Hormonal Therapy for Breast Cancer: Focus on Fulvestrant

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The understanding that estrogen has a role in the initiation and development of breast cancer is foundational to understanding breast cancer (Theriault, 2002). Understanding the role of hormones and increasing clinical sophistication with manipulation of hormonal agents against breast cancer has progressed slowly over the past 100 years (Theriault). Antiestrogen hormonal treatments have been important components of adjuvant and metastatic breast cancer treatment. Since the 1970s, tamoxifen was the mainstream of hormonal adjuvant breast cancer treatment in women with estrogen receptor-(ER-) positive breast cancer following adjuvant radiation and/or chemotherapy. Tamoxifen acts antagonistically toward estrogen by competing for binding sites. The drug originally was developed in 1969 as a possible contraceptive agent but demonstrated activity against advanced breast cancer in clinical trials (Powles, 1997). Tamoxifen’s efficacy in advanced breast cancer led to its use as adjuvant therapy (Carlson, 1997). Its efficacy is undisputed. Overall, for women with ER-positive primary breast cancer, tamoxifen allows an improved disease-free survival with a 47% reduction in the risk of recurrence and a 26% reduction in the risk of death (Early Breast Cancer Trialists’ Collaborative Group, 1998). However, tamoxifen is a selective ER modulator (SERM) and may act as an agonist in endometrial tissue and tumor cells that initially had been responsive to antiestrogen therapy (Terakawa, 2000). This may result in patients eventually becoming refractory to conventional antiestrogen therapies because of exhaustion of the ER sites or the growth of tamoxifen-stimulated ER-positive disease (England & Jordan, 1997). This exhaustion of ER sites can allow overgrowth of tissue (endometrial cancer) or lack of protective antioxidant benefit (metastatic disease or breast cancer recurrence). This agonistic activity may allow tamoxifen to serve as a growth factor, rather than an inhibitor, for breast cancer cells (Terakawa). Tamoxifen also has a side-effect profile that includes a slightly increased risk for endometrial cancer, bone pain, and hot flashes. The drug creates an increased risk of cataracts, headache, hair thinning or loss, vaginal discharge, deep vein thrombosis, and menopause-like symptoms (Carlson, 1997).

Fulvestrant, the first drug of the pure estrogen antagonists to be approved for clinical use, is a new therapeutic option for metastatic breast cancer. Fulvestrant offers a unique metastatic breast cancer treatment option because its mechanism of action is the destruction, rather than the blockade, of estrogen receptors. No known agonistic activity exists, limiting potential side effects and receptor exhaustion. The side effect profile of fulvestrant is related to its antiestrogen effect and includes gastrointestinal disturbance, urinary tract infection, and vaginitis. Suggestions for managing the side effects of fulvestrant are described, and a case study is provided as an illustrative aid in understanding the role of this new hormonal agent.

Key Words: breast neoplasms, estrogen antagonists, aromatase inhibitors

Aromatase Inhibitors

As tamoxifen became integrated into general adjuvant and metastatic treatment protocols for women with breast cancer, a concurrent increase occurred in the understanding of the role of aromatases in the production of estrogen (Theriault, 2002). In postmenopausal women, estrogen is obtained from the conversion of androgen (from the adrenal glands) to estrogen. This process requires the enzyme aromatase (Goodman, 1988).

Selective aromatase inhibitors (SAIs) block the conversion of androgen to estrogen by inhibiting the aromatase enzyme necessary for the conversion. SAI drugs can be used only in postmenopausal women. If used in premenopausal women, SAIs may cause an increase in gonadotropins and a subsequent increase in estradiol levels that may result in a breast cancer tumor flare or disease progression. To prevent this gonadotropic surge in premenopausal women, SAIs must be combined with a leutening hormone-releasing hormone agonist for chemical ovarian ablation. SAIs’ treatment role in breast cancer to date predominantly has been in metastatic breast cancer. Two studies, one in North America (Nabholtz et al., 2000) and one larger international trial (Bonnerterre et al., 2000), established the equivalence, if not superiority, of anastrozole to tamoxifen in treatment of metastatic breast cancer. Tamoxifen was the mainstay of hormonal adjuvant breast cancer treatment (Terakawa, 2000). This may result in patients eventually becoming refractory to conventional antiestrogen therapies because of exhaustion of the ER sites or the growth of tamoxifen-stimulated ER-positive disease (England & Jordan, 1997). This exhaustion of ER sites can allow overgrowth of tissue (endometrial cancer) or lack of protective antioxidant benefit (metastatic disease or breast cancer recurrence). This agonistic activity may allow tamoxifen to serve as a growth factor, rather than an inhibitor, for breast cancer cells (Terakawa). Tamoxifen also has a side-effect profile that includes a slightly increased risk for endometrial cancer, bone pain, and hot flashes. The drug creates an increased risk of cataracts, headache, hair thinning or loss, vaginal discharge, deep vein thrombosis, and menopause-like symptoms (Carlson, 1997).

Submitted October 2002. Accepted for publication December 3, 2002. This article was written as a result of the Nurse Practitioner (NP) Special Interest Group’s mentoring program in which NPs are matched with NP mentors to implement a specific project. (Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Clinical Journal of Oncology Nursing or the Oncology Nursing Society.)
metastatic breast cancer in postmenopausal women.

The role of SAI agents continues to expand. The results of the Arimidex® (AstraZeneca Pharmaceuticals, LP, Wilmington, DE), Tamoxifen, Alone or in Combination (ATAC) trial supported the U.S. Food and Drug Administration’s approval of anastrozole for adjuvant therapy in postmenopausal women. The data, with two-and-a-half year follow-up, demonstrated longer time to progression and a less severe side-effect profile than tamoxifen (ATAC Group, 2002). The official position of the American Society of Clinical Oncology (2002) is that although SAI data look promising, the long-term follow-up data is not mature enough to warrant the recommendation of anastrozole for all postmenopausal women needing adjuvant breast cancer treatment. The role of SAs in adjuvant therapy, as well as breast cancer treatment in general, continues to expand and evolve.

**Metastatic Breast Cancer and Endocrine Therapy**

Women with metastatic breast cancer have many new treatments options available to prolong life, decrease symptoms, and improve quality of life. In metastatic breast cancer treatment, endocrine therapy may produce an overall response in 20%–35% of patients. In ER-positive tumors, the response rate may reach 50% (Costa, 2001). For metastatic breast cancer treated with hormonal therapy, the mean time to response is two months, with mean response duration of one to two years. If the first hormonal treatment was effective, the second hormonal treatment will produce an objective response in 10%–20% of all patients. Some patients continue to have tumor response to three to four endocrine therapies. Although endocrine therapies clearly are effective and reasonably well tolerated in metastatic cancer, the algorithm of hormonal therapies in metastatic breast cancer is not completely defined (Hudis, 2002) (see Table 1).

**Case Study**

Ms. R is a 65-year-old woman originally diagnosed in February 1995 with T1, N1, M0, ER-positive, progesterone receptor (PR)-positive, HER2-neu–negative infiltrating ductal breast carcinoma. Treatment included a segmental mastectomy with lymph node dissection (2 of 10 nodes were positive), followed by doxorubicin and cyclophosphamide chemotherapy in standard doses plus local breast irradiation. She completed all chemotherapy and radiation treatments by September 1995. Tamoxifen 10 mg twice daily for five years was prescribed; this treatment was discontinued in September 2000. Ms. R presented in July 2001 with increasing back pain. Complete restaging with computerized tomography of the chest and abdomen, a bone scan, liver function tests, and a physical examination were completed. The bone scan was positive for increased uptake along the lateral aspects of the left second and eighth ribs, consistent with metastatic disease. No other foci of abnormal increased uptake were seen. She was placed on Arimidex 1 mg every day and monthly biphosphonate. Three months after the institution of Arimidex, a repeat bone scan revealed stable disease.

**National Comprehensive Cancer Network Guidelines**

The National Comprehensive Cancer Network guidelines state that patients with ER- and PR-positive breast cancer who have metastatic disease within one year of tamoxifen discontinuation should be prescribed “second-line” hormonal agents. If the metastatic disease occurs more than 12 months following tamoxifen discontinuation, tamoxifen can be considered as first-line hormonal therapy for metastatic breast cancer even if it has been used on an adjuvant treatment basis (Carlson et al., 2000). In this case study, the patient presented with metastatic disease within a year of tamoxifen discontinuation and then was prescribed an aromatase inhibitor as second-line therapy. The decision regarding the most optimal second-line hormonal therapy for metastatic breast cancer remains difficult. Chemotherapy would be considered in this patient with the failure of two consecutive hormonal agents or if the metastatic disease became visceral and interfered with bodily functions (Carlson et al.).

Many choices exist for second-line hormonal therapy in metastatic breast cancer. Traditionally, the choice has been the selective aromatase inhibitors. A new option for second-line hormonal therapy is fulvestrant—a selective ER downregulator (SERD).

**Fulvestrant**

SERDs are antiestrogens that bind to the ER receptor, block transcription in the cancer cell, and degrade the receptor. Unlike with SERMs and SAI, the receptor is destroyed rather than blocked. The pure antiestrogen therapies do not have the partial agonist effect on uterine tissues and tissues previously responsive to tamoxifen. The lack of partial agonistic effect prevents the increased risk of uterine cancer and may have more clinical usefulness than the traditional antiestrogen therapies (Howell, 2000). Although ERs are degraded and ultimately destroyed by SERDs, they do regenerate, necessitating the ongoing administration of the SERD.

Fulvestrant is indicated for second-line hormonal treatment in postmenopausal women with metastatic breast cancer. In postmenopausal women refractory to tamoxifen comparing only Faslodex® (fulvestrant, AstraZeneca Pharmaceuticals, LP) to Arimidex, 45% of the patients receiving Faslodex experienced clinical benefit (Cheung & Robertson, 2002). In an early, phase III, double-blind trial of fulvestrant and anastrozole in North America, patients were randomized to two arms. Patients with ER- and PR-negative and -positive disease were included. Prior treatment was not restricted. Patients on fulvestrant experienced a longer time to progression compared to anastrozole (5.4 months compared to 3.4 months). Duration of response was 19.3 months on fulvestrant and 10.5 months for patients receiving anastrozole (Carlson, 2002).

An open-label European study of fulvestrant versus anastrozole did not demonstrate that fulvestrant prolonged time to progression (5.5 months on fulvestrant and 5.1 months on anastrozole), but the researchers noted that an open-label maneuver and difference in the interval follow up (one month in the North American study and three months in the European study) may have caused the nonsignificant results (Osborne, 2000). The median duration of response for the European trial was 14.3 months for fulvestrant and 14 months for anastrozole (Osborne).

**Fulvestrant Side Effects**

Approximately 48% of all breast cancers occur in women over the age of 65, and more than 30% occur in women over the age of 70 (Balducci & Extermann, 2001). When treating older patients, healthcare providers must consider not only physiologically based chronic conditions, such as renal and cardiac function, but also economic and social issues.

With these considerations, fulvestrant may be a beneficial therapeutic option for older women. Fulvestrant’s side-effect profile was comparable in the European and North American studies. When directly compared with anastrozole, the rate of GI disturbances (51.5% fulvestrant versus 48% anastrozole) and urogenital system disturbances, including vaginitis and urinary tract infections
Table 1. Hormonal Therapy Options

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Side Effects</th>
<th>Nursing Activities and Patient-Teaching Topics</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulvestrant (Faslodex®, AstraZeneca Pharmaceuticals, LP, Wilmington, DE)</td>
<td>Hormone-refractory breast cancer in postmenopausal women</td>
<td>Vaginal dryness, urinary tract infection, arthralgia, gastrointestinal disturbances, and injection site reactions</td>
<td>Provide psychosocial support regarding disease recurrence and progression. Educate patients about the need for intramuscular route administration and side effects and their management.</td>
<td>$930 per month (5 ml) (covered by Medicare)</td>
</tr>
<tr>
<td>Anastrozole (Arimidex®, AstraZeneca Pharmaceuticals, LP)</td>
<td>First- or second-line therapy in postmenopausal women with estrogen receptor-negative (ER-) and progesterone receptor-positive or unknown receptor status</td>
<td>Asthenia, nausea, headache, hot flashes, thrombotic events, weakness, fatigue, and diarrhea</td>
<td>Assess for blood clots or pulmonary emboli. Educate patients regarding likely side effects and their management.</td>
<td>$180 per month for 1 mg tablets (coverage dependent on outpatient prescription coverage plan)</td>
</tr>
<tr>
<td>Exemestane (Aromasin®, Pharmacia Oncology, Peapack, NJ)</td>
<td>For postmenopausal women with advanced breast cancer after not responding to tamoxifen therapy</td>
<td>Fatigue, nausea, hot flashes, sweating, increased appetite, and weight gain</td>
<td>Advise patients to take the drug once a day after a meal. Educate patients regarding likely side effects and their management.</td>
<td>$180 per month (coverage dependent on outpatient prescription coverage plan)</td>
</tr>
<tr>
<td>Toremifene citrate (Fareston®, Shire US Inc., Florence, NJ)</td>
<td>Metastatic breast cancer in postmenopausal women with ER-positive or unknown receptor tumors</td>
<td>Hot flashes, sweating, nausea, vaginal discharge, thrombophlebitis, fatigue, and tumor flare</td>
<td>Assess for hypercalcemia and tumor flare. Educate patients regarding likely side effects and their management.</td>
<td>$120 per month for 60 mg tablets (coverage dependent on outpatient prescription coverage plan)</td>
</tr>
<tr>
<td>Letrozole (Femara®, Novartis Pharmaceuticals, East Hanover, NJ)</td>
<td>First-line treatment of postmenopausal women with hormone-receptor-positive or unknown disease; also indicated for disease progression following antiestrogen therapy</td>
<td>Bone and back pain, hot flashes, nausea, dyspnea, arthralgia, headache, cough, constipation, and fatigue</td>
<td>Advise patients that this drug may be taken on an empty stomach. Educate patients regarding likely side effects and their management.</td>
<td>$182 per month (coverage dependent on outpatient prescription coverage plan)</td>
</tr>
<tr>
<td>Tamoxifen (Nolvadex®, AstraZeneca Pharmaceuticals, LP)</td>
<td>Treatment of node-positive, premenopausal women and ER-positive breast cancer in women and men; also indicated for adjuvant treatment, ductal carcinoma in situ, and breast cancer prevention in high-risk women</td>
<td>Bone and tumor pain; hot flashes; loss of libido and impotence (in men); vaginal discharge; thrombotic events, including myocardial infarction and stroke; and endometrial cancer</td>
<td>Instruct patients to report vaginal bleeding, pelvic pain, leg pain or swelling, or shortness of breath. Educate patients regarding likely side effects and their management.</td>
<td>$50 per month for 10 mg tablets and $100 per month for 20 mg tablets (coverage dependent on outpatient prescription coverage plan)</td>
</tr>
</tbody>
</table>

* Treatment is dependent on age, gravida, age at the time of first live birth, age of menarche, breast biopsy history, and number of first-degree relatives with breast cancer.

Note. Based on information from ePocrates, 2001; Physician’s Desk Reference, 2002.

(6.1% fulvestrant versus 3.5% anastrozole), were higher in the fulvestrant groups (Carlson, 2002). The side effects were attributed to the total blockade of estrogen. Arthralgias were reported more often with anastrozole than fulvestrant (6.1% versus 2.8%, respectively) (Carlson, 2002) (see Table 2).

**Administration Issues**

Fulvestrant is given at a dose of 250 mg as a viscous monthly (every 28 days) injection. The drug is available in two (125 mg) 2.5 ml injections or one (250 mg) 5 ml prefilled injection. Fulvestrant should be stored in a refrigerator but can be warmed to room temperature before administration. Fulvestrant should be given as an intramuscular (IM) injection in the dorsal gluteus maximus muscle, with the Z-track injection method recommended to decrease the chance of local irritation to the subcutaneous tissue. Because fulvestrant is given in the office setting, Medicare pays for its reimbursement, which is important for women aged 65 and older who may not be able to pay for daily oral medication. Medication adherence also is promoted. For women of large stature with adequate muscle mass, one 5 ml IM injection can be given and has been found to be safe in clinical trials. The two 2.5 ml IM injections should be used for smaller women or women with less muscle mass (AstraZeneca Pharmaceuticals, LP, 2002). Injection site reactions of pain and inflammation were noted in 7% of patients given the 5 ml injection and 27% of patients given the two 2.5 ml injections (however, this group received twice as many injections) (AstraZeneca Pharmaceuticals, LP, 2002).

Anastrozole and the other selective aromatase inhibitors still are important second-line hormonal therapies in patients with metastatic breast cancer. Fulvestrant is contraindicated in patients who are on coumadin or have other hematologic problems that may prohibit an IM injection (e.g., thrombocytopenia).
Management of Fulvestrant-Related Side Effects

Nursing care to manage side effects is essential to maintain quality of life. Women may have physiologic, chemotherapy-induced, or oophorectomy-induced menopause and continue to be sexually active. The significant decrease in estrogen caused by the receptor downregulation and eventual destruction may cause vaginal dryness, hot flashes, night sweats, insomnia, fatigue, decreased cognition, dysuria, and dyspareunia (AstraZeneca Pharmaceuticals, LP, 2002).

Although often not addressed during office or clinic visits, questions regarding sexual side effects should be routinely incorporated into the assessment of women receiving hormonal therapy for breast cancer. These symptoms should be assessed and education provided regarding the management of sexual side effects of hormonal therapy.

Suggestions for relief of sexual side effects include the use of local estrogen, lubricants, and referral to a sexual therapist if necessary. Even women with ER-positive breast cancer can safely use the estradiol vaginal ring. The ring is inserted into the vagina every three months. The amount of estrogen absorbed is minimal, making the estradiol ring a safe treatment for estrogen depletion-related dysuria and vaginal dryness in women with breast cancer. Most oncologists prefer that their patients see and follow-up with their gynecologists for insertion and management of the estradiol ring. Other modalities for symptom management of vaginal dryness include over-the-counter lubricants, such as Replens® (Johnson & Johnson, San Antonio, TX) and KY Jelly® (Warner-Lambert, Morris Main, NJ), but these need to be applied daily.

Vasomotor symptom assessment should include questions about the frequency and severity of hot flashes, sleep interruption, level of associated irritability, and self-help methods used by patients. Management of night sweats and hot flashes may include exercise, folic acid, vitamin E 400–1,200 IU per day, stress-management techniques, increased fluid intake, and avoidance of caffeine, hot weather, alcohol, and spicy foods (Cormier, 2000). The use of soy supplements by women with breast cancer remains controversial.

Urogenital symptoms may occur among women receiving fulvestrant. Nurses should teach patients using principles of anticipatory guidance and instruct them about the signs and symptoms of urinary tract infection and strategies to prevent them, such as maintaining adequate fluid intake and voiding immediately after vaginal intercourse.

Fatigue, although not specific to fulvestrant therapy, is a common complaint among women with metastatic breast cancer and remains difficult to treat because of its chronicity and multifactorial etiology. If a specific, treatable fatigue etiology is not identified, some generic interventions have clinical efficacy, including exercise (Courneya & Friedenreich, 1999), energy conservation using energy diaries (Richardson, Ream, & Wilson-Barnett, 1998), and focused, enjoyable activities, such as reading, gardening, or crafts (Cimprich, 1993).

Conclusion

Fulvestrant has an emerging role in the treatment of metastatic breast cancer. Implications for the future include the evaluation of fulvestrant as adjuvant therapy in postmenopausal women who have ER-positive breast cancer in direct comparison to tamoxifen. Clinical trials evaluating the timing of this new estrogen downregulator in clinical treatment will provide vital new information. This new drug prototype may improve the quality of life of patients undergoing adjuvant and metastatic breast cancer treatment and extend survival for all women with metastatic breast cancer.

Nurses contribute to the drug evaluation process and have critical roles as clinical coordinators, educators, providers of direct patient assessment and symptom management, and experts in the detection and reporting of adverse events. Therefore, nurses play an important role in the evaluation and delivery of new pharmacologic options.

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- Selective estrogen-receptor modulators and selective aromatase inhibitors are antiestrogen medications that have been the cornerstone of hormonal treatment for adjuvant and metastatic breast cancer.
- Fulvestrant is a prototype antiestrogen drug, representing the pure antiestrogen drug classification; this class of drugs represents a new therapeutic option for women with metastatic breast cancer.
- The antiestrogen effect is achieved through the destruction, rather than the blockade, of tissue receptors.
- Fulvestrant is administered at a dose of 250 mg as a single, monthly (every 28 days), intramuscular (IM) injection. The drug also may be given as two 125 mg IM injections to women with less muscle mass.