3rd Generation Non-steroidal Aromatase Inhibitors in the Treatment of Breast Cancer

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ABSTRACT

Breast cancer strikes upwards of 250,000 and kills more than 30,000 women annually. These figures are sobering, and the issue of what treatment options are available to women with breast cancer is a global topic. Determining what treatment options are available is intimately connected to the specific type of breast cancer that has been diagnosed. Treatment for hormone receptor negative breast cancer is different from treatment options for hormone receptor positive cancer or hormone receptor unknown cancer forms.

Design of a treatment course is further impacted by the stage of breast cancer, i.e. Stage I, II, III or IV. Breast cancer in Stages I-III can be treated with a reasonable chance for cure of the disease, and includes chemotherapy, radiation, endocrine therapy with non-steroidal aromatase inhibitors. Unfortunately, Stage IV breast cancer patients are typically limited to a palliative treatment course that seeks to make a patient comfortable during the end stages of the disease.

Women diagnosed with hormone receptor positive or hormone receptor unknown breast cancer in Stages I-III have available to them the most treatment options. Because menopause effects hormone levels and concentrations, a distinction must be drawn in treating patients between pre and post-menopausal women. The population focus for this paper is post-menopausal women with hormone receptor positive or hormone receptor unknown breast cancer.

Traditionally, tamoxifen has been the gold standard for treating this patient population, however, over the past five or six years, new medications have gained FDA approval and are demonstrating significant efficacy as compared with tamoxifen. The use of these new medications, including Anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin), are quickly gaining popularity among oncologists because they are such a viable and more efficacious drug than tamoxifen.
BACKGROUND

Of all cancer forms, breast cancer is the most prevalent form of cancer among women. However, it is not the deadliest. This fact is largely attributed to early detection through mammograms and the great strides made in the research and development of breast cancer treatment drugs. A woman’s chance of developing breast cancer at some point in her lifetime increases with age; one in eight, or 12.5% of women in the United States will develop the disease. (Tierney 2002) According to the American Cancer Society in 2003, 39,800 breast cancer deaths were reported, as 267,000 new cases were diagnosed.

A woman diagnosed with hormone receptor positive tumors has more treatment options available to her pharmacologically than does a woman with a hormone receptor negative tumor. Tamoxifene has traditionally been the gold standard of adjuvant therapy for women with hormone receptor positive tumors. In 2001, the United States Food and Drug Administration (FDA) approved letrozole, an aromatase inhibitor, for use in the treatment of advanced breast cancer in postmenopausal women with hormone receptor positive or unknown breast cancer that failed anti-estrogen treatment. (Cohen 2002)

Recent research studies have shown that letrozole has achieved some success in practice. In fact, many studies, discussed below, indicate that letrozole may be better than tamoxifen. For example, in one study, letrozole “demonstrated superiority when compared to tamoxifen in a prospective randomized double-blind trial.” (Ingle 2003)

Within the past three or four years, aromatase inhibitors have increasingly established their place in the treatment of postmenopausal women with hormone receptor positive tumors, however, much research must still be undertaken in treating younger women with the drugs.

The purposes of this paper are to discuss (1) breast cancer pathophysiology and overview,
(2) pathophysiology and pharmacokinetics of non-steroidal aromatase inhibitors, (3) endocrine therapy in breast cancer, and (4) future use and research of aromatase inhibitors in breast cancer treatment.

**BREAST CANCER PATHOPHYSIOLOGY AND OVERVIEW**

Breast cancer diagnosis rates have been on the rise for more than two decades, according to Essentials of General Surgery. (Lawrence 2000) The rise is almost exclusively attributed to an increase in the rate of breast cancer screening.

The unique anatomical features of the breast and its compositional tissues directly impact the manner in which cancer spreads. The breast, which extends at its full limits from the clavicular region superiorly, to the sixth rib inferiorly, to the midsternal line medially, to the axilla laterally, is composed of four major tissues. These tissues include glandular, ductal, connective and adipose. (Lawrence 2000) The breast is made up of multiple lobes (as many as 15-20) which are implanted into fat or adipose tissue. Anatomically, the lobes, as they descend into the areola, become ducts. Coopers’ ligaments, which are composed of connective tissue, provide the suspensory attribute of the breast. (Lawrence 2000) Finally, the “tail of Spence,” which is the breast tissue that tapers into the axilla, provides the primary breast lymph node drainage site.

Physiologically, the breast is considered an apocrine gland that undergoes continuous development and change throughout a woman’s life. The continual change is associated with hormonal production, especially estrogen. The breast is constantly proliferated for milk production pre-ovulatorily. At ovulation, decreased estrogen levels cause decreases in the proliferation of the ductal system of the breast. As a female ages, and estrogen levels begin to decrease, the cyclic proliferation of the breast halts and the breast parenchyma is lost and
replaced by adipose tissue. (Lawrence 2000)

A thorough history and physical examination are important in evaluating the presence of risk factors or signs and symptoms of breast carcinoma. Major risk factors associated with breast cancer (in no particular order) are a family history of breast cancer, a personal history of breast cancer, a previous breast biopsy, fibrocystic disease accompanied by proliferative changes, increasing age, early menarche (before age 12), a long interval between menarche and first live birth, nulliparity, a history of ovarian or endometrial cancer or use of hormone replacement therapy. (Lange 2002). Any hard palpable mass, dimpling of breast skin or nipple discharge (particularly discharge with blood) can all be indications of malignancy.

Generally accepted precautionary measures that can be taken in order to prevent the onset of breast cancer include yearly screening mammograms beginning at age 40 (or at age 35 with a strong family history for breast cancer), yearly gynecological breast examination beginning at age 20 and monthly self breast examinations. These preventative measures are highly effective, according to Lawrence, “[o]ver the last 25 years, there has been a highly significant change in stage at diagnosis of breast cancer with gradually more cancer in situ and cancers confined to the breast.”

With regard to cancer types and categories, there are many: ductal carcinoma in situ; infiltrating ductal carcinoma; Paget’s disease of the nipple; lobular carcinoma; inflammatory carcinoma; as well as other less prevalent sarcomas, lymphomas and malignant phyllodes tumors. These need not exist in isolation, and in fact can be mixed. In a mixed finding, staging typically follows the least favorable type of cancer. (Lawrence 2000)

Breast cancer is diagnostically evaluated by a mammogram (there is a 5-10% false
negative rate) which show views of breasts bilaterally in the craniocaudal and media-lateral views. Based upon mammography findings, additional views may be ordered by the radiologist to further evaluate possible positive findings. These additional films include oblique, magnified or compression. Suspicious mammography views which are highly suggestive of malignancy include dominant masses, microcalcifications or spiculated legions. Additionally, the radiologist may order an ultrasound of a palpable breast mass, particularly to differentiate between solid masses and cystic masses which may be revealed by the mammogram. Because women under the age of 35 have particularly dense breast tissue, ultrasound is the most appropriate diagnostic test for any solid breast mass identified in this age group. Finally, with regard to diagnostics, abnormal mammogram or ultrasound findings warrant either a fine needle aspiration or a core biopsy to confirm the malignant diagnosis. (Lawrence 2000)

The approach for the treatment of breast cancer is multidisciplinary. Any treatment team may include radiologists, breast and plastic surgeons, medical and radiation oncologists, nurses, pathologists and mental health providers. All malignancies confirmed by a biopsy should be surgically excised. The particular procedure depends upon the mass size. For malignancies less than one (1) cm, a wide excision or lumpectomy is indicated. For malignancies greater than one (1) cm, a partial or total mastectomy is indicated. Because the axilla provides a favorable transmission route for cancer to the lymphatic system, any surgery may include an axillary dissection depending on the size of the tumor.

Breast tumors, when detected, are staged in two ways. First, it is staged clinically following the TNM system (of the International Union Against Cancer), which accounts for a variety of factors, including tumor size, clinical assessment of lymph nodes and the presence or absence of metastases. (DeCherney 2003) Second, tumors are histologically staged following
Both staging methods are important to determining treatment and prognosis for the patient. (DeCherney 2003). The table above, taken from page 1102 of Current Obstetrics and Gynecology, Ninth Edition, summarizes breast cancer carcinoma staging.

Following tumor extraction, it is sent for study by a pathologist to assign the stage and type of breast cancer. Also, the pathologist will determine the presence or absence of hormone receptors on the cytoplasm surface of the tumor cells and also tested for genetic markers BRCA1 and BRCA2. (DeCherney 2003) Each of these three primary tasks is critically important to determining the available treatment options for a woman diagnosed with breast cancer.

Treatment options available to a woman diagnosed with breast cancer are either curative or palliative. Curative forms of treatment are considered those whose primary goal is to cure the patient’s cancer, while palliative forms of treatment are considered those whose primary goal is to provide comfort and relief from pain but do not typically cure the disease. Curative treatment
options are considered during stages I-III, while palliative treatment is considered for stage IV patients and those who have previously been treated and who developed distant metastases or unresectable local recurrence. (DeCherney 2003)

Curative treatment types include chemotherapy and hormonal therapy. The National Institute of Health (NIH) recommends that chemotherapy be offered to women with localized breast cancer with a tumor greater than one (1) centimeter. regardless of nodal, menopausal, or hormone receptor status. Moreover, polychemotherapy (greater than two agents) has been found to be superior to a single chemotherapy agent for a duration of three to six months. (DeCherney 2003) With regard to hormonal therapy, according to the NIH, all women whose breast cancer tumors express hormone receptors, the patient should be treated with Tamoxifen or an aromatase inhibitor. (DeCherney 2003)

Palliative therapy types include chemotherapy, radiation, bisphosphonate therapy and hormonal therapy. Chemotherapy in stage IV patients is considered when there are brain or lung metastases if the hormonal therapy failed or the tumor was hormonal receptor negative, or several other chemotherapies have already failed. Radiation is useful for localized pain management or irradiation of the chest wall and supraclavicular nodes, among other things. Because bone is a common site for breast metastases, bisphosphonate therapy is often initiated because they have been shown to reduce bone and visceral metastases.

Finally, hormonal therapy is initiated for hormone receptor positive tumors. Advanced disease has been shown to respond to prolonged treatment with hormone therapy. Primary hormonal therapy for advanced disease is tamoxifen 10mg twice daily. New adjuvant therapy with non-steroidal aromatase inhibitors has been shown to be effective in postmenopausal women with advanced disease (DeCherney 2003).
Non-steroidal aromatase inhibitors are principally utilized to treat post-menopausal women with hormone receptor-positive, hormone receptor-unknown, locally advanced or metastatic breast cancer. Hormone receptor cancers are characterized by the presence of either estrogen, progesterone or both. (Novartis 2004) Hormone dependent breast cancers contain certain protein molecules called estrogen receptors. If estrogen is present and the receptor is activated it will cause tumor cell growth and tumor multiplication. (Novartis 2004) The mechanism of action for these drugs involves the synthesis of estrogen which is mediated by the aromatase enzyme. Non-steroidal third generation aromatase inhibitors will selectively bind to the portion of the aromatase enzyme known as the cytochrome P450 subunit. The synthesis of estrogen occurs along the pathway of adrenal hormones which include cortisol, androstenedione and aldosterone. These adrenal hormones are activated by the aromatase enzyme to convert to estrone and testosterone which then continues down the cascade to estradiol. Estradiol is subsequently converted to its end product estrogen. (Novartis 2004)

The third generation non-steroidal aromatase inhibitors are distinct from the previous first and second generation aromatase inhibitors because they selectively block the aromatase enzyme after the adrenal hormones are produced therefore only blocking the conversion of estrone and testosterone to estrogen. Early generations of these drugs blocked the cascade before the synthesis of the adrenal hormones and patients were required to take corticosteroid supplementation in order to achieve adequate levels of cortisol and aldosterone. (Novartis 2004)

A study published in the Journal of Steroid Biochemistry and Molecular Biology looked at two of the third generation non-steroidal aromatase inhibitors and their effects on plasma cortisol after stimulation with ACTH. When comparing letrozole 2.5mg to anastrozole 10mg
and cortisol levels after stimulation with ATCH, the anastrozole group showed no reduction in cortisol levels. However, in the letrozole group, 1 of 23 patients studied showed an abnormal response to the synthetic ATCH before treatment with Letrozole. After three months of treatment with letrozole, however, 5 of 22 showed an abnormally low response at 30 minutes while only 1 patient of 22 showed an abnormal response after 60 minutes. This data suggests an overall slowing in response to ATCH but an essentially normal response to ACTH. (Dowsett 2003) This study supports the belief that the third generation non-steroidal aromatase inhibitors selectively inhibit estrogen synthesis late in the pathway, therefore sparing the unwanted suppression of aldosterone and cortisol.

To completely appreciate the significance of suppressing estrogen in the role of women with hormone dependent breast cancer, one must understand the locations within the body where aromatization takes place. Androgen, a hormone found in both men and women, is produced in many peripheral body tissues, including adipose tissue, skin fibroblasts, muscle and bone. The location of androgens, as described above, are where aromatization from androgens to estrogens occurs. According to a study by Cohen in the Journal of Clinical Cancer Research, “[a]pproximately two-thirds (2/3) of human breast cancers contain measurable aromatase activity. In order to deprive these hormone dependent cancer cells of estrogen, non-steroidal aromatase inhibitors will lower estrogen levels in postmenopausal women.” (Cohen 2002)

In premenopausal women, estrogens are derived predominantly from the ovarian origin; in postmenopausal women, estrogens are primarily derived from conversion of circulating androgens to estrogens. (Cohen 2002) According to Jurgen Geislerthe’s article in the Journal of Steroid Biochemistry and Molecular Biology “[a]romatization of androgens derived from the adrenal and the ovaries is the only established production pathway for estrogens in
postmenopausal women…” Because of the location of androgens in the breast tissue, it is important for the aromatase inhibitors to target these estrogen rich tissues. Giesler emphasized this fact stating, “[t]oday, it is generally accepted that the aromatase- pathway (either in peripheral tissues or in the tumor itself) is the most important source for breast cancer tissue estrogen levels in postmenopausal women.”

Currently there are three third generation non-steroidal aromatase inhibitors on the market: Anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin). Each of these drugs is orally administered and rapidly and completely absorbed from the gastrointestinal tract. Letrozole has a half life of approximately two days and is weakly protein bound. (PDR 2004) All three drugs are excreted primarily through the kidneys, although some of the drug is found unchanged in the urine. Because of the drugs’ involvement in the cytochrome p450 pathway, there is evidence of liver metabolism as well. In Arimidex (anastrozole), for example, over 85% of the drug is secreted hepatically. (PDR 2004)

Third generation non-steroidal aromatase inhibitors are contraindicated in pregnant women due to the drugs’ blockade of estrogen. Each drug seems to have no effect on patients with renal insufficiency. In a study involving 347 patients taking letrozole 2.5 mg with varying renal function, the results did not show any effect on the plasma concentration of letrozole. (PDR 2004)

All three drugs were tested on patients with some form of hepatic insufficiency. In a trial of subjects with mild to moderate hepatic dysfunction (e.g., cirrhosis, Child-Pugh disease) each was given Femara (letrozole) 2.5 mg. Each subject experienced approximately twice the exposure of the drug as patients without liver dysfunction. Therefore, it is recommended that patients who have hepatic insufficiency be placed on a reduced dose of Femara (letrozole). (PDR
Aromasin (exemestane) and Arimidex (anastrozole) also were studied in patients with hepatic insufficiency. A study of Arimidex (anastrozole) 1mg given to patients with alcoholic cirrhosis found that the concentrations of Arimidex were the same as in an individual without liver disease. (PDR 2004) Aromasin (exemestane) 25mg was also administered to patients with hepatic insufficiency and the concentration of Aromasin increased by approximately three (3) times the dose. (PDR 2004) However, unlike Femara, it is not recommended that the dose be adjusted for patients with hepatic disease. Drug manufacturers note that the increased concentration of Aromasin only causes an increase in non-life-threatening side affects and that levels up to 800mg daily have been tolerated by women with metastatic breast cancer. (PDR 2004)

Drug interactions were studied with the three aromatase inhibitors and certain drugs know to interfere with the cytochrome P450 pathway. Warfarin was studied with Arimadex and found to not interfere with the therapeutic levels of the drug. (PDR 2004) A known and documented drug interaction was seen when all three third generation non-steroidal aromatase inhibitors were administered with tamoxifen. The prescribing information in the 2004 PDR showed a 38% reduction of Femara (letrozole) serum levels when co-administered with Tamoxifen. When dosed with Arimidex (anastrozole), tamoxifen had similar results and a documented 27% reduction in anastrozole serum levels. (PDR 2004) Due to the decreased serum levels of these drugs when dosed with tamoxifen, co-administration of these agents is not recommended.

The adverse effects of all three non-steroidal aromatase inhibitors are similar: they
include fatigue, chest pain, peripheral edema, weakness, hot flashes, hypertension, nausea, constipation, diarrhea, vomiting, influenza, urinary tract infections, anorexia, bone pain, back pain, arthralgia, headache, insomnia, breast pain, vaginal discharge, dyspnea, cough, and chest wall pain. More severe adverse reactions include deep venous thromboses (including pulmonary emboli), ischemic cerebrovascular events and cardiovascular events. (Ingle 2003) The most common side effects related to the third generation aromatase inhibitors are hot flashes, nausea, bone pain, back pain, and arthralgias. (PDR 2004) James Ingle’s study appearing in the Journal of Steroid Biochemistry and Molecular Biology concluded that, “[a]lthough nausea and hot flashes can be troublesome, thromboembolic events can be life-threatening and a lower incidence of these adverse events favors aromatase inhibitors over tamoxifen.” This position is supported by a large study of 9366 patients who were randomized to receive Arimidex (anastrozole), tamoxifen or the combination of the two. “Anastrozole was associated with a significant reduction in hot flashes (35% on anastrozole vs. 40% on tamoxifen), vaginal discharge, vaginal bleeding, ischemic cerebrovascular events, venous thromboembolic events, including deep venous thrombosis.” (Coombs, 2003) Charles Coombs continues to conclude that although the above reactions are less in the anastrozole group an increase in musculoskeletal disorders and fractures were significantly more prevalent in the anastrozole group than the tamoxifen group. (Coombs 2003)

In another study looking at letrozole (Femara) there were three treatment arms. (Cohen 2002) First arm was treated with letrozole 2.5mg, second arm was given 20mg tamoxifen and arm three was the combination of letrozole with tamoxifen. There were 344 patients in the letrozole group and 336 in the tamoxifen group. The treatment arm treated with both letrozole and tamoxifen was canceled due to the pharmacokinetics interactions between the two drugs.
Adverse events including hot flashes, nausea and chest pain were reported in 90% of patients in the letrozole arm and only 87% in the Tamoxifen arm. Bone pain was reported in the letrozole arm in 20% of patients and in 18% of those treated with Tamoxifen. The incidence of bone fractures was equal in both groups: 21 letrozole treated patients and 20 in the Tamoxifen group. The author noted that these fractures were more likely disease related than osteoporotic. Severe adverse reactions, such as peripheral thromboembolic events and cardiovascular events, occurred in less than 2% of both treatment arms. (Cohen 2002) Since there was not a placebo group it is important to point out that the some of the adverse effects could have been from the disease itself and not the medications.

Overall the studies show the third generation non-steroidal aromatase inhibitors have similar adverse reactions to Tamoxifen in all clinical trails. There does show to be some increase in bone pain and fractures in the groups treated with aromatase inhibitors and perhaps some studies should dose these patients with bone building medications like biphosphonates. The evidence does show that treatment with aromatase inhibitors has significantly fewer severe adverse effects such as thromboembolic and cardiovascular events.

**ENDOCRINE THERAPY AND ITS ROLE IN BREAST CANCER**

Following a diagnosis of breast cancer, pathologists determine whether or not a patient is a candidate for endocrine therapy. This determination is made based upon the patient’s tumor’s estrogen and progesterone status. Endocrine therapy offers the potential for substantial palliation in the majority of postmenopausal women with hormone receptor positive status. (Ingle 2004) According to the Second International Conference on Recent Advances and Future Directions in Endocrine Manipulation of Breast Cancer, “[a]ll women with breast cancer should be tested for estrogen receptor status, and adjuvant endocrine therapy should be considered for all patients
with positive results or receptor unknown status.” If a patient is determined to have estrogen receptor positive or progesterone receptor positive tumor the patient has more therapeutic options offered to her. Until recently, tamoxifen was considered the first line “gold standard” of treatment for women with hormone receptor positive tumors. Tamoxifen was approved by the FDA in 1986 for adjuvant therapy in women with hormone receptor positive tumors, and until the FDA approved letrozole (Femara) and anastrozole (Arimidex) for first line adjuvant therapy in postmenopausal women with ER or PR receptor positive tumors in 2001 and 2002, Tamoxifene was the only available agent.

The first major trial that earned letrozole (Femara) its FDA approval for first line adjuvant therapy in postmenopausal women with receptor positive cancers was a large randomized trial that was conducted in 29 different countries. The 907 patient study was conducted double-blind, double-blind and randomized between letrozole (Femara) 2.5 mg and tamoxifen 20mg. The total number randomized in the study was 907 patients. Inclusion criteria for the study were postmenopausal women with histological or cytological evidence of breast cancer presenting with locally advanced or loco-regionally recurrent disease that was not amenable to treatment by surgery or radiotherapy. Additionally, the study included subjects with metastatic breast cancer. As part of the inclusion criteria, patients could not have been treated with endocrine therapy for their advanced disease, but could have received antiestrogen therapy as long as they had a period without disease or therapy for greater than 12 months between antiestrogen treatment and enrollment in the study. Furthermore, patients had to be estrogen-receptor positive and or progesterone-receptor positive or have status of both receptors unknown to be included in the study. (Cohen 2002)

Within the two monotherapy treatment groups, 453 subjects were administered letrozole
and 454 tamoxifen. The results showed that letrozole was superior to tamoxifen in many areas. When looking at TTP (time to progression) letrozole was 9.4 months (95% CI 9.1-12.2) and Tamoxifen was 6.0 months (95% CI 5.8-8.5) p=0.0001. When looking at RR (response rate) letrozole was greater than tamoxifen, 32% vs. 21% respectively (p=0.0003, odds ratio 1.74, 95% CI 1.29-2.34) Based upon these superior results of letrozole over tamoxifen for both RR and TTP, letrozole was given fist line hormonal treatment approval by the FDA in January of 2001. (Cohen 2002)

A smaller non-blinded, randomized trial compared anastrozole 1 mg and tamoxifen 20mg. The study included 238 patients with locally advanced or metastatic breast cancer that was ER-positive or PR positive. The participants could not have a history of tamoxifen treatment. Unlike the letrozole study, there was no significant difference in RR (response rate) as between tamoxifen and anastrozole: 34% in anatrozole arm and 27% in the tamoxifen arm. However, clinical benefit (82% anastrozole arm and 55% in tamoxifen arm) was significantly higher in the non steroidal-aromatase inhibitor arm. The median time to progression of the disease was longer in the anastrozole arm 12.3 months vs. 5.3 months (p< 0.05). Another significant finding in this study was survival rate at 35 months was higher in the anastrozole arm than tamoxifen (39% versus 8%). As a result of this trial, anastrozole gained first-line indication for adjuvant therapy in postmenopausal women with hormone receptor positive breast cancer/ receptor unknown from the FDA in 2002. (Ligibel 2003)

These new third generation non-steroidal aromatase inhibitors have gained credibility among oncologists as an efficacious first line therapy for postmenopausal women with hormone receptor positive/ receptor unknown breast cancer. Until these new drugs were introduced many women only had tamoxifen as an option for hormonal therapy. The new aromatase inhibitors
showed superiority in many areas over tamoxifen and should be considered a likely option for patients with hormone receptor positive/receptor unknown tumors.

**FUTURE RESEARCH AND USE OF AROMATASE INHIBITORS**

One limitation of using the third generation non-steroidal aromatase inhibitors is the increased incidence of bone pain, osteoporosis and fractures. Future studies could address these issues by conducting a randomized trials with use of biphosphonates to decrease the incidence of osteoporosis and fractures. (Coombes 2003)

Another area of future research is a randomized trial comparing two of the third generation non-steroidal aromatase inhibitors. This would allow the effective comparison of say anastrozole and letrozole. These drugs have only been compared to Tamoxifen and never to each another. The outcomes might suggest that one drug may be efficacious in response rate but may have more side effects. This is an important area of investigation because it may help the oncologist to choose one non-steroidal aromatase inhibitor over another keeping each individual patient in mind.

A trial should be considered for premenopausal women with hormone receptor positive/receptor unknown tumors. Premenopausal women mostly process estrogen through the ovaries and not through the aromatase pathway. The previous first and second generation aromatase inhibitors showed an inability to suppress estrogen levels in premenopausal women. According to one study in the Journal of Steroid Biochemistry and Molecular Biology by M. Dowsett stated, “Low dose of a third generation inhibitor might have significant effects on the estrogen synthesis occurring in breast carcinomas and the surrounding tissues while any systemic effects might be compensated for by increased stimulation of gonadal synthesis.” (Dowsett 2003) Pre-clinical trials of third generation aromatase inhibitors have indicated an increase in gonadal
stimulation after aromatase inhibition which can result in multiple follicles. Because of this gonadal stimulation third generation aromatase inhibitors have only been studied in premenopausal women in combination with GnRH agonist. (Dowsett 2003) Further research should be done to effectively understand the role, if any, the third generation aromatase inhibitors play in premenopausal women.

CONCLUSION

Anastrozole, letrozole and exemestane, third generation non-steroidal aromatase inhibitors, are evidently the most promising treatment option available to postmenopausal women with hormone receptor positive or hormone receptor unknown breast cancer. While these drugs do have side effects, they have not been shown through a variety of studies to be any worse than side effects experienced with tamoxifen, and the curative effects are significantly better.
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