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Review paper

Exemestane in advanced breast cancer

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Exemestane is an orally active steroidal aromatase inhibitor that has demonstrated efficacy in the treatment of postmenopausal patients with advanced breast cancer. This compound exhibits a good tolerability and safety profile, which may result from its highly selective mechanism of action. Exemestane binds irreversibly to the aromatase enzyme causing inactivation of the enzyme. This irreversible loss of enzyme may contribute to the sustained inhibition of estrogen synthesis noted following exemestane administration. Exemestane is a potent inhibitor of aromatization reducing estrogen synthesis *in vivo* by greater than 97%. The recommended dose of exemestane is 25 mg once daily. Although dosages up to 600 mg/day have been tested, the maximum tolerated dose of exemestane has not been reached in clinical study. The most frequently reported drug-related adverse events are hot flushes, nausea and fatigue, which are consistent with the estrogen-suppressive effects of the drug. Discontinuation due to adverse events is rare. Exemestane is a safe and well-tolerated alternative for the treatment of postmenopausal patients with advanced breast cancer. [© 2000 Lippincott Williams & Wilkins.]

Key words: Adverse events, aromatase inhibitor, exemestane, hormone therapy, postmenopausal breast cancer, tolerability.

Introduction

Endocrine therapy is an effective treatment for advanced breast cancer. Since the earliest observation over 100 years ago that oophorectomy impaired tumor growth, researchers have worked to elucidate the mechanisms by which hormones, primarily estrogen, influence the development and growth of breast cancer. The two major strategies for hormonal therapy of advanced breast cancer involve decreasing endogenous estrogen levels (aromatase inhibitors and possibly progestins) and decreasing estrogen-mediated events by blocking estrogen's interaction with its receptor (antiestrogens). A variety of agents have been developed to target these pathways and, although efficacious, most are associated with undesirable side effects and drug interactions (Table 1).[1,2]

The non-steroidal antiestrogen tamoxifen has been used for almost 30 years for the treatment of breast cancer and is still accepted as the first-line therapy for advanced breast cancer in postmenopausal patients. Tamoxifen displays both estrogen antagonist and agonist qualities, and, therefore, is associated with both estrogen deprivation and stimulation side effects.[3,4] Although toxic side effects are rare, there are concerns regarding the increased incidence of endometrial cancer and thrombosis observed with the use of this agent.[5,6] Attempts are ongoing to develop more selective estrogen receptor modulators, in the hopes that these agents will exhibit more acceptable side-effect profiles.

Although progestins have been used in the treatment of breast cancer for almost 50 years, their exact mechanism of action has not been established. However, effects on estrogen levels are thought to play a role. Megestrol acetate, a synthetic derivative of progesterone, is the only progestin in the US indicated for use in postmenopausal advanced breast cancer patients.

Although megestrol acetate exhibits equal efficacy to tamoxifen, side effects such as chronic weight gain, dyspnea and edema make it a less acceptable agent.[4,7,8] Megestrol acetate has also been associated with exacerbation of pre-existing diabetes.[9] Once the standard second-line therapy, progestins are now mainly used as third-line therapy, following the approval of the second-generation aromatase inhibitors.

The final step in estrogen synthesis, conversion of androgens to estrogen, is catalyzed by the cytochrome P450 enzyme aromatase and requires the presence of

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Table 1. Side effects associated with current hormonal therapies for advanced breast cancer.

Agent	Side effect	Drug–drug/drug–disease interactions
Antiestrogen		
tamoxifen	hot flushes, amenorrhea, vaginal bleeding, weight gain, fluid retention, mild nausea, 'flare' reaction, and increased risk of thrombosis and uterine cancer[3–6]	increases anticoagulation effects of coumarin-type anticoagulants; increases risk of thromboembolic events when used in combination with cytotoxic agents; is a potent inhibitor of hepatic cytochrome P450 mixed function oxidase
Progestin		
megestrol acetate	weight gain, hypertension, thrombophlebitis, vaginal bleeding and glucocorticoid effects[7]	has been associated with exacerbation of pre-existing diabetes
Aromatase inhibitors		
aminoglutethimide	skin rash, ataxia, drowsiness, fatigue, adrenal insufficiency, thrombocytopenia and CNS toxicity[10,11]	accelerates the metabolism of dexamethasone; if glucocorticoid replacement is needed, hydrocortisone should be prescribed; diminishes the effects of warfarin and coumarin; accelerates the metabolism of tamoxifen
letrozole	headache, hot flushes and gastrointestinal effects[14–16]	eliminated almost exclusively by hepatic metabolism, therefore patients with severe impairment of liver function should be dosed with caution
anastrozole	gastrointestinal effects (nausea, vomiting, diarrhea), hot flushes, bone/back pain, asthenia and headache[12,13]	inhibits reaction catalyzed by cytochrome P450 (1A2, 2C8/9 and 3A4); however, co-administration of a 1 mg dose of anastrozole with drug metabolized by these enzymes is unlikely to be of clinical significance
exemestane	hot flushes, nausea and fatigue[43] (see Table 2 for details)	none observed (not extensively studied)

the cofactor NADPH (Figure 1). The specificity of this reaction has made inhibition of aromatase an attractive, alternative approach to antiestrogen therapy. Aminoglutethimide was the first non-steroidal (reversible-competitive) inhibitor of aromatase evaluated clinically for the treatment of advanced breast cancer and, for many years, was considered suitable second-line therapy, as an alternative to progestins. Although efficacious, severe side effects, lack of selectivity for aromatase and the need for glucocorticoid replacement therapy limited its popularity.[4,10,11]

Prompted by the efficacy of aminoglutethimide, more selective, less toxic, reversible aromatase inhibitors were developed. The triazole derivatives anastrozole and letrozole are approved for use in postmenopausal breast cancer patients who have progressed on tamoxifen or, in the case of letrozole, other antiestrogens, such as toremifene. These agents have the advantage of suppressing serum levels of estrogen without affecting levels of other hormones.[4] These agents are better tolerated than megestrol acetate, and are associated with a lower incidence of cardiovascular and thromboembolic events, weight gain, and dyspnea. The most frequently reported side effects associated with anastrozole use are asthenia, nausea, headache, hot flushes, pain and back pain.[12,13]

As many as 30% of patients receiving anastrozole experience gastrointestinal disturbances (nausea, vomiting and diarrhea). Letrozole has a side-effect profile that includes nausea, vomiting, heartburn, diarrhea, headache, peripheral edema, hot flushes and fatigue.[14,15] Letrozole is eliminated almost exclusively by hepatic metabolism; therefore, patients with severe liver impairment may require dosage reduction.[16]

The potential for increasing the efficacy of hormonal therapy by combining an aromastase inhibitor with an antiestrogen is high; both classes are well tolerated and operate through different mechanisms of action. However, early studies combining aminoglutethimide and tamoxifen did not result in a higher response rate than tamoxifen alone.[17,18] This lack of effect may be explained by the 50% reduction in tamoxifen plasma concentrations seen with co-administration of aminoglutethimide.[19] Newer aromatase inhibitors exhibit a higher degree of selectivity and are weaker inducers of cytochrome P450 compared with aminoglutethimide.[20] In two pharmacokinetic studies, neither

letrozole nor anastrozole co-administration had a significant effect on tamoxifen plasma concentrations.[21,22] In addition, co-administration of tamoxifen did not appear to alter the estrogen-suppressive effects of either agent, although plasma concentrations of letrozole were reduced by 30.6%.[21] Further studies are required to evaluate the clinical benefits of combination hormonal therapy.

Exemestane—an irreversible aromatase inactivator

Exemestane, an analog of androstenedione, is a potent aromatase inactivator that offers a novel approach to the hormonal treatment of advanced breast cancer.[23] Exemestane is initially recognized by the aromatase enzyme as a false substrate, then transformed (through an NDPH-dependent mechanism) to an intermediate which binds irreversibly to the enzyme causing inactivation (also known as mechanism-based or suicide inhibition).[24] Therefore, the enzyme is permanently inactivated and *de novo* enzyme synthesis is required for estrogen production (Figure 1). Such irreversible inhibitors are also known as 'aromatase inactivators'. In contrast, the non-steroidal aromatase inhibitors, such as aminoglutethimide, anastrozole and letrozole, are known as reversible inhibitors. They interfere reversibly with the heme moiety of the aromatase enzyme and do not require the presence of the NADPH cofactor (Figure 1).

Efficacy

Exemestane is highly potent, exhibiting near total *in vivo* aromatase inactivation (above 97.9%).[25] At maximal suppression, estrogen concentrations are in the range of 6–15% of pretreatment levels.[26,27] The minimally effective exemestane dose producing maximal inhibition of circulating estrogen suppression is 25 mg/day. Higher doses have been evaluated but no further effects on estrogen levels have been seen. The effect on aromatization has been evaluated only at 25 mg.[28–30] Clinical studies support the use of oral, once-daily doses of 25 mg of exemestane.[26–29] Exemestane has demonstrated superiority to megestrol acetate in tamoxifen-refractory postmenopausal patients with advanced breast cancer in terms of overall survival and time to progression (Table 2). Table 2 summarizes the efficacy data of three available aromatase inhibitors (exemestane, anastrozole and letrozole). Prospective randomized trials have not been done to compare the safety or efficacy of these drugs; thus one cannot comment on the efficacy of one drug relative to other agents. Exemestane has also demonstrated efficacy in patients who progress following nonsteroidal aromatase inhibitor therapy[31] (Lonning, in preparation).

Selectivity

Exemestane exhibits a high degree of specificity. No suppression in plasma concentrations of cortisol,

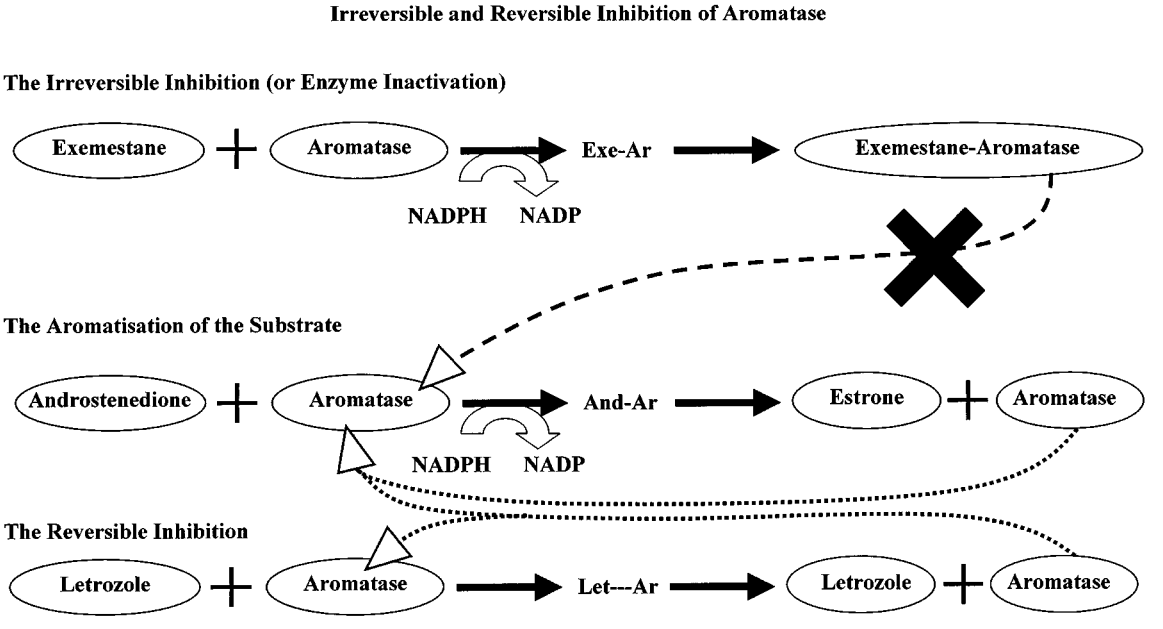

Figure 1. Schematic representation of steroidal versus non-steroidal mechanism of aromatase inhibition.

Table 2. Efficacy of exemestane, anastrozole and letrozole versus megestrol acetate as second-line hormonal therapy for postmenopausal patients with advanced breast cancer

	Complete response (%)	Partial response (%)	Overall response[a] (%)	Stable disease (%)	Overall success[b] (%)	Progressive disease (%)	Median survival (months)
Exemestane, 25 mg/day[31]	2.2 vs 1.2	12.8 vs 11.2	15 vs 12.4	40.7 vs 41.9	37.4 vs 34.6	35 vs 36.2	NR vs 28.7[4]
Anastrozole, 1 mg/day[8]	4.2 vs 4.3	8.4 vs 7.9	12.5 vs 12.2	29.7 vs 28.1	42.2 vs 40.3	57.4 vs 59.3	26.7 vs 22.5[3,4]
Letrozole, 2.5 mg/day[14]	6.9 vs 4.2	16.7 vs 12.2	23.6 vs 16.4[4]	10.9 vs 15.3	34.5 vs 31.7	53.4 vs 56.1	25.3 vs 21.5

[a]Complete plus partial response.
[b]Complete plus partial response, plus stable disease greater than or equal to 24 weeks.
[c]Based on data from a pooled retrospective analysis.
[d]Difference is statistically significant, $p \leqslant 0.05$.
NR, not reached.

aldosterone, dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone, testosterone or androstenedione has been noted at the 25 mg dose, suggesting that, at clinically effective doses, exemestane does not inhibit adrenal steroidogenesis or other steroidogenic enzymes.[26,28,19,32] Exemestane does not exhibit affinity for the estrogen receptor, and has very low affinity for the androgen, progesterone and mineralocorticoid receptors.[30] Prolonged treatment with exemestane causes a non-dose-dependent increase in serum luteinizing hormone and follicle stimulating hormone levels.[32,33] This is probably a result of biofeedback at the pituitary level due to reduction in estrogen levels that stimulates the pituitary secretion of gonadotropins. A dose-dependent suppression in plasma sex-hormone binding globulin (SHBG) levels is observed at exemestane doses above 25 mg. Although exemestane has little intrinsic androgenic activity,[28,34] androgenic effects observed with high doses of this agent may result from exposure of the liver to exemestane metabolites (i.e. 17-hydro-exemestane).[30]

Pharmacokinetics

Exemestane is rapidly absorbed and reaches peak concentration approximately 2 h after drug administration.[29] The terminal half-life for exemestane is 18–24 h.[27] The inhibitory effects of exemestane on plasma and urinary estrogen levels can be observed as early as 8–24 h following single-dose administration and persist for 5–7 days.[28,29] With daily administration of exemestane, maximum suppression of estrogen synthesis is reached after 7 days and maintained over time.[32] The long-lasting inhibitory effect of exemestane on estrogen synthesis may be due to the irreversible nature of its enzyme-inactivating properties, rather than its intrinsic pharmacokinetic properties.[29]

Safety and tolerability of exemestane

Safety

The safety of exemestane has been evaluated in five open label, phase I studies in a total of 107 postmenopausal breast cancer patients.[26,32,33,35–39] Dosages as high as 600 mg daily and 1200 mg weekly (well above the level of maximal estrogen inhibition) were not associated with major adverse events, and the maximum tolerated dose was not reached in any of these studies. Although the exact therapeutic index of exemestane remains undefined, this agent is associated with a large therapeutic window.

Tolerability

Safety data from two open label phase I studies,; five open label, uncontrolled phase II studies, and one phase III study in postmenopausal patients with breast cancer progressing under previous hormonal therapy, totaling 1058 patients, are compiled in Table 3.[31–33,37,39–43] (PNU data on file; Lonning, in preparation). Treatment-emergent adverse events either drug-related or of indeterminate cause were reported in 47.5% of patients. Adverse events occurring in greater than 10% of patients include hot flushes (14%) and nausea (11.9%). Androgenic effects including alopecia (2%), dysphonia (below 1%) and hypertrychosis (below 1%) were observed in a limited number of patients (4.3%). (Dysphonia and hypertrycosis were only seen at doses of 100 mg and above.) The percent

Table 3. Exemestane 25 mg daily: drug-related or of indeterminate cause treatment-emergent adverse events in phase I, II and III studies[a]

Body system/adverse event	NCI-CTC grade 1–4 (%)
Any event	503 (47.5)
Hot flushes	148 (14)
Nausea	126 (11.9)
Fatigue	81 (7.7)
Dizziness	59 (5.6)
Increased sweating	59 (5.6)
Headache	49 (4.6)
Cardiovascular	38 (3.6)
Insomnia	37 (3.5)
Pain	36 (3.4)
Rash	30 (2.8)
Abdominal pain	29 (2.7)
Musculoskeletal	28 (2.6)
Anorexia	27 (2.6)
Vomiting	28 (2.6)
Depression	25 (2.4)
Reproductive[b]	21 (2.0)
Alopecia	21 (2.0)

[a]Events occurring in 2% or more of a total of 1058 evaluable patients.
[b]Including disorders of the breast and vagina.
NCI-CTC = National Cancer Institute–Common Toxicity Criteria.[31–33,37,39–43]
(PNU data on file; Lonning, in preparation).

Table 4. Exemestane 25 mg daily: drug-related or of indeterminate cause treatment-emergent grade 3/4 adverse events in phase I, II and III studies[a]

Body system/ adverse effect	NCI-CTC Grade 3 (%)	NCI-CTC Grade 4 (%)
Any adverse event	41 (3.9)	2 (0.2)
Autonomic nervous	5 (0.5)	–
Body as a whole	8 (0.8)	1 (0.1)
Cardiovascular	4 (0.4)	–
Central and peripheral nervous	6 (0.6)	–
Gastrointestinal	9 (0.9)	1 (0.1)
Heart rate and rhythm	2 (0.2)	–
Liver and biliary system	1 (0.1)	–
Metabolic and nutritional	2 (0.2)	–
Psychiatric	2 (0.2)	–
Respiratory	2 (0.2)	–
Skin and appendages	3 (0.3)	–
Urinary	1 (0.1)	–
Vascular (extracardiac)	1 (0.1)	–

[a]Total of 1058 evaluable patients.
NCI-CTC = National Cancer Institute–Common Toxicity Criteria[31–33, 37, 39–43] (PNU data on file; Lonning, in preparation).

of patients experiencing Grade 3 and 4 events was 3.9 and 0.2%, respectively (Table 4). Discontinuation of treatment because of adverse events is uncommon with exemestane. At the 25 mg dose, 11 patients (1%) withdrew from treatment due to drug-related adverse events. Estrogen depletion can have deleterious effects on bone mineralization, resulting in osteoporosis and an increased risk of fracture. Although exemestane lowers plasma estrogen to almost undetectable levels, a low incidence of fracture is associated with use of this agent. In comparative studies versus megestrol acetate, the incidence of pathological fractures was low (around 3%) and was similar in both groups (PNU data on file). In patients with metastatic disease, however, the duration of estrogen deprivation is not long enough to adequately address this issue. Adjuvant studies will more clearly define the impact of exemestane on bone density.

Exemestane also demonstrated excellent safety and tolerability in several high-dose studies. Two phase II studies assessed exemestane at a 100 mg, once-daily dose in a total of 73 postmenopausal breast cancer patients.[40] (Lonning, in preparation). Adverse events that were considered drug-related or of indeterminate causation occurred in 46.6% of patients. The most frequently reported adverse events were hot flushes (9.6%), nausea (8.2%) and alopecia (6.8%). Two patients discontinued therapy with one withdrawal considered drug-related.

A phase II multicenter, multinational trial assessed the efficacy of exemestane 200 mg daily in 80 patients failing multiple hormonal therapies.[43] Adverse events were mild to moderate and occurred in 76.9% of patients. Hot flushes (20.5%), nausea (19.2%), sweating (12.8%), weakness and dizziness (11.5%), and alopecia (10.3%) were the most frequently reported side effects. Discontinuation rates were low (3%), with only one case (roughly 1%) attributed to study drug. The high tolerability of exemestane is validated by the high degree of compliance (above 80%) noted during phase III study (see next section).[31]

Current clinical experience with exemestane suggests no evidence of emergence of different adverse events following prolonged exemestane administration (182 weeks; 3.5 years) than those observed in the first 6 months of therapy. In spite of long-term treatment (31 weeks) with 200 mg of exemestane daily, clinical signs of hypertricosis have been mild and evident in only a few patients (5%).[26,43]

Estrogen is known to reduce the risk of cardiovascular disease; estrogen's protective effects are most likely mediated through changes in plasma concentrations of cholesterol.[44] Therefore, decreasing endogenous estrogen levels may affect plasma lipid levels and, on a long-term basis, result in clinical consequences and potential side effects. Preliminary reports indicated that long-term adjuvant treatment with tamoxifen might reduce cardiovascular mortality. Tamoxifen

decreases total cholesterol (12%) and low-density lipoprotein cholesterol (20%), and increases Apo A1 and plasma triglycerides, effects similar to those observed with estrogen. In contrast, tamoxifen causes a decrease in high-density lipoprotein cholesterol.[38] Escalating doses of exemestane (5 to 200 mg over a 12 week period) result in a decrease in total cholesterol (13%) and high-density lipoprotein cholesterol (32%), apo A1 (25%), and triglycerides (16%)[38] (PNU data on file). The clinical significance of these changes has not been established.

Comparative tolerability

Megestrol acetate. In a phase III controlled study, exemestane was shown to exhibit a better tolerability profile compared with megestrol acetate.[31] Fewer patients experienced drug-related or indeterminate cause adverse events with exemestane compared with megestrol acetate (39.1 and 45.8%, respectively). Side effects associated with exemestane were mild to moderate in severity. The most frequently reported symptoms were low-grade hot flushes, nausea and fatigue, events consistent with the estrogen-suppressive effects of exemestane. Compared with megestrol acetate, significantly more exemestane-treated patients reported hot flushes (12.6 versus 5.0%), nausea (9.2 versus 5%) and vomiting (2.8 versus 0.8%). In contrast, megestrol-treated patients experienced a higher incidence of fatigue (41 versus 27%), sweating (30 versus 16%), dyspnea (12 versus 1%), abdominal pain (17 versus 10%), constipation (10 versus 3%) and increased appetite (23 versus 10%).

Weight gain is a particularly troubling side effect associated with megestrol acetate use. Patients experienced less weight gain with exemestane than with megestrol acetate—the percentage of overweight patients exhibiting a 10% weight gain was 4 and 21.3%, respectively. Megestrol acetate was also associated with more severe (grade 3 or 4) adverse events compared with exemestane; 7.5% of patients receiving megestrol acetate experienced grade 4 events compared with 0.3% of exemestane-treated patients. Thrombotic or thromboembolic events were more frequent in megestrol acetate-treated patients (2%) compared with exemestane (below 1%).[31] (PNU data on file). Withdrawal due to adverse events was significantly more common with megestrol acetate (5.0 versus 1.7%; p=0.011). No deaths occurring during the study were attributed to exemestane use. In contrast, two deaths were considered probably related and one possibly related to megestrol acetate use.

Because palliation is a primary objective of current therapy, side-effect profile and potential impact on quality of life is a serious consideration when selecting therapy. In the phase III study comparing exemestane with megestrol acetate, patients treated with exemestane exhibited a significant improvement in quality of life parameters including global health, physical functioning, role functioning and emotional functioning.[31] In general, this improvement was superior to that reported for megestrol acetate.

Aromatase inhibitors. Although a direct comparison has not been performed, the reversible aromatase inhibitors, anastrozole and letrozole, appear to exhibit a similar tolerability profile to exemestane. The type and frequency of individual adverse events may differ between these agents; however, withdrawal rates in controlled studies are similar-approximately 2% for exemestane, 3% for anastrozole (1 mg daily), and 3 and 5% for letrozole (0.5 and 2.5 mg/day, respectively).[12–14] Both anastrozole and exemestane are better tolerated than megestrol acetate.[31,45]

Since reversible aromatase inhibitors have estrogen agonist activity, they like tamoxifen and progestins may produce thrombotic or thromboembolic events. The incidence of these events is similar between anastrozole and megestrol acetate (3.4 and 4.7%, respectively).[8] In contrast, no increased incidence of thrombotic or thromboembolic events has been associated with the use of exemestane.[31–33,37,39–43] (Lonning, in preparation). Similarly, letrozole use was not associated with thromboembolic events, when compared with megestrol acetate (0 and 9%, respectively)[14] (see Table 1).

Drug–drug and drug–disease interactions

Drug–drug interactions between exemestane and concomitantly administered medications have not been formally investigated, except for the effects of ketoconazole on exemestane pharmacokinetics (PNU data on file). However, since exemestane does not inhibit any of the major cytochrome P450 enzymes (CYP1A2, 2C9, 2D6, 2E1 and 3A4). It is unlikely that exemestane will modify the metabolism of co-administered medications. In addition, exemestane metabolism is not affected by alterations in CYP 3A4. In patients with renal impairment, changes in pharmacokinetics of exemestane were minor suggesting that dose adjustments are not required.

Conclusion

Some of the currently available hormonal therapies for postmenopausal advanced breast cancer may be

associated with a less than optimal tolerability profile, which can negatively impact compliance and quality of life. Due to the palliative intent of current therapy, side effect profiles are important considerations when selecting therapy. Exemestane is a highly selective aromatase inactivator that has shown superior efficacy to standard second-line therapy. Exemestane has demonstrated excellent tolerability and safety in clinical studies, and is associated with improved quality of life compared with megestrol acetate. Pharmacokinetic studies do not indicate the presence of clinically significant drug–drug or drug–disease interactions. Based on the clinical profile, exemestane is a safe and well-tolerated alternative to current therapeutic options for the management of postmenopausal advanced breast cancer. To compare the efficacy and safety of newly available aromatase inhibitors, prospective comparative studies are needed.

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