Fulvestrant: Pharmacologic Profile Versus Existing Endocrine Agents for the Treatment of Breast Cancer

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OBJECTIVE: To compare the pharmacologic profile of fulvestrant with that of tamoxifen and the aromatase inhibitors with respect to the choice of treatment for advanced breast cancer (ABC).

DATA SOURCES: Principal literature and review articles were obtained from MEDLINE (1991–March 2006). Key search terms included fulvestrant, tamoxifen, aromatase inhibitors, pharmacology, and breast cancer. Further data sources were identified from the bibliographies of selected articles.

STUDY SELECTION AND DATA EXTRACTION: English-language preclinical and clinical research and review articles reporting pharmacologic and safety data for fulvestrant, tamoxifen, and the aromatase inhibitors were evaluated to identify relevant information. Randomized clinical trial data were preferred over preclinical or Phase I and II trial data.

DATA SYNTHESIS: A total of 52 clinical papers (including 10 reviews) and 17 clinical abstracts were evaluated reporting results from controlled Phase I–III studies and pilot studies. Eleven preclinical papers (including 2 reviews) and 6 preclinical abstracts were also included. Fulvestrant has little effect on sex hormone endocrinology, bone metabolism, and lipid biochemistry and appears unlikely to be the subject or cause of CYP3A4-mediated drug interactions. Tamoxifen has a protective effect on bone (due to its partial estrogen agonist activity) and reduces plasma low-density lipoprotein cholesterol but increases triglyceride levels. The aromatase inhibitors have variable effects on lipid profiles and sex hormone endocrinology but have detrimental effects on bone due to inhibition of estrogen synthesis. Drug interactions have been noted between tamoxifen and anticoagulants and tamoxifen and aromatase inhibitors, which may be due to CYP-mediated mechanisms.

CONCLUSIONS: Fulvestrant appears to have little effect on sex hormone endocrinology, bone metabolism, and lipid biochemistry and is unlikely to be subject to or the cause of CYP3A4-mediated drug–drug interactions. As such, fulvestrant represents a valuable new endocrine therapy for the treatment of ABC and broadens the options available to clinicians in the treatment of this disease.

KEY WORDS: advanced breast cancer, aromatase inhibitors, estrogen, fulvestrant, tamoxifen.

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The treatment of advanced breast cancer (ABC) is essentially palliative, in that its goal is to halt or slow disease progression for as long as possible and manage symptoms, rather than achieve a cure. In postmenopausal women, approximately 75% of breast cancers are estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive,[1] and their growth is stimulated by both systemic estrogen and estrogen produced within the tumor by the enzyme aromatase. Endocrine therapy targets ER-mediated tumor growth and is as effective as cytotoxic chemotherapy, but is better tolerated by patients.[2]

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Currently available endocrine treatments for hormone receptor–positive ABC include the third-generation, nonsteroidal aromatase inhibitors anastrozole and letrozole, the steroidal aromatase inhibitor exemestane, the selective ER modulator tamoxifen, and the ER antagonist fulvestrant. Aromatase inhibitors reduce circulating estrogen levels by blocking the production of estrogen by the aromatase enzyme (the primary source of estrogen in postmenopausal women), while fulvestrant and tamoxifen are active at the ER itself, inhibiting ER-related tumor growth and signaling by blocking the action of estrogens at the ER. Tumors eventually develop resistance to individual endocrine therapies, leading to disease progression. Pa-

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tients must then be switched to another endocrine treatment with a different mode of action to circumvent such resistance. Increasing the range of available endocrine agents, therefore, invites the possibility of extending the period of endocrine treatment before cytotoxic chemotherapy is the only option.

The current National Comprehensive Cancer Network guidelines recommend that tamoxifen or an aromatase inhibitor be used as first-line endocrine therapy for ABC and that cytotoxic chemotherapy be employed only when the patient has derived no clinical benefit from 3 consecutive endocrine treatments.[3] Clinical trial data show that aromatase inhibitors are at least as effective as tamoxifen as first-line therapy for hormone receptor–positive ABC, but offer several tolerability advantages, including reduced incidence of vaginal bleeding and thromboembolic events.[4–6] As such, aromatase inhibitors should be considered as first-line endocrine therapy for hormone receptor–positive ABC.[7]

Fulvestrant is an endocrine agent, an ER antagonist with no estrogen-agonist effects,[8] and it is the latest addition to the endocrine therapy armamentarium. Fulvestrant binds the ER and prevents it from dimerizing, a necessary step preceding the binding of the ER dimer to, and the subsequent transcription of, estrogen-sensitive genes in the cell nucleus. Transcription of estrogen-sensitive genes is abrogated because fulvestrant blocks both activation functions on the ER. In addition, binding of fulvestrant to the ER subsequently increases the rate of ER degradation and reduces the amount of ER protein in the cell.[9,10] In comparison, tamoxifen blocks only one activation function and some ER-dependent gene transcription is possible, which accounts for tamoxifen's estrogen-agonist effects in some tissues.[11]

In Phase III trials, fulvestrant has proven to be at least as effective as anastrozole in postmenopausal women whose ABC had progressed during prior endocrine therapy (usually tamoxifen). Fulvestrant was also well tolerated and was associated with a significantly lower incidence of joint disorders compared with anastrozole.[12]

Because many patients with ABC are postmenopausal women, consideration of the wider effects of endocrine therapies will be influenced by the particular characteristics of this population. The effects of cancer therapies on bone and blood lipid profiles must be considered due to the possibility of patients experiencing concurrent osteoporosis or cardiovascular disorders. In addition, as patients age, it is likely that they will be receiving treatment for concurrent medical conditions, and it is desirable that their cancer treatment does not affect such drug therapy.

We review aspects of the pharmacologic profiles of the 4 most frequently prescribed endocrine treatments for ABC, focusing on fulvestrant as the newest addition to this field. Fulvestrant 250 mg once monthly is the only treatment to be administered by intramuscular injection; tamoxifen 20 mg, anastrozole 1 mg, letrozole 2.5 mg, and exemestane 25 mg are all once-daily oral medications. We focus particularly on the clinical pharmacology relating to estrogen levels, effects on bone homeostasis and lipid profiles, and potential for drug–drug interactions of these agents. For completeness, we have included safety data relating to the adjuvant treatment of early breast cancer (EBC) where applicable, as such data describe the safety aspects of these therapies over a potentially longer time course compared with ABC treatment.

Data Sources

Principal literature and review articles were obtained via a MEDLINE search (1991–March 2006). Key search terms included fulvestrant, tamoxifen, aromatase inhibitors, pharmacology, and breast cancer. Further data sources were identified from the bibliographies of selected articles.

Clinical Pharmacology

The effect of endocrine therapies on circulating estrogen levels, or modification of the action of the ER, has the potential to influence other body processes, such as endometrial maintenance, bone homeostasis, and blood lipid composition; when making treatment decisions, the possibility of an effect on such systems must be balanced with the probability of disease progression.

In premenopausal women, estrogen secretion by the ovaries is regulated by the sex steroids follicle-stimulating hormone (FSH) and luteinizing hormone (LH; Figure 1). A small contribution to total body estrogen is made by the aromatization of systemic androgens in peripheral tissue by the aromatase enzyme. FSH and LH are in turn regulated by LH-releasing hormone (LHRH), which is released by the hypothalamus and stimulates LHRH receptors in the pituitary gland. The menstrual cycle of premenopausal women results from the pulsatile secretion of LHRH, FSH, and LH, and the action of both positive and negative feedback control. After menopause, ovarian estrogen production ceases and peripheral aromatase becomes the primary estrogen source. The systemic level of estrogen falls markedly, while FSH and LH levels rise to a plateau. In postmenopausal women, increased levels of estrogen or drugs with estrogen-agonist effects, such as tamoxifen, may still stimulate uterine proliferation and cause gynecologic adverse events such as vaginal bleeding and endometrial cancer.[7]

Sex hormones are carried in the blood by sex hormone binding globulin (SHBG), a protein produced by the liver and regulated by systemic estrogens and androgens. Increased SHBG levels increase the capacity of the systemic blood supply for estrogens. Consequently, the effects of ABC therapies on both the levels of sex hormones and of SHBG

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are pertinent when considering their impact on systemic estrogen levels. These effects are summarized in Table 1.

FULVESTRANT

Both preclinical and clinical data support the lack of estrogen-agonist effects with fulvestrant treatment. Preclinical studies in immature female rats showed that fulvestrant, unlike tamoxifen, was completely devoid of uterotrophic activity. Moreover, coadministration of fulvestrant with either estradiol or tamoxifen completely blocked the maximal and partial uterotrophic activity of estradiol or tamoxifen, respectively, in a dose-dependent manner.[8]

Fulvestrant's lack of estrogen-agonist activity has also been demonstrated in a clinical study involving healthy volunteers.[13] This single-center, double-blind, randomized, parallel-group trial evaluated the effects on the endometrium of fulvestrant 125 and 250 mg with or without ethinylestradiol in 30 postmenopausal women. In addition to blocking the proliferative effects of ethinylestradiol on the endometrium, fulvestrant had no proliferative effects on healthy uterine tissue over the 14 day assessment period.

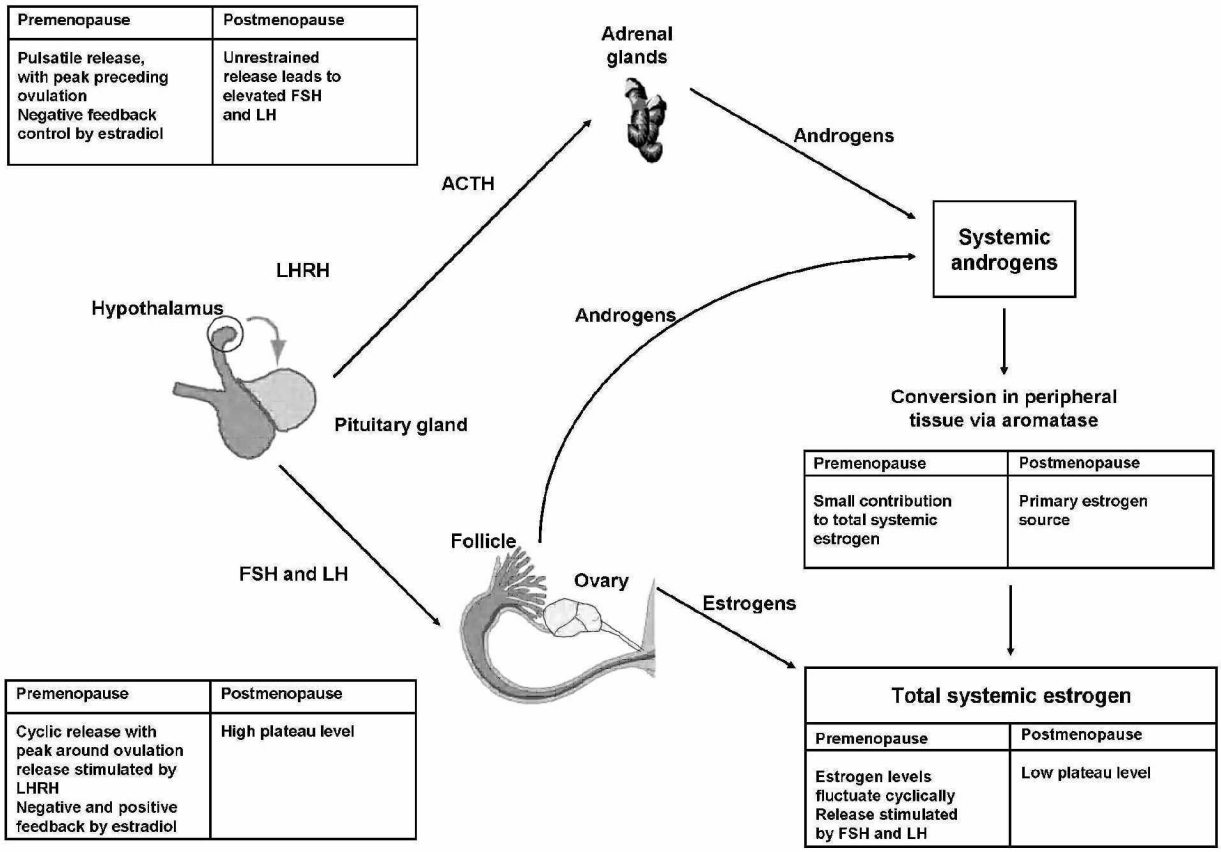

Figure 1. Control of sex steroid levels in pre- and postmenopausal women. ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; LHRH = LH-releasing hormone.

Table 1. Influence of Endocrine Breast Cancer Therapies on Clinical Pharmacology in Postmenopausal Women

Drug	Parameter			Clinical Effect
	FSH/LH	SHBG	Estrogen	
Fulvestrant	small increase	no significant changes	no significant effect; no agonist activity	no specific concerns
Tamoxifen	decrease	significant increase	significant increase; also, estrogen agonist activity	increased incidence of gynecologic events and endometrial proliferation
Aromatase inhibitors		significant suppression with exemestane	significant decrease	small differences in estrogen suppression among drugs; unlikely to be important

FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone–binding globulin.

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In a 12 week clinical trial comparing fulvestrant with goserelin in premenopausal patients with uterine fibroids (n = 307), fulvestrant did not significantly alter endometrial thickness or change endometrial histology.[14] It can therefore be assumed that fulvestrant has no proliferative effect on the healthy human endometrium.

The effect of fulvestrant on endocrine parameters was measured as part of the laboratory chemistry investigations of 2 Phase III comparative studies versus anastrozole in 851 postmenopausal women with ABC that had progressed after adjuvant endocrine therapy or after first-line endocrine therapy for ABC (primarily with tamoxifen).[15,16] Small increases in mean FSH and LH levels were observed in both treatment groups, consistent with a feedback mechanism in the pituitary gland triggered either by cessation of tamoxifen, which has been shown to reduce serum levels of FSH and LH,[17] or by the initiation of antiestrogen therapy without agonist properties. Median estradiol levels remained unchanged in both treatment groups throughout the studies.[15,16] The majority of patients (96–97%) in each of these trials had received tamoxifen at some point as either adjuvant or first-line therapy for ABC, and baseline SHBG levels were elevated in this population as a result of tamoxifen's partial estrogen-agonist activity. Consequently, the concentration of SHBG decreased over time with subsequent fulvestrant or anastrozole treatment. Previously, a small study of 19 patients with ABC resistant to tamoxifen reported similar findings.[18] LH and FSH levels increased in the patients after withdrawal of tamoxifen and initiation of fulvestrant and then plateaued, suggesting no effect of fulvestrant on the pituitary–hypothalamic axis. In this study, no significant changes were observed in serum SHBG levels.

The lack of impact on endometrial proliferation or systemic estrogen levels with fulvestrant treatment is an important factor compared with the consequences of increased estrogen activity in the uterine tissue of postmenopausal women treated with tamoxifen (as discussed below). The gynecologic adverse events experienced by patients receiving tamoxifen are not only distressing for patients, but also lead to unnecessary investigation to check for the presence of endometrial malignancy in patients who already have a significant illness.[19]

TAMOXIFEN

The estrogenic activity of tamoxifen is associated with significantly increased plasma levels of SHBG.[20,21] Decreased plasma levels of FSH and LH have also been observed.[17,20–22] Tamoxifen treatment has also been associated with a change in the balance of plasma estrogens, with increased plasma estrone sulfate levels, increased estrone sulfate:estradiol ratio, and decreased estradiol levels, but no effect on plasma estrone levels.[20] Furthermore, tamoxifen's weak estrogen-agonist effects may contribute to the phenomenon of tumor flare (temporary worsening of tumor lesions accompanied by diffuse musculoskeletal pain, erythema, and hypercalcemia associated with the initiation of antiestrogen treatment).[23,24]

Tamoxifen has long been associated with an increased risk of endometrial cancer and gynecologic abnormalities as a result of its estrogen-agonist properties in uterine tissue.[25] The effect of tamoxifen on estrogen levels, and its estrogen-agonist properties in certain tissues, have an impact on its use. While the significance of an increased risk of endometrial cancer with long-term tamoxifen therapy depends on the individual patient's prognosis, short-term gynecologic problems associated with tamoxifen therapy (eg, increased incidence of endometrial proliferation and vaginal bleeding and discharge) have resulted in aromatase inhibitors being recommended as first-line endocrine therapy for ABC.[7]

AROMATASE INHIBITORS

All 3 aromatase inhibitors (the nonsteroidal anastrozole and letrozole and the steroidal exemestane) effectively reduce estrogen levels in postmenopausal women through the inhibition of aromatase-mediated conversion of androgens (androstenedione and testosterone) to estrogens (estrone and estradiol). One study compared the extent of suppression of plasma estrone, estrone sulfate, and estradiol after 6 weeks of treatment with letrozole or anastrozole in postmenopausal women with metastatic breast cancer.[26] Although letrozole significantly reduced plasma estrone (84.3% vs 81.0%; p = 0.019) and estrone sulfate (98% vs 93.5%; p = 0.019) levels compared with anastrozole, there were no significant differences in the reduction in estradiol levels (84.9% vs 87.8%, respectively). It is likely that once a certain threshold of aromatase inhibition has been achieved, these small differences in estrogen suppression between the aromatase inhibitors will not lead to clinically significant differences in overall efficacy.[27] However, it is not yet known whether the greater reduction in estrone and estrone sulfate with letrozole will result in a greater incidence of the long-term adverse effects of estrogen deprivation such as bone loss, particularly in the adjuvant setting. With exemestane treatment, estradiol levels were suppressed by 92.2%, estrone levels by 94.5%, and estrone sulfate by 93.2% after 6–8 weeks.[28]

In contrast to exemestane, which has weak androgenic properties,[29] anastrozole and letrozole have no androgenic, progestogenic, or estrogenic activity that may result in effects such as weight gain, acne, or hypertrichosis.[30] Indirect comparisons show that anastrozole has the highest degree of selectivity for aromatase compared with letrozole and exemestane and, consequently, has the least effect on adrenosteroidogenesis.[31]

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Therefore, aromatase inhibitors provide effective reduction of estradiol levels in postmenopausal women for the treatment of ABC. However, aromatase inhibitors are not suitable for ABC monotherapy in premenopausal women,[32] as their effect on estradiol levels is negligible compared with the background level of circulating ovarian estrogens. Furthermore, administration of aromatase inhibitors to premenopausal women has been shown to increase systemic estrogen by activation of the negative feedback control of estradiol by FSH.[33]

Effects on Bone

Estrogens inhibit bone resorption and maintain bone homeostasis.[34] In postmenopausal women, the main source of endogenous estrogen is the aromatization of androgenous precursors in peripheral tissue (including bone osteoblasts and chondrocytes). Consequently, estrogen levels within bone tissue may be independent of systemic estrogen levels.[35] The effects of cancer therapies on bone homeostasis are important when considering the increasing incidence of osteoporosis with age following menopause combined with the common presence of bone metastases in ABC patients. The effects of endocrine treatments for ABC on bone metabolism are summarized in Table 2.

FULVESTRANT

The effect of fulvestrant on bone was initially investigated in rats. The available data suggest that fulvestrant appears to reduce cancellous bone volume, which comprises only a small proportion of total bone,[36] and its effects are consistent with blockade of ER-mediated bone resorption and formation.[37]

In a clinical study involving premenopausal women undergoing hysterectomy, fulvestrant did not produce changes in markers of bone resorption (cross-linked N-telopeptides and unbound deoxypyridinoline), suggesting that it did not affect bone turnover in this patient group.[14,38] However, the administration of a single 250 mg dose of fulvestrant to a group of premenopausal women with breast cancer 2–3 weeks prior to primary surgery was found to have no effect on ER, PgR, and Ki67 protein levels.[39] It is therefore possible that the logarithmically higher endogenous estradiol levels in premenopausal women compared with postmenopausal women, coupled with the similar affinities of fulvestrant and estradiol for the ER, may have negated any biological effect of fulvestrant on bone turnover. Further research is necessary to assess the effect of fulvestrant on bone turnover in postmenopausal women with ABC. This consideration will become especially pertinent if fulvestrant is considered for the adjuvant treatment of EBC in the future.

TAMOXIFEN

In postmenopausal women, the weak estrogen agonist activity of tamoxifen can lead to significant increases in bone mineral density, particularly in the lumbar spine.[40,41] Significant decreases in markers of bone resorption (eg, urinary cross-linked aminoterminal telopeptide of type I collagen) and markers of bone formation (eg, osteocalcin) have also been observed with tamoxifen treatment, further confirming the protective effect of this agent in postmenopausal women.[42] However, as bisphosphonates confer additional benefit over tamoxifen with respect to maintenance of bone mineral density, tamoxifen should not be considered a substitute for bisphosphonate therapy for women with breast cancer and concurrent osteoporosis or osteopenia.[43]

AROMATASE INHIBITORS

In a study of healthy volunteers, both steroidal and nonsteroidal aromatase inhibitors were shown to increase markers of bone turnover.[44] Anastrozole increased markers of bone resorption and formation in clinical studies, whereas letrozole increased bone resorption markers, but without a compensatory increase in bone formation markers.[44–47] However, any differences between the nonsteroidal aromatase inhibitors regarding their clinical effects on bone are not yet known. The steroidal aromatase inhibitor exemestane appears to increase both markers of formation and resorption to a greater extent than does either of the nonsteroidal agents.[44]

Clinical trials including postmenopausal women with EBC have confirmed that aromatase inhibitors have detrimental effects on bone, which may give rise to an increased risk of osteopenia, osteoporosis, and an increased susceptibility to fractures. In the ATAC (Anastrozole, Ta-

Table 2. Influence of Endocrine Breast Cancer Therapies on Bone Metabolism in Postmenopausal Women

Drug	Effect on Bone Metabolism Markers	Clinical Effect
Fulvestrant	no changes in bone resorption in postmenopausal women; further data required	no specific concerns; further data required
Tamoxifen	significant decreases in bone resorption and formation	protective effect leading to reduced fractures
Aromatase inhibitors	increased bone resorption and formation markers	increased risk of fracture from reduced serum estrogen levels

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moxifen, Alone or in Combination) trial, postmenopausal women with EBC were randomized to receive anastrozole, tamoxifen, or both therapies for 5 years as adjuvant treatment following primary surgery. In the initial report of results at a median treatment duration of 33.3 months, 5.9% of patients in the anastrozole-only arm reported fractures, as opposed to 3.6% in the tamoxifen-only arm, a statistically significant difference ($p < 0.0001$) but not necessarily a surprising observation, given the known protective effect of tamoxifen on bone.[48] Fracture rate in the combination therapy arm was 4.9%. At a follow-up of 37 months, incidence of fracture was 7.1%, 4.4%, and 5.7% for the anastrozole, tamoxifen, and combination arms, respectively, indicating a stabilization of the difference in fracture rates between the monotherapy groups.[49] The combination arm was subsequently discontinued due to similar efficacy compared with the tamoxifen-only group, and at the completed treatment analysis of ATAC (median follow-up 68 mo), the incidence of fracture was 11.0% and 7.7% for the anastrozole and tamoxifen arms, respectively.[50]

Letrozole has been shown to increase bone loss at the clavicle and rib in postmenopausal patients with ABC.[51] In addition, the National Cancer Institute of Canada MA.17 study compared 5 years' letrozole treatment with placebo following completion of 5 years' adjuvant tamoxifen in postmenopausal women with EBC.[52] This study found that, at 1.9 years' follow-up, letrozole showed a trend toward increased osteoporosis (5.8% and 4.5%, respectively) and fractures (3.6% and 2.9%, respectively) compared with placebo.

Although early preclinical studies suggested that exemestane might have a protective effect on bone,[53] this finding is not supported by clinical trial data. In postmenopausal patients with advanced breast cancer, exemestane increased markers of bone formation and resorption.[54-56] In a 5 year trial assessing the effect of switching from tamoxifen to exemestane after 2–3 years versus continued tamoxifen therapy (median follow-up 2.5 y), more exemestane-treated patients developed osteoporosis (7.4% vs 5.7%; $p = 0.05$), and there was also a trend toward more fractures in this group (3.1% vs 2.3%; $p = 0.08$).[57] Exemestane has also been found to decrease bone mineral density at the lumbar spine and femoral neck relative to placebo to approximately the same extent as anastrozole (~2% per year) in postmenopausal women being treated for EBC.[58]

Effects on Lipids

Elevated total cholesterol, low-density lipoprotein cholesterol (LDL-C), and ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C) are important risk factors for the development and progression of cardiovascular disease.[59] High levels of HDL-C are associated with a reduced risk of coronary heart disease (CHD). Healthy postmenopausal women experience a decrease in the HDL C:LDL-C ratio, possibly as a result of reduced estrogen production (irrespective of hormone replacement therapy usage) and therefore are already at elevated risk of cardiovascular disease. Thus, drugs that alter lipid profiles may have an impact on the risk of cardiovascular morbidity, such as CHD and thromboembolic conditions, and mortality. The effects of these endocrine therapies on lipid profile are summarized in Table 3.

FULVESTRANT

The effect of fulvestrant on lipid variables was monitored as part of laboratory investigations in 2 Phase III comparative studies of fulvestrant versus anastrozole as second-line endocrine therapy for breast cancer.[15,16] The most robust assessments of plasma lipids are performed on blood samples from fasting patients. However, only samples from non-fasting patients were available for lipid assessments in these trials. No major changes in lipid variables occurred with either treatment. Mean triglyceride and HDL-C levels did not change, whereas total cholesterol and LDL-C levels were mildly increased with fulvestrant treatment.

In both treatment groups, unusually high levels of cholesterol were reported in samples from approximately 10% of non-fasting patients who were considered to have normal levels at baseline.[60] In the combined analysis of

Table 3. Influence of Endocrine Breast Cancer Therapies on Lipid Profile in Postmenopausal Women

Drug	Lipid Profile Component				Clinical Effect
	TC	LDL-C	HDL-C	Triglycerides	
Fulvestrant	small increase	small increase	no effect	no effect	no significant changes
Tamoxifen	decrease	decrease	increase	increase	no cardioprotection
Anastrozole	insignificant fluctuations				no significant profile changes
Letrozole	increased incidence of hypercholesterolemia			no data	no long-term data
Exemestane	conflicting data; decrease/no effect		no effect/decrease	no effect/decrease	no long-term data

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

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these trials,[12] there were no significant differences in rates of thromboembolic disease between patients receiving fulvestrant and those receiving anastrozole. There were also no significant differences in terms of thromboembolic disease between patients receiving fulvestrant and tamoxifen as first-line endocrine therapy for ABC.[61]

TAMOXIFEN

Long-term tamoxifen treatment has differential effects on lipid profiles with respect to cardiovascular risk factors. For example, it lowers total serum cholesterol and LDL-C levels[62,63] and has also been shown to increase HDL-C levels in some studies.[64,65] However, the estrogenic effect of tamoxifen on the liver also significantly increases serum triglyceride levels.[65,66] Tamoxifen therapy has been shown to increase the risk of thromboembolic events (stroke, pulmonary embolism, deep-vein thrombosis)[67] and to exert no cardioprotective effect in the adjuvant setting when 5 years of endocrine therapy is given following primary surgery to reduce the risk of cancer recurrence.[4] Although it was anticipated that tamoxifen may have a favorable influence on lipid profiles, these effects have not been translated into a protective effect with respect to cardiovascular and thromboembolic morbidity and mortality.[68]

AROMATASE INHIBITORS

The 3 third-generation aromatase inhibitors have somewhat different effects on lipid profiles. Data from comparative studies of anastrozole and tamoxifen suggest that anastrozole does not markedly affect lipid profiles compared with baseline values. Small increases in total cholesterol and LDL-C and a decrease in HDL-C were observed after 84 weeks of anastrozole treatment for ABC.[63] A 12 week study of anastrozole versus tamoxifen in Japanese women with EBC reported unchanged total cholesterol and LDL-C levels, increased HDL-C, and decreased triglycerides in the anastrozole arm, albeit in a population with traditionally low rates of CHD.[69] Similar theoretically beneficial but nonsignificant changes in lipid profile were reported with anastrozole in a 12 week trial comparing adjuvant treatments for breast cancer.[70]

These data are supported by those from a smaller study (N = 44) in postmenopausal women with ABC in which 32 weeks of anastrozole treatment did not significantly alter any lipid parameters.[71] In the completed treatment analysis of the ATAC trial, there were significantly fewer ischemic cerebrovascular events and venous thromboembolic events in the anastrozole group compared with the tamoxifen group, although no effect on the incidence of ischemic cerebrovascular disease was observed.[50]

Letrozole significantly increased total cholesterol and LDL-C from baseline after 8 and 16 weeks of treatment in a study of 20 women with ABC.[72] Another study reported no significant effect of letrozole on lipid profiles.[45] Recently, there has been a presentation of initial efficacy and tolerability data from the primary core analysis of the Breast International Group (BIG) 1-98 trial, a study including 8010 women randomized to receive either letrozole or tamoxifen as adjuvant therapy.[73] At a median follow-up of 25.8 months, 43.5% of patients receiving letrozole had experienced hypercholesterolemia, compared with 19.1% of those receiving tamoxifen. Of these instances, 80% (letrozole) and 90% (tamoxifen) were of grade 1 severity, with the remainder of cases being grade 2 or greater. These data also identified an increased risk of cardiac morbidity with letrozole treatment that has yet to be fully investigated.

Exemestane appears to have effects on the lipid profile that are different from those of the nonsteroidal aromatase inhibitors. In a 9 week trial in patients with ABC, exemestane treatment was associated with decreased total cholesterol, HDL-C, and total triglyceride levels.[74] In other studies, exemestane had no effect on lipid profiles.[75,76]

The LEAP (Letrozole, Exemestane, and Anastrozole Pharmacodynamics) study investigated pharmacodynamic differences in lipid levels arising from 24 weeks' treatment with the third-generation aromatase inhibitors in healthy postmenopausal women.[77] Data from 90 evaluable subjects revealed several differences in the effects of the aromatase inhibitors on lipid profiles. After 24 weeks of treatment, the largest rise in triglycerides occurred with letrozole therapy and the greatest increase in the ratio of LDL-C:HDL-C was observed with exemestane therapy. In contrast, anastrozole appeared to have relatively little effect on lipid profiles.

Potential for Drug Interactions

Given that the majority of women with ABC are postmenopausal and therefore in the mid-to-later stages of their lives, it may be expected that many will be receiving concomitant therapy for the myriad of conditions that increase in incidence with age.[78] It is therefore desirable that endocrine therapy for ABC does not interfere with existing medication regimens. Certain pharmacodynamic drug interactions are not always predictable and may be identified only during postmarketing surveillance. It is possible, however, to anticipate potential pharmacokinetic drug interactions via cytochrome P450 (CYP)–mediated metabolic mechanisms in vitro before they occur in patients. CYP enzymes mediate the rate-limiting step of primary phase I metabolic reactions for the vast majority of drug compounds. Screening methodologies are now routinely used to study the potential of a drug to inhibit specific CYP enzymes and identify those most likely to affect the metabolism of other pharmacologic treatments.

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FULVESTRANT

Preclinical studies using human liver microsomes have indicated that fulvestrant does not appear to markedly inhibit any of the major drug-metabolizing CYP isoenzymes in vitro (1A2, 3A4, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1).[79] Less than 20% inhibition was observed at the highest concentration of fulvestrant (10 µg/mL), suggesting that fulvestrant is unlikely to cause clinically significant reversible inhibition or mechanism-based inactivation of these isoenzymes.

Studies using human hepatocytes have also shown that sulfate conjugation is a predominant metabolic pathway and that CYP3A4 does not appear likely to have a major role in the clearance of fulvestrant.[80] Phase I clinical drug interaction studies in healthy volunteers supported these preclinical observations, suggesting that fulvestrant has minimal potential to be involved in drug interactions based on the inhibition/induction of human CYP3A4. In these studies, coadministration of neither the CYP3A4 inducer rifampin nor the CYP3A4 inhibitor ketoconazole affected the pharmacokinetics of fulvestrant. Furthermore, coadministration of fulvestrant with midazolam, a CYP3A4 substrate and established marker of CYP3A4 activity, did not alter the pharmacokinetics of midazolam.

In summary, while fulvestrant appears to have little effect on CYP–mediated metabolism, only further experience of the use of this drug in patients will identify its potential for interactions via other mechanisms.

TAMOXIFEN

Tamoxifen's well-documented interaction with coumarin anticoagulants (enhanced anticoagulant effect) may preclude its use in patients at risk for thromboembolic events who are already receiving warfarin. It has been suggested that this interaction occurs through the inhibition of CYP2C9 (responsible for warfarin metabolism) by tamoxifen.[81] In human liver microsomes, tamoxifen is metabolized by CYP3A4 and CYP2D6/9 to 4-hydroxy-tamoxifen, which is approximately 100 times more potent than the parent drug as an ER antagonist.[82–84]

AROMATASE INHIBITORS

Anastrozole inhibits CYP1A2, CYP2C8/9, and CYP3A4, but has no effect on CYP2A6 or CYP2D6 in vitro.[85] However, the level of inhibition during therapy with anastrozole 1 mg/day (inhibition predicted to be ~3%) would not be expected to cause clinically significant interactions with other CYP-metabolized drugs. Clinical studies have confirmed the absence of drug–drug interactions between anastrozole and other drugs via CYP–mediated metabolism.[86,87] Letrozole inhibits CYP2A6 and CYP2C19 and has a low affinity for CYP3A4,[88] and exemestane is metabolized by CYP3A4 alone.[89] Recent in vitro data have implicated CYP3A as a major catalyst of letrozole metabolism, with some contribution from CYP2A6.[90]

There are known interactions between tamoxifen and anastrozole and tamoxifen and letrozole; concomitant administration of these agents leads to a reduced plasma concentration of the aromatase inhibitor.[91,92] Letrozole interacts with tamoxifen to a greater extent than tamoxifen interacts with anastrozole, with combination treatment reducing plasma AUC of letrozole on average by 38%[91] and anastrozole by 27%,[92] although the clinical impact of this interaction has been questioned.[92] Exemestane appears to have no pharmacokinetic interaction with tamoxifen.[93]

In either the adjuvant or ABC setting, tamoxifen and aromatase inhibitors are unlikely to be coadministered. Discontinuation of the concomitant anastrozole and tamoxifen arm of the ATAC trial on efficacy grounds[48] means that this strategy is unlikely to be investigated further. Trial results support the increased efficacy of completing adjuvant treatment with an aromatase inhibitor after starting tamoxifen compared with tamoxifen monotherapy.[57,94-96] However, this finding reflects the increased efficacy of aromatase inhibitors in terms of reducing recurrence compared with tamoxifen therapy in women who have already started adjuvant therapy with tamoxifen, rather than supporting an adjuvant therapy regimen involving 2 drugs.[97]

In the ABC setting, endocrine treatments are given sequentially and only changed on progression in order to extend the period of hormonal therapy for as long as possible; co-administering endocrine agents would reduce the subsequent endocrine options available to patients.

Summary

The estrogen agonist properties of tamoxifen make its effects on endocrine parameters different from those of fulvestrant. Tamoxifen increases SHBG levels and decreases plasma FSH and LH. It also increases plasma estrone sulfate (but not estrone) and has been shown to increase plasma estradiol in some studies, and, thus, may cause tumor flare. In contrast, fulvestrant treatment results in only small increases in FSH and LH levels, consistent with a feedback mechanism triggered by an antiestrogen without agonist properties. All aromatase inhibitors significantly reduce estrone, estrone sulfate, and estradiol levels. Exemestane, being steroidal in origin, also has androgenic properties.

Tamoxifen's agonist–antagonist properties also account for its protective effects on bone. Fulvestrant appears to have little or no effect on bone homeostasis, whereas the aromatase inhibitors, because of their mode of action, appear to increase the rate of bone loss and risk of fracture.

Fulvestrant appears to have no significant effect on serum lipid profile with respect to plasma triglycerides, LDL-C, or HDL-C, whereas the aromatase inhibitors have

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variable effects on lipid balance. Anastrozole has little effect on cholesterol but reduces plasma triglyceride levels. There is conflicting evidence as to the effect of letrozole on lipid profiles, with increased LDL-C and total cholesterol levels reported in some studies and no effect in others. Similarly, exemestane appears to have little effect, producing minor decreases in triglyceride, HDL-C, and total cholesterol levels. There are, however, few long-term data available for the latter 2 aromatase inhibitors, as their main Phase III trials in the extended adjuvant (letrozole) and switched adjuvant (exemestane) were halted early, preventing the collection of robust tolerability data over the past few years. The 68 month follow-up data for the ATAC trial reported significant benefits in terms of ischemic cardiovascular and venous thromboembolic events for patients treated with anastrozole compared with tamoxifen, but data of this maturity for letrozole and exemestane will not be available for some time.

Fulvestrant appears to have low potential to be the subject or cause of clinically significant drug interactions, which is clinically relevant when considering that postmenopausal women with ABC may be receiving other medication for comorbid conditions. Further experience of the use of fulvestrant with a variety of drugs is necessary before this potential can be fully assessed.

The apparent lack of impact upon bone and lipid homeostasis and low potential to interact with other therapies make fulvestrant an attractive addition to the range of endocrine therapies available to treat breast cancer in postmenopausal women. The decision to use fulvestrant is not complicated by apprehension relating to possible long-term effects on other body systems, and the patient need not be concerned with such effects or inconvenienced by prophylactic therapy to deal with them. The ABC treatment course is inherently of shorter duration than that of adjuvant therapy and would therefore not be expected to provide information on the longer-term consequences of fulvestrant administration. However, there are no indications in the currently available data indicating that long-term administration of fulvestrant is likely to cause undue concern with respect to cardiovascular and bone complications.

Fulvestrant has a novel pharmacologic profile that, to date, compares favorably with the other available endocrine treatments for ABC. These properties, along with its proven efficacy and tolerability, make fulvestrant a valuable new therapy option in this setting.

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EXTRACTO

OBJETIVO: Comparar el perfil farmacológico de fulvestrant con el de tamoxifen y los inhibidores de aromatasas con respecto a la selección de tratamiento para cáncer de mama.

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FUENTES DE INFORMACIÓN: La literatura primaria y artículos de revisión utilizados se obtuvieron de motor de búsqueda de artículos científicos MEDLINE entre 1991 y marzo de 2006. Los términos usados incluyeron: fulvestrant, tamoxifen, inhibidores de aromatasa, farmacología, y cáncer del mama. Otras fuentes adicionales se identificaron de las bibliografías de artículos selectos.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se evaluaron estudios clínicos y pre-clínicos y artículos de revisión informando datos farmacológicos de fulvestrant, tamoxifen, y de los inhibidores de aromatasa para identificar información relevante. Se daba preferencia a datos de estudios clínicos aleatorios sobre os estudios preclínicos o estudios clínicos fase I o fase II.

SÍNTESIS: Fulvestrant es un antagonista del receptor de estrógeno que contrario a tamoxifen, carece de propiedades como agonista estrogénico. Se resume y compara los aspectos del perfil farmacológico de fulvestrant y 4 otras terapias endocrinas ampliamente recetadas para cáncer de mama avanzado (tamoxifen, anastrozole, letrozole, y exemestane). Se discuten las diferencias entre los efectos de estos agentes en los parámetros endocrinos tales comos los niveles en las hormonas folículo-estimulate, luteinizante, y estradiol con una descripción de su impacto en los perfiles de lípidos y el metabolismo óseo como una fuente de eventos adversos. El potencial de desarrollar interacciones entre medicamentos también se discute.

CONCLUSIONES: Fulvestrant parece tener poco efecto en las hormonas sexuales del sistema endocrinológico, en el metabolismo del hueso, y la bioquímica de los lípidos. Es improbable que sea sujeto o causa de interacciones entre medicamentos mediadas por el citocromo CYP3A4. Como tal, fulvestrant representa una nueva terapia endocrina valiosa para el tratamiento de cáncer de mama avanzado y amplía las opciones disponibles para el tratamiento de esta condición.

Jorge R Miranda-Massari

RÉSUMÉ

OBJECTIF: Comparer le profil pharmacologique du fulvestrant avec ceux du tamoxifène et des inhibiteurs de l'aromatase quant au choix du traitement du cancer du sein.

SOURCES DES DONNÉES: Littérature primaire et articles de revues en anglais ont été obtenus au moyen d'une recherche sur MEDLINE (1991 à mars 2006) avec les mots-clés fulvestrant, tamoxifen, aromatase inhibitors, pharmacology, et cancer du sein. D'autres données ont été repérées dans la bibliographie des articles sélectionnés.

SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Les articles de recherche pré-clinique et clinique et les articles de revues rapportant des données pharmacologiques et de tolérance sur le fulvestrant, le tamoxifène, et les inhibiteurs de l'aromatase ont été évalués pour identifier les informations pertinentes. Lorsqu'elles étaient disponibles, les données des essais cliniques à allocation aléatoire ont été préférées à celles des essais pré-cliniques ou de phase 1 ou 2.

SYNTHÈSE DES DONNÉES: Au total, 52 publications (dont 10 articles de revue) et 17 communications sous forme résumée rapportant des résultats cliniques d'études de phases 1 à 3 et d'études pilotes ont été évaluées. Onze publications (dont 2 articles de revue) et 6 communications sous forme résumée relatives à des essais pré-cliniques ont aussi été incluses. Le fulvestrant apparaît n'avoir que peu d'effet sur les hormones sexuelles, le métabolisme osseux, et la biochimie des lipides. Il est peu susceptible d'être l'objet ou la cause d'une interaction médicamenteuse liée au CYP3A4. Le tamoxifène a un effet protecteur sur l'os (du à son activité agoniste estrogénique partielle) et il réduit les lipoprotéines de basse densité cholestérol mais il augmente les triglycérides. Les inhibiteurs de l'aromatase présentent des effets variés sur le profil lipidique et les hormones sexuelles mais entraînent des effets osseux délétères dus à leur inhibition de la synthèse estrogénique. Des interactions médicamenteuses, susceptibles d'être liées à des mécanismes touchant les CYP3A4, ont été signalées entre le tamoxifène et des anticoagulants ainsi qu'entre le tamoxifène et des inhibiteurs de l'aromatase.

CONCLUSIONS: Le fulvestrant possède un profil pharmacologique innovant, favorable par rapport à d'autres médicaments d'hormonothérapie utilisés dans le traitement du cancer du sein. En tant que tel, il représente une nouvelle thérapeutique intéressante pour le traitement du cancer du sein avancé hormono-dépendant et élargit la gamme des options disponibles aux cliniciens pour le traitement de cette maladie.

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