patients on exemestane showed a significantly improved DFS compared with those on tamoxifen (DFS estimates at three years in favor of exemestane over continued tamoxifen: 91% versus 86.8%). Overall survival was not significantly different between the treatment groups, and long-term survival and tolerability data are not available from this trial.

A smaller trial with a similar design reported significant improvement in DFS for patients who switched to anastrozole after two to three years versus continuing on tamoxifen (Boccardo et al., 2003). These trials did not test primary adjuvant therapy. At the start of both trials, those patients who could enter already completed two to three years of tamoxifen treatment without breast cancer recurrence or withdrawal because of intolerance.

Advanced disease: A series of large clinical trials has established the effectiveness of newer endocrine agents in the treatment of advanced disease. The AIs, anastrozole and letrozole, are at least as effective as megestrol acetate in second-line treatment and as tamoxifen in first-line treatment of metastatic breast cancer (Bonneteerre et al., 2001; Buzdar et al., 1997, 1998, 2001; Mouridsen et al., 2003). Exemestane is also at least equivalent to megestrol acetate in second-line therapy (Kaufmann et al., 2000). Fulvestrant has been shown to be as effective as anastro-

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**Figure 2. Probability of Recurrence in the Hormone Receptor-Positive Subgroup**

Note. Based on information from Baum et al., 2003.
zole in second-line therapy for metastatic breast cancer and is approved in the United States for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer following progression on antiestrogen therapy (Buzdar, 2003; Howell et al., 2002; Osborne et al., 2002). Current recommendations on endocrine therapy in advanced breast cancer are updated regularly in the National Comprehensive Cancer Network (2004) guidelines (see Figure 3).

Please refer to the print version of this article to view this figure.
Safety and Tolerability

Nurses should understand the safety and tolerability of treatment choices (see Table 1), because of their potential impact on patients’ lives. Treatment for advanced disease, not currently curative, needs to have low toxicity to justify its palliative role. Adjuvant treatments need to be very tolerable and have low toxicity to endorse long-term use. Concerns about the potential toxicity of tamoxifen in the long-term adjuvant therapy setting, including an increased risk of endometrial cancer (Fisher, Dignam, Bryant, & Wolmark, 1996) and thromboembolic disease (Fisher et al., 1996; Jayesimí, Buzdar, Decker, & Hortobagyi, 1995), have led to multiple studies with AIs as alternatives to tamoxifen.

Side Effects During Treatment

AIs appear to have a better toxicity profile than tamoxifen (Goss & Strasser, 2001; Miller & Jackson, 2003). All of the treatment options in the ATAC trial generally were well tolerated. However, the number of treatment withdrawals was significantly lower with anastrozole compared with tamoxifen (21.9% versus 26.0%, respectively; p = 0.0002) and included significantly fewer withdrawals because of drug-related adverse events. In contrast to tamoxifen alone, anastrozole was associated with significantly less hot flashes, vaginal discharge, and vaginal bleeding. An increased number of myalgias and arthralgias was seen with anastrozole compared with tamoxifen in the ATAC trial (Baum et al., 2002, 2003) (see Figure 4), and overall fracture risk elevated mildly compared with tamoxifen. In the MA17 extended adjuvant trial, adverse events such as hot flashes, arthralgia, and myalgia were more common in the letrozole group than the placebo group (p < 0.05), whereas vaginal bleeding was more common in the placebo group (p = 0.01) (Goss et al., 2003). In the BIG 97-02 switching trial, gynecologic symptoms, such as vaginal bleeding and muscle cramps, were more common with tamoxifen than exemestane, whereas exemestane was associated with a higher incidence of arthralgia and diarrhea than tamoxifen (Coombs et al., 2004).

Side effects of fulvestrant are comparable to those of AIs in most areas. The most common adverse events with fulvestrant are gastrointestinal disturbances (Buzdar, 2003; Carlson, 2002; Curran & Wiseman, 2001). Injection site reactions are infrequent (1.1%–4.6% of monthly injections) and mild (AstraZeneca Pharmaceuticals LP, 2004; Howell et al., 2002; Osborne et al., 2002).

Long-Term Considerations

Osteoporosis: A potential benefit of tamoxifen is its estrogen agonist effect on bone, slowing the development of osteoporosis and fracture risk (American College of Obstetricians and Gynecologists, 2004; Fisher et al., 1998). However, this effect is moderate, and tamoxifen is not indicated for the prevention or treatment of osteoporosis. Both AIs and pure estrogen antagonists, such as fulvestrant, lack any estrogen agonist effect and are highly effective in reducing or blocking estrogen in all tissues. For women with the potential for long-term survival, consideration must be given to risk for osteoporosis and subsequent fracture.

An increased number of fractures was seen in patients in the anastrozole group compared with the tamoxifen group in the ATAC trial (Baum et al., 2002, 2003). The increased fracture risk with anastrozole compared with tamoxifen appeared to be stable over two years of observations (Locker & Eastell, 2003). Indirect comparisons of fracture rates in the ATAC trial with other trials or surveys show that they fall within the broad range of fracture rates observed in placebo-treated groups, suggesting that the increase in fracture risk with anastrozole is modest (Howell, 2003). All postmenopausal women, with or without breast cancer, should be evaluated for fracture risk because of low bone mineral density and the need for nutritional, lifestyle, and therapeutic interventions.

Comparative data about the relative effects of various AIs on bone are lacking. In studies of healthy volunteers, anastrozole resulted in a nonsignificant increase in bone resorption (Lai, Taxel, & Raisz, 1998), whereas letrozole resulted in a significant increase in bone resorption (Harper-Wynne et al., 2001). In the MA17 trial, a trend was identified toward an increased incidence of newly diagnosed osteoporosis in the letrozole group compared with the placebo group. Fracture rates were similar in the letrozole and placebo groups (Goss et al., 2003). Recently released data from the BIG 97-02 trial comparing exemestane versus tamoxifen following two to three years of adjuvant tamoxifen showed an increase in osteoporosis with exemestane (Coombes et al., 2004). Clearly, more data are needed on the effects of these AIs on bone. Information also is limited on the skeletal effects of fulvestrant; however, Robertson, Osborne, and Howell (2003) reported fewer joint disorders with fulvestrant compared with anastrozole when used in an advanced setting.

Cardiovascular disease: Anastrozole has been associated with significantly fewer ischemic cerebrovascular events and venous thromboembolic events, including deep vein thrombosis, than tamoxifen (Baum et al., 2003; Bonnetterre et al., 2001; Nabholz et al., 2000). Data comparing the cardiovascular effects and risk factors of the various AIs are limited, but the Framingham Study supports the finding that an elevated total cholesterol to high-density lipoprotein ratio is an important risk factor for cardiovascular disease (Kannel, 1997). Anastrozole does not markedly alter lipid profiles when used in the advanced setting (Bonnetterre et al., 2000; Dewar et al., 2001; Nabholz et al.; Wójcicki et al., 2001). In the adjuvant setting, a small trial determined that anastrozole had no effect on the levels of total cholesterol or low-density lipoprotein C but increased high-density lipoprotein C, a beneficial effect (Sawada & Sato, 2003). Small studies of other AIs have yielded conflicting results (Atalay et al., 2004; Elisaf et al., 2001; Engan, Krane, Johannessen, Lonning, & Kvinsland, 1995). Further evidence is required to assess the effects of AIs on lipid profile.

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Table 1. Side Effects Associated With Endocrine Therapies

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EVENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole</td>
<td>Hot flashes, bone pain, back pain, dyspnea, nausea, fatigue, cough, constipation</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Fatigue, nausea, hot flashes, pain, depression, dyspnea, insomnia, anxiety</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Hot flashes, nausea, headache, asthenia, back pain, bone pain, cough, dyspnea, peripheral edema</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Asthenia, nausea, bone pain, headache, back pain, injection site pain, constipation, diarrhea, cough, dyspnea</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Hot flashes, vaginal discharge and vaginal bleeding, bone pain, tumor pain</td>
</tr>
</tbody>
</table>

* All adverse events listed were reported in > 10% of women in the trials. The most common adverse events are shown in bold.

** May be mild or signal the start of side effects, including cancer of the uterus.

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Endometrial cancer: In contrast to tamoxifen, anastrozole was associated with significantly fewer cases of endometrial cancer when used in both the early and advanced breast cancer settings (Baum et al., 2003; Bonneterre et al., 2001; Duffy & Greenwood, 2003; Duffy & Jackson, 2002; Nabholtz et al., 2000). This is to be expected as AIs do not possess the partial agonist activity exerted on the estrogen receptor seen with tamoxifen. No large-study data are available for fulvestrant or other AIs regarding endometrial safety.

Quality of Life

Most definitions of QOL include disease- or treatment-related symptoms, physical and psychological health and functioning, social and role functioning, and perceptions of well-being (Soni & Cella, 2002). Managing side effects is an essential role for nursing staff and is crucial to maintaining QOL. Hormonal therapies are far less toxic than chemotherapy, where substantial short- and long-term side effects can occur (Partridge, Burstein, & Winer, 2001). Several clinical trials have included QOL measurements in the evaluation of hormonal therapies in metastatic breast cancer (Costantino, 2002). In general, AIs resulted in stable QOL in patients with stable disease and better QOL when compared with older hormonal therapies, such as megestrol acetate (Buzdar et al., 1997). QOL data on tamoxifen are limited, although the drug has not been associated with significant psychological distress when administered as a chemopreventive, adjuvant, or metastatic breast cancer therapy in clinical trials. A QOL substudy of the ATAC trial has demonstrated that adjuvant anastrozole therapy was similar to tamoxifen in its impact on patients’ QOL, although some differences were found among patient-reported side effects (Fallowfield & Cella, 2003). Therefore, the greater efficacy of anastrozole is not at the expense of safety or QOL compared with tamoxifen.

A potential negative impact on perception of well-being is the monitoring and follow-up required for vaginal bleeding, which occurs more frequently in women on tamoxifen. Although incidence of endometrial cancer is low, each woman who has vaginal bleeding and has to be tested to rule out endometrial cancer may experience anxiety, concern, and negative impact on perception of well-being.

Route of administration may impact perception of well-being, one facet of QOL. For some women, daily oral medications serve as a reminder of their illness. Treatment requiring a monthly injection, such as with fulvestrant, may, for some patients, eliminate that reminder on most days and potentially enhance perception of well-being. In addition, monthly visits allow nursing assessment of patients and ensure medication compliance.

Drug Administration and Nursing Considerations

The practical aspects of using new treatments are likely to be of particular interest to oncology nurses, especially if they confer benefits for patients and/or
simplify the administration and monitoring of anticancer treatment (see Table 2). All treatments described in this review are taken orally except fulvestrant, which is an injection that is administered once a month in an office setting. Nurses should provide education about the need for intramuscular administration in this instance (Versea & Rosenzweig, 2003). Both anastrozole and letrozole can be taken on an empty stomach, whereas exemestane should be taken after a meal. Patients must inform nurses of side effects that occur with their treatment. For example, when patients take tamoxifen, nurses must assess for risk of blood clots or pulmonary emboli. Patients also should report severe nausea, vomiting, or diarrhea and increases in bone pain to the nurse (Wilkinson, 2004). Nurses should instruct patients receiving tamoxifen to report any vaginal bleeding, pelvic pain, leg swelling, or shortness of breath.

The metabolism among AIs differs. Letrozole inhibits the cytochrome P-450 enzymes 2A6 and 2C19 (Wirz et al., 1996), whereas anastrozole has no significant drug interactions resulting from stimulation or inhibition of cytochrome P-450 enzymes (Grimm & Dyroff, 1997). These differences in interaction profiles may become clinically relevant during periods of long-term administration when patients often receive treatment for other medical conditions.

Nurses need to consider populations in which dosing of breast cancer drugs may require adjustment. For example, patients with breast cancer and severe hepatic impairment are exposed to a higher level of letrozole than patients with normal liver function because of the decreased ability to metabolize the drug (Novartis Oncology, 2002). Therefore, dosing should be reduced by 50% in these patients.

### Conclusion

Numerous endocrine breast cancer treatment options are available, particularly for postmenopausal women. Patients need information about efficacy, side effects, administration issues, and QOL as they may participate in making treatment decisions and take endocrine therapies for extended periods of time.

Although tamoxifen has been the established treatment for adjuvant therapy in postmenopausal hormone receptor-positive patients with early-stage breast cancer, anastrozole is becoming widely used, with a favorable risk-benefit profile. Anastrozole has shown improved DFS and a decreased risk of recurrence compared with tamoxifen in the adjuvant setting. The safety and tolerability profiles of tamoxifen and anastrozole are distinctly different, and these differences may be factors in selecting one or the other for specific patients. In particular, concerns about the increased incidence of endometrial cancer with prolonged tamoxifen use that does not appear to be present with anastrozole use have to be considered. For patients already taking tamoxifen, Coombes et al. (2004) showed that switching to exemestane may be effective after two to three years; however, this use has not yet been approved by the U.S. Food and Drug Administration. Likewise, a trial of letrozole following completion of five years of tamoxifen has shown an efficacy benefit compared to placebo (Goss et al., 2003). Both drugs have shown significant efficacy benefit in patients who previously were treated with tamoxifen, although the safety data on the long-term use of letrozole or exemestane are not known. Following tamoxifen failure in metastatic breast cancer, fulvestrant and AIs are effective options.

Nurses play an important role in the breast cancer team in educating patients about the use of endocrine therapies, observing patients’ experiences with treatment, and relaying these observations to clinicians, contributing to the growing understanding of endocrine therapy in the treatment of breast cancer.

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**Rapid Recap**

**Advances in Endocrine Therapy for Breast Cancer: Considering Efficacy, Safety, and Quality of Life**

- Nurses play a vital role in supporting patients in the decision-making process.
- For women with estrogen and/or progesterone receptor-positive tumors, adjuvant endocrine therapy often is recommended.
- Nurses can educate patients about their endocrine therapy options and the associated potential short- and long-term side effects.
- Anastrozole is now becoming widely used as an adjuvant therapy in postmenopausal hormone receptor-positive patients with early-stage breast cancer.
- The safety and tolerability profiles of tamoxifen and anastrozole are distinctly different.
- Fulvestrant and aromatase inhibitors are effective options in metastatic breast cancer.