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 the understanding of breast cancer (Theriault, 2002). Understanding of the role of hormones and increasing clinical sophistication with manipulation of hormonal agents against breast cancer has progressed slowly over the past 100 years (Terakawa, 2000). Antiestrogen hormonal treatments have been important components of adjuvant and metastatic breast cancer treatment. Since the 1970s, tamoxifen was the mainstay 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 anticancer 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).

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. SAIs 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 predominately has been in metastatic breast cancer. Two studies, one in North America (Nabholtz et al., 2000) and one larger international trial (Bonnetre et al., 2000), established the equivalence, if not superiority, of anastrozole to tamoxifen in treatment of metastatic breast cancer (Bonneterre et al., 2000). Estrogens have been demonstrated to be critical in the growth and survival of breast cancer cells; therefore, it is logical to target the aromatase enzyme necessary for the conversion of testosterone to estrogen and thereby reduce the estrogen available to breast cancer cells (Powles, 1997). In addition, aromatase expression in breast cancer cells is associated with patients having a poor prognosis (England & Jordan, 1997). This information supports the concept that the use of aromatase inhibitors in women with hormone receptor-positive breast cancer may result in a survival benefit.

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, fulvestrant, hormone therapy, metastatic cancer, tamoxifen, tamoxifen receptor, breast cancer recurrence, aromatase enzyme, aromatase inhibitors, endometrium, bone pain, estrogen production, aromatase (aromatase) inhibitors, fulvestrant, drug therapy, breast cancer.