REVIEW ARTICLE

Drug Safety 1999 Oct; 21 (4): 297-309
0114-5916/99/0010-0297/$06.50/0

Risks and Benefits of Aromatase Inhibitors in Postmenopausal Breast Cancer

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Abstract

Aromatase inhibitors were first reported in the early 1970s and have been used to treat breast cancer since that time. Until recently, essentially the only agent available in this class was aminoglutethimide, a nonspecific inhibitor with multiple adverse effects and drug interactions. Selective and potent aromatase inhibitors are now available (formestane, exemestane, fadrozole, anastrozole and letrozole), and we review the risks and benefits of these agents in order to assist clinicians in making treatment decisions.

Formestane is an injectable steroidal aromatase inhibitor with significant activity against metastatic breast cancer. It has been shown to have similar efficacy and superior tolerability compared with megestrol, and is similar to tamoxifen in the metastatic setting. Exemestane is an oral steroidal aromatase inhibitor. It has been shown to be effective third-line therapy after tamoxifen and megestrol in postmenopausal patients with metastatic breast cancer. All the nonsteroidal (imidazole/triazole) aromatase inhibitors are orally available. Fadrozole has similar activity to megestrol and tamoxifen in the setting of metastasis, but has been shown in phase II trials to inhibit cortisol and aldosterone production. Anastrozole and letrozole have similar toxicity profiles. Compared with megestrol, anastrozole improves overall survival and has superior tolerability. Letrozole is superior to megestrol and aminoglutethimide in terms of overall survival and time to progression, and is also better tolerated.

Although there is a strong rationale for using these agents in the treatment of breast cancer, the information presently available is insufficient to recommend any one agent over another. Direct comparative studies are lacking, and comparing agents across studies is limited by many biases and may not be valid. Formestane is only available as an injection and exemestane is not commercially available in many countries, making these agents more difficult to recommend over the other 3 agents. Fadrozole is less potent and less selective in inhibiting aromatase than letrozole. The efficacies of fadrozole, megestrol and tamoxifen appear to be similar; however, comparative data show no advantage of fadrozole over letrozole. Anastrozole and letrozole are generally considered to be similar agents.

The clinical future of the selective aromatase inhibitors is promising, and these agents may change the way postmenopausal breast cancer is treated at all stages of the disease.

Aromatase inhibitors are a growing class of endocrine agents used to treat postmenopausal breast cancer. They are effective inhibitors of the enzyme responsible for conversion of androgen precursors to estrone and estradiol in peripheral tissues. In postmenopausal women, this conversion is the main source of estrogen and occurs mainly in adipose and muscle tissue. The breast also synthesises estrogen and may contribute to the high local levels of estrogens found in approximately 60% of breast tumours, as well as in epithelial and stromal cells of the healthy breast.[1]

Aminoglutethimide was the first aromatase inhibitor utilised for the treatment of breast cancer, but was first used as an anticonvulsant and only later found to inhibit steroid synthesis and reduce estrogen production. The first selective aromatase inhibitor developed for the treatment of breast cancer was formestane (4-hydroxyandrostenedione, 4-OHA). This class of agents is often subdivided into steroidal (formestane and exemestane) and nonsteroidal (aminoglutethimide, fadrozole, anastrozole, letrozole and vorozole) compounds.

In this review, the clinical risks and benefits of the available aromatase inhibitors are discussed and compared, both with each other and with other endocrine agents available for the treatment of breast cancer. This is not meant to be an exhaustive review of this class of drugs, but rather is intended to assist clinicians with decisions regarding endocrine therapy for postmenopausal breast cancer patients. Vorozole will not be undergoing further clinical investigation, is no longer available for clinical use and is not discussed further in this manuscript.

1. Pharmacodynamic/Pharmacokinetic Properties

Differences between the aromatase inhibitors are clinically apparent in their binding affinity to and selectivity for the aromatase enzyme and in their pharmacokinetic properties, especially relating to their oral bioavailability.

Aminoglutethimide was the first aromatase inhibitor to be utilised for the treatment of breast cancer. It is a nonsteroidal, nonspecific aromatase inhibitor that requires concurrent glucocorticoid replacement and is associated with multiple adverse effects (e.g. somnolence, rash and nausea).[2] The nonspecific nature of its enzyme inhibition leads to adrenal insufficiency when concurrent glucocorticoid replacement is not given. The newer generation of agents are selective inhibitors, are more potent (greater binding affinity), and have less toxicity than aminoglutethimide. Aminoglutethimide is metabolised by the cytochrome P450 (CYP) enzyme system and inhibits many of the CYP enzymes responsible for drug metabolism, causing multiple problems with drug interactions.[3] Overall, the adverse effects associated with aminoglutethimide are more severe than with other aromatase inhibitors, and the availability of newer, more effective, less toxic agents with little possi-

bility for drug interactions limits the usefulness of this product.

Steroidal aromatase inhibitors (formestane and exemestane) are derivatives of androstenedione and retain androgenic properties. The binding of these molecules to the enzyme binding site is believed to be irreversible, requiring synthesis of new enzyme to overcome this inhibition even after the drug has been cleared from the body.[4] This is referred to as 'suicide' inhibition and is believed to prolong drug action and potentially improve the risk-benefit ratio for these agents. However, the androgenic properties of these drugs are seen clinically at high dosages, which may offset the potential for clinical benefit.[5,6] These agents do not have any known clinically significant drug interactions, but such interactions have not been investigated to date with either drug. Formestane and exemestane are metabolised by the CYP enzyme system.[5,6]

Nonsteroidal aromatase inhibitors are either derivatives of aminoglutethimide (e.g. rogletimide) or imidazole/triazole derivatives (fadrozole, anastrozole, letrozole) that coordinate with the haem complex of the aromatase enzyme without affecting other enzymes required for steroidogenesis.[7] This binding is reversible and these drugs do not possess any androgenic or other intrinsic hormonal properties. Many analogues of aminoglutethimide have been investigated with little success or improvement over other available compounds. These agents are not currently available for clinical use and are not discussed further in this manuscript.

Compared with letrozole, fadrozole is less specific in its binding to aromatase and suppresses cortisol and aldosterone production at higher dosages.[8] Drug interactions are minimal with anastrozole and letrozole.[9,10] However, extensive testing has not been accomplished to date. Pharmacokinetic data regarding an interaction between letrozole and tamoxifen warranted a change in an adjuvant combination trial to a sequential design with 3 years of letrozole and 2 years of tamoxifen therapy or the reverse sequence.[11] Tamoxifen was found to decrease the plasma concentration of letrozole when given concurrently. There does not appear to be a pharmacokinetic interaction between anastrozole and tamoxifen.[12] Preclinical animal data show both positive and negative results when combining aromatase inhibitors with tamoxifen.[1,13,14] Ongoing clinical trials will determine the clinical utility of these combinations.

There is a great deal of available information regarding the pharmacokinetics of these agents. Clinically relevant facts that differentiate these drugs include elimination half-life, which determines the frequency of administration, and oral bioavailability. The fact that formestane must be injected every 2 weeks because of its poor oral bioavailability may be somewhat inconvenient for some patients, although compliance is assured.[15] Formestane is active by both the oral and intramuscular routes. When given orally, it undergoes extensive first-pass metabolism, and estrogen suppression appears to be less than with the parenteral route.[5] These facts need to be considered when making treatment decisions, as the injectable route is the recommended route of administration. Of the orally bioavailable agents (exemestane, fadrozole, letrozole and anastrozole), anastrozole and letrozole have near-complete bioavailability.[16,17] Exemestane is 60% orally bioavailable, but so far there are no comparative data to indicate whether this difference is clinically significant.[6] Fadrozole has a shorter half-life than the other drugs and is the only agent that requires twice-daily administration; exemestane, letrozole and anastrozole require once-daily administration. The liver extensively metabolises all of these agents; dosage adjustments are not required in patients with renal impairment and are not required unless the patient has severe hepatic impairment. Other available data regarding the pharmacokinetics of these agents are reviewed elsewhere and are beyond the scope of this article.

2. Tolerability

Risks associated with drug therapy often relate to adverse effects experienced secondary to treatment. Adverse events experienced with endocrine

agents should be compared with those from drugs in the same class, from drugs in other classes (e.g. progestins and androgens), and, ultimately, from tamoxifen. For many years, tamoxifen has been the standard front-line endocrine therapy for the treatment of metastatic breast cancer in postmenopausal women. Furthermore, adjuvant endocrine therapy in postmenopausal patients has historically consisted of tamoxifen. Recently, results from adjuvant clinical trials have indicated an additional benefit from the addition of chemotherapy for some postmenopausal patients.[18] Because of more frequent adverse effects, aminoglutethimide was usually reserved for third-line therapy after a tumour had progressed on megestrol, the standard second-line hormonal therapy at that time. Compared with aminoglutethimide, newer agents in this class are better tolerated and do not require replacement corticosteroids, making them more desirable to patients and clinicians (table I).

Formestane has been associated with hot flashes, difficulty sleeping, rash and facial swelling. These effects are generally mild and tolerance may develop. Local injection site reactions and sterile abscesses at the injection site have been reported.[25] These appear to be related to the intramuscular injection of higher volumes of solution (500 mg/4ml) utilised in dose-finding studies.[26] Cases of anaphylactic reactions have been reported secondary to inadvertent intravenous administration.[5] Formestane has been compared with megestrol and appears to be better tolerated in terms of less bodyweight gain and fewer serious thromboembolic events.[27] Formestane has also been compared with tamoxifen as first-line endocrine therapy for metastatic breast cancer. Both agents were well tolerated. The only differences were seen in injection site reactions with formestane that were mild and transient.[19] Formestane is approved in many countries, but is not available for use in the US.

Exemestane appears to be more potent compared with formestane.[20,28] Phase II data with exemestane in breast cancer patients resistant to tamoxifen demonstrated a generally well tolerated agent, with hot flashes, dizziness, nausea, and increased sweating reported with its use.[29] In this trial only 3% of patients discontinued therapy secondary to adverse events. There are no data available comparing exemestane with megestrol or tamoxifen. However, ongoing trials are being conducted to compare these agents. Exemestane is approved for clinical use in some countries, but is not yet available in the US.

Fadrozole has been compared with megestrol and tamoxifen in patients with metastatic breast cancer. Two parallel, randomised, controlled multiinstitutional studies compared megestrol with fadrozole.[22] Fadrozole was associated with less dyspnoea and oedema; however, aldosterone levels were more frequently suppressed in the fadrozole arms of these studies (fadrozole 46.6% *vs* megestrol 25%). In 2 studies conducted separately, tamoxifen and fadrozole were compared as frontline therapy for metastatic breast cancer.[30,31] In 1 study fadrozole was found to be better tolerated than tamoxifen, demonstrating a lower percentage of clinically relevant adverse effects (World Health Organization grade ≥2).[30] Severe cardiovascular events (thromboembolic) were seen only in patients on tamoxifen. In the other comparative study, fadrozole and tamoxifen had similar adverse events associated with their administration.[31] This study was smaller than the previous study (74 *vs* 211 participants) and may not have had enough statistical power to detect subtle yet important differences between these agents. Issues related to endometrial changes were not addressed in either study. Fadrozole is approved in Japan as a 1mg tablet given twice daily; however, it is not available in the US.

Anastrozole has been compared with formestane in postmenopausal patients with advanced breast cancer. These data are available in abstract form, address only estrogen suppression and do not refer to adverse events.[32] Therefore, comparisons regarding tolerability cannot be made. Efficacy comparisons between anastrozole and formestane are discussed in section 3.3. Anastrozole was compared with megestrol in 2 large, randomised, multi-

centre, parallel studies and demonstrated superior tolerability.[23] These studies compared anastrozole 1 (n = 262) and 10 mg/day (n = 246) to megestrol 160 mg/day (n = 253). Bodyweight gain associated with megestrol was significantly greater than with anastrozole (anastrozole 1 mg/day 2%, megestrol 12%). Other adverse effects associated with anastrozole were asthenia, nausea, headache, hot flashes, pain and back pain. These were mild to moderate in severity, and only 2.7% of patients receiving anastrozole 1 mg/day and 3.3% of patients receiving anastrozole 10 mg/day discon-

Table I. Common adverse events of the aromatase inhibitors

Adverse event	Percentage of patients experiencing event with:				
	formestane[19]a	exemestane[20,21]b	fadrozole[22]c	anastrozole[23]d	letrozole[24]e
Abdominal pain		7	7-9		6
Anorexia			9-20		5
Anxiety			7-9		
Arthralgias			3-11		13
Asthenia			6-11	16	4
Back pain				11	
Bodyweight increase				2	2
Bone pain/pain				7/11	-/3
Chest pain					7
Constipation			13-14		7
Diarrhoea		4	10-11		6
Discontinued therapy[f]	2[g]	0-3	6-7	3	3
Dizziness		2-9	6-7		3
Dyspepsia		16			5
Dyspnoea/cough			7-15	9	9/8
Fatigue/lethargy	2		16-20		11/-
Gastrointestinal disturbances				29	
Hot flashes/flushing	8	2-20	12-15	12-13	6
Headaches		1-17	7-15	13	13
Hypercalcaemia		1-			
Increased sweating		1-5			
Injection site reactions					
inflammation	3	NA	NA	NA	NA
nodules/pain	1-3	NA	NA	NA	NA
Musculoskeletal pain			8-12		27
Nausea	2	8-20	22-36	16	11
Peripheral oedema			12	5	9
Rash/pruritis	1	2	6-12		6/2
Thromboembolic disease				3	
Vaginal dryness				2	
Vomiting			9-18	9	7

a 250mg intramuscularly every 2 weeks.
b Variable dosages orally daily.
c 1mg orally twice daily.
d 1 mg orally daily.
e 2.5 mg orally daily.
f Patients who discontinue therapy secondary to adverse events.
g Local site reactions only.
NA = not applicable.

tinued therapy because of adverse events. Anastrozole is approved in many countries as a 1mg tablet to be taken daily.

Letrozole underwent a similar comparison in a trial investigating letrozole 0.5 and 2.5 mg/day and megestrol 160 mg/day.[24] This trial was a double-blind, multicentre, randomised comparison. The most common adverse events considered to be letrozole-related were nausea (2.5mg 6%, 0.5mg 11%), headache (2.5mg 7%, 0.5mg 6%), peripheral oedema (2.5mg 6%, 0.5mg 3%), hot flashes (2.5mg 5%, 0.5mg 5%) and fatigue (2.5mg 5%, 0.5mg 4%). Significantly more cardiovascular events were experienced in the megestrol arm of the study (20%) compared with the letrozole 2.5 mg/day (10%, $p = 0.02$) or 0.5 mg/day (11%, $p = 0.02$) arms. More patients experienced a serious adverse event (death, life-threatening, hospitalisation) with megestrol (29%) compared with letrozole 2.5 mg/day (10%) or letrozole 0.5 mg/day (15%). Overall, only 3% of patients in the letrozole 2.5 mg/day arm and 6% of patients in the letrozole 0.5 mg/day arm discontinued therapy because of poor tolerability. Letrozole is approved in many countries at the 2.5 mg/day dosage.

Letrozole has also been directly compared with aminoglutethimide in a randomised multicentre study. This trial demonstrated the difference in tolerability and efficacy between the 2 aromatase inhibitors (table I).[33] Anastrozole and letrozole are currently part of comparative clinical trials with tamoxifen in the metastatic and adjuvant settings. These trials are also investigating the question of combined endocrine therapy with tamoxifen and anastrozole or letrozole. Adverse events may be worse with the combination regimens and will need to be carefully evaluated.

To date, the only endocrine therapy with sufficient data in the adjuvant setting to warrant its use is tamoxifen; with this drug, therapy is usually continued for 5 years.[34] The long term adjuvant use of aromatase inhibitors remains to be defined. Adverse effects of therapy that may alter other aspects of health become concerning for women who are more likely to be cured of their breast cancer. The long term risks related to absolute estrogen deprivation, beyond that which is achieved by natural menopause, relate to cardiovascular disease, serum lipid levels and bone integrity. There are currently no data available to determine the risk for developing osteoporosis, cardiovascular disease and/or hyperlipidaemia with the long term administration of these potent and selective aromatase inhibitors. Ongoing trials will address these issues and results are eagerly awaited. The use of bisphosphonates in the adjuvant setting to prevent bone loss and possibly prevent bone metastases is intriguing and may be an option to overcome at least 1 obstacle to long term therapy with the aromatase inhibitors.

3. Therapeutic Benefits

The therapeutic effects of the aromatase inhibitors can be measured in many different ways. Measurement of plasma or urinary estrogen suppression and direct measurement of *in vivo* aromatisation are biochemical methods of determining therapeutic effect in the absence of clinical response data.[35] Some agents in this class have data available regarding only 1 of these measurements. Correlation of these measurements with clinical efficacy has not yet been accomplished and may vary with different patient or tumour characteristics. Theoretically, the level of plasma estrogen suppression or aromatase inhibition should correlate with efficacy, but this has not yet been proven. Ultimately, however, the only reliable measure of efficacy is clinical response to therapy.

3.1 Estrogen Suppression

Correlations between estrogen suppression and clinical activity have not been established to date; however, because of the absence of comparative response data between the aromatase inhibitors, estrogen suppression is often utilised as a surrogate marker for clinical activity. Until recently, the assay for detection of estradiol in plasma was not sensitive enough to detect the very low levels produced when potent aromatase inhibitors are present. With a new ultrasensitive assay, this information is now available for most of these agents.[36]

Formestane (500 or 250mg intramuscularly) is effective in suppressing 60% of estrogen production with the initial dose; however, this suppression decreases with subsequent administration to approximately 50%.[28] Exemestane 25mg suppresses serum estradiol and estrone levels to 60 to 76% of control.[20,21] Blood estradiol and estrone levels were suppressed by 38 to 54% with fadrozole at dosages ranging from 0.6 to 8mg twice daily.[8] The endocrine effects of anastrozole have been compared with those of formestane in postmenopausal women. Anastrozole 1mg suppresses estrogen to near the level of detection (<3 pmol/L) and is associated with significantly greater estrogen suppression than formestane (79 *vs* 58% reduction, p = 0.0001).[32] Anastrozole has also been studied in higher doses (up to 10mg), but 1 mg/day produces maximal estrogen suppression. Letrozole 0.5 and 2.5mg suppress estrogen levels by over 90% (to <0.5 pmol/L).[36]

3.2 *In Vivo* Aromatisation

Another method for measuring the endocrine effects of the aromatase inhibitors is to measure urinary estrogens after injection of [^{3}H]androstenedione and [^{14}C]estrone.[37] This directly estimates the degree of aromatase inhibition. Correlations between plasma estrogen levels and degree of aromatase inhibition have not yet been made, but provide different information. Associations between either of these surrogate end-points and clinical efficacy have yet to be identified. Formestane suppresses aromatisation by 86 to 92% from baseline levels.[38] Letrozole and anastrozole inhibit aromatase by >99 and 96% from baseline, respectively.[39,40] Data are not available regarding *in vivo* aromatisation in humans with fadrozole and exemestane.

3.3 Metastatic Breast Cancer

Comparing endocrine therapies is difficult, at best, without direct comparative data to establish the relative safety and efficacy of these agents. Most of the studies incorporating aromatase inhibitors into therapy for metastatic breast cancer are executed in similar patient populations, but subtle differences are important to establish equal patient characteristics and to ultimately compare agents across studies (table II). This should be kept in mind when evaluating any data and is important in the context of decision making.

In a non-blind, comparative, randomised trial of formestane versus megestrol, both agents were found to have similar efficacy as second-line therapy in postmenopausal patients with advanced breast cancer (table II).[27] Overall response rates were 16.3% with formestane and 20.3% with megestrol, and time to progression and overall survival were similar between groups. Compared with tamoxifen as front-line therapy for postmenopausal metastatic breast cancer patients, formestane demonstrated similar response rates (formestane 33% *vs* tamoxifen 37%), but significant differences in time to progression and time to treatment failure favoured tamoxifen.[19]

Most of the studies with formestane have included patients who have demonstrated a response to tamoxifen or another endocrine therapy and patients with *de novo* endocrine resistance. In 1 small study, formestane was administered to patients with *de novo* tamoxifen-resistant metastatic breast cancer and demonstrated response rates of 33% with a median duration of response of 9.5 months.[41] Differences in mechanism of action between tamoxifen and formestane may account for this benefit. Formestane therapy following aminoglutethimide has also been investigated with a response rate of 29%. Patients who responded to formestane in this trial had both previously responded and then relapsed on aminoglutethimide or failed to respond to aminoglutethimide.[42] This benefit may be due to the more selective and potent inhibition of aromatase by formestane compared with aminoglutethimide, or may represent the indolent natural history of hormonally-sensitive breast cancer.

Exemestane is currently undergoing clinical trials in comparison with megestrol and tamoxifen. Exemestane has also been investigated as third-line therapy in the treatment of postmenopausal

women with metastatic breast cancer refractory to tamoxifen and megestrol. In this setting, response rates were 13% and an additional 16% of patients had stable disease for ≥6 months.[43] Exemestane has also been investigated in postmenopausal patients with tamoxifen-resistant metastatic breast cancer (n = 134) with an overall response rate of 22% [95% confidence interval (CI) 16 to 30%].[29] A further 42 patients (31%) had stable disease for ≥24 weeks. This study included women who were unresponsive to tamoxifen (n = 12), progressed after initial response to tamoxifen (n = 54), recurred

Table II. Clinical trials of the therapeutic efficacy of the aromatase inhibitors

Study	n	Comparator drug	Overall response (complete + partial) [%]	Stable disease for ≥24wk (%)	Patient population/comments
Formestane					
Perez Carrion et al.[19]	409	Tamoxifen	Formestane 33 *vs* tamoxifen 37	NA	First-line metastases
Rose et al.[27]	547	Megestrol	Formestane 16.3 *vs* megestrol 20.3	Formestane 34.4 *vs* megestrol 32.8	Second-line metastases
Noberasco et al.[41]	24		33	NA	Tamoxifen-resistant; second-line metastases
Murray & Pitt[42]	112		21	22	Prior aminoglutethimide; multiple prior therapies, metastases
Exemestane					
Kvinnsland et al.[29]	134		22	31	Tamoxifen-resistant; second-line metastases
Jones et al.[43]	91		13	16	Third-line metastases; refractory to tamoxifen and megestrol
Fadrozole					
Buzdar et al.[22]	677	Megestrol	Fadrozole 11.3-13.4 *vs* megestrol 10.7-16.3	NA	Second-line metastases
Thurlimann et al.[30]	209	Tamoxifen	Fadrozole 20 *vs* tamoxifen 27	NA	First-line metastases; time to treatment failure longer with tamoxifen (6.1 *vs* 8.5 mo, p = 0.05)
Falkson & Falkson[31]	74	Tamoxifen	Fadrozole 50 *vs* tamoxifen 44.7	NA	First-line metastases; response duration longer with tamoxifen (343 days *vs* not reached, p = 0.009)
Anastrozole					
Buzdar et al.,[23] Howell et al.[44]	516	Megestrol	Anastrozole 10.3 *vs* megestrol 7.9	Anastrozole 25.1 *vs* megestrol 26.1	Second-line metastases; improved survival with anastrozole (hazard ratio 0.78, p = 0.02)
Letrozole					
Dombernowsky et al.,[24] Smith et al.[45]	363	Megestrol	Letrozole 23.6 *vs* megestrol 16.4	Letrozole 10.9 *vs* megestrol 15.3	Second-line metastases; improved survival with letrozole (hazard ratio 0.82, p = 0.15)
Marty et al.,[33] Smith et al.[45]	363	Aminoglutethimide	Letrozole 17.8 *vs* aminoglutethimide 11.2	NA	Second-line metastases; improved survival with letrozole (hazard ratio 0.68, p = 0.02)

n = number of patients; **NA** = not assessed.

with metastatic disease within 12 months of discontinuation of adjuvant tamoxifen (n = 34) or had unevaluable tamoxifen response (n = 34). Of the women who were unresponsive to tamoxifen, 25% demonstrated an objective response to exemestane. This is important information that refutes the dogma of abandoning endocrine therapy at the first sign of progression.

Fadrozole has been compared with megestrol as second-line therapy and with tamoxifen as first-line therapy for metastatic breast cancer. In the 2 large randomised studies (protocols 03 and 06) comparing megestrol and fadrozole, the overall response rates were comparable (protocol 03: fadrozole 11.3%, megestrol 16.3%; protocol 06: fadrozole 13.4%, megestrol 11.5%).[30,31] Duration of response appeared to be slightly longer with megestrol compared with fadrozole; however, time to progression and overall survival were no different between the groups. Two randomised comparisons of fadrozole to tamoxifen have been completed and have slightly different results. The Swiss trial[30] demonstrated similar response rates between the 2 agents (fadrozole 20%, tamoxifen 27%), but time to treatment failure appeared to be longer with tamoxifen, although this difference was not significant (tamoxifen 8.5 months *vs* fadrozole 6.1 months; p = 0.05). There was no difference in overall survival between fadrozole and tamoxifen in this trial. The study conducted in South Africa[31] demonstrated similar response rates that appeared quite high (fadrozole 50%, tamoxifen 44.7%). Time to treatment failure and overall survival were not statistically different between groups, although a trend toward longer survival was seen with tamoxifen (time to treatment failure: fadrozole 4.9 months *vs* tamoxifen 5 months; overall survival: fadrozole 22.7 months *vs* tamoxifen 27.5 months). This study was small (n = 74) and may have shown a statistical difference if the number of patients had been larger. There is probably little difference between fadrozole and tamoxifen in terms of overall benefit for patients with metastatic breast cancer, but there does appear to be a trend towards tamoxifen having superior efficacy compared with fadrozole.

Two large, randomised, phase III trials compared anastrozole 1 and 10 mg/day with megestrol 160 mg/day.[23] The overview analysis of these studies demonstrated an overall response rate of 10.3% with anastrozole 1mg, 8.9% with anastrozole 10mg and 7.9% with megestrol; 25.1, 22.6, and 26.1% of patients, respectively, had stable disease for ≥24 weeks. In a follow-up analysis, anastrozole also demonstrated a significant prolongation of survival compared with megestrol (hazard ratio 0.78; p = 0.02).[44] In a retrospective review of patients with metastatic breast cancer, anastrozole was found to be effective in some patients who were estrogen receptor–negative (benefit 50%, n = 10).[46] This information leads to an interesting issue of endocrine therapy for estrogen receptor–negative tumours. There are data to substantiate the fact that endocrine therapy in general is somewhat effective (approximately 11%) in patients with estrogen receptor–negative disease.[47] This sampling of patients on anastrozole may be coincidental or may be due to the nature of the aromatase inhibition caused by anastrozole. Some breast cancer cells, as mentioned previously, contain aromatase and may be affected by its inhibition, regardless of hormone receptor status.[48]

Letrozole has been compared with megestrol and aminoglutethimide in large randomised phase III trials.[24,33] Response rates with letrozole were superior to that seen with megestrol and aminoglutethimide (letrozole 24% *vs* megestrol 16%, p = 0.04; letrozole 17.8% *vs* aminoglutethimide 11.2%, p = unknown). Letrozole 2.5 mg/day showed a significant prolongation of survival compared with aminoglutethimide (hazard ratio 0.68, 95% CI 0.50 to 0.94, p = 0.02), but the difference in survival compared with megestrol, although improved, was not significantly better (hazard ratio 0.82, 95% CI 0.63 to 1.08, p = 0.15).[24,45] A subset analysis of patients with visceral disease was performed in these studies and demonstrated a response rate of 18 to 24% with letrozole, 16% with megestrol and 11% with aminoglutethimide.[49]

The goals of therapy in patients with metastatic breast cancer are palliation of symptoms and prolongation of life. The success or failure of a therapy in this setting has historically been measured in terms of documented objective responses of bidimensionally measurable lesions. This definition is often not adequate when investigating endocrine therapies. Disease sites often include bone, which is difficult to assess, and clinical benefit may be demonstrated with relief of symptoms or stabilisation of disease for prolonged periods of time. Also, studies indicate that patients who have stabilisation of disease for prolonged periods of time (>5 months) have similar time to progression and overall survival as patients who achieve complete or partial responses.[50,51] Many trials with the new generation aromatase inhibitors have included patients with prolonged stabilisation of disease (≥6 months) in the benefit/responders group. This is controversial, but appears to be reasonable in regard to the goals of therapy (table III).

Patients with tumours that are estrogen receptor–positive or of unknown status are more likely to respond to endocrine therapy and are the largest patient population included in most trials of endocrine therapy for metastatic breast cancer. Historically, patients with bone or soft tissue metastases are also more likely to respond to therapy compared with patients with visceral disease; however, newer agents may demonstrate efficacy in visceral dominant disease as well. If a patient fails to respond to front-line therapy with tamoxifen, most clinicians would abandon endocrine therapy and move to chemotherapy. This practice may not be justified in light of the activity seen with selective aromatase inhibitors in tamoxifen-resistant disease.

3.4 Adjuvant Therapy of Breast Cancer

Results from trials in metastatic breast cancer patients have led to the investigation of anastrozole and letrozole in the adjuvant setting. A large randomised, multicentre, international trial comparing anastrozole with tamoxifen and with the combination (the ATAC trial) is currently underway with a planned accrual of 6000 patients. Patients will receive anastrozole 1mg for 5 years, tamoxifen 20mg for 5 years or the combination for 5 years. Letrozole is also being investigated in this setting in a trial originally designed to compare 5 years of tamoxifen 20mg with 5 years of letrozole 2.5mg [the FEMTA (Femara/Tamoxifen Adjuvant) trial]. This trial is being amended to incorporate the Breast Cancer International Group (BIG) and will include a 4-arm randomisation to tamoxifen for 5 years, letrozole for 5 years, tamoxifen for 2 years followed by letrozole for 3 years, or the reverse sequence (FEMTA/BIG). A third trial to be conducted by the National Cancer Institute of Canada will investigate the addition of letrozole versus placebo after 5 years of tamoxifen adjuvant therapy. This trial may demonstrate an advantage of the new aromatase inhibitors in late relapsing patients (>5 years after diagnosis). Data from these comparative trials may change the way breast cancer therapy is treated in postmenopausal women.

Table III. Comparative efficacy of aromatase inhibitors versus megestrol

Parameter	Formestane[27]		Fadrozole[22]		Anastrozole[23,44]		Letrozole[24,45]	
	formestane	megestrol	fadrozole	megestrol	anastrozole	megestrol	letrozole	megestrol
n	547 total	547 total	345	332	263	253	174	189
Overall response (%)[a]	16.3	20.3	11.3-13.4	10.7-16.3	10.3	7.9	23.6	16.4
Progressive disease (%)	37	33.6	62.7-64.1	58.8-64.1	54	54	53.4	56.1
Median overall survival	561 days	597 days	814 days	692 days	26.7mo	22.5mo	25.3mo	21.5mo
					(HR 0.78, p = 0.02)		(HR 0.82, p = 0.15)	

a Complete + partial.

HR = hazard ratio; **n** = number of patients.

Table IV. Risks and benefits of the aromatase inhibitors

Feature	Aminoglutethimide	Formestane	Exemestane	Fadrozole	Anastrozole	Letrozole
Risks						
Drug interactions[a]	!!!	!	!	!	!	!!
Administration[b]	!!!	!!	!	!	!	!
Tolerability[c]	!!!	!	!	!	!	!
Benefits						
Estrogen suppression[d,e]	+	++	+++	+++	++++	++++
Clinical efficacy in metastatic breast cancer[e]	+	++	+++	+++	++++	++++
Clinical efficacy in adjuvant therapy of breast cancer	Not applicable	No data	No data	No data	Ongoing trials	Ongoing trials

a **!** Indicates minimal interactions/little data; **!!** indicates significant documented interactions; **!!!** indicates multiple documented interactions.

b **!** Indicates minimal toxicity related to administration; **!!** indicates moderate toxicity related to administration; **!!!** indicates complex administration.

c **!** Indicates mild to moderate adverse events; **!!** indicates moderate to severe adverse events, but low incidence; **!!!** indicates moderate to severe adverse events, but high incidence.

d Based on estrogen suppression and *in vivo* aromatisation data when available.

e + Indicates least effective, ++++ indicates most effective, relative to each other.

4. Conclusions

The risk-benefit ratio for all of the new aromatase inhibitors is quite acceptable. With the exception of aminoglutethimide, this class of agents is well tolerated and appears to be very effective. There should be little doubt that these agents are useful in the treatment of breast cancer.

The question regarding comparative information is controversial, and there are not enough data to warrant the use of any one agent over the other (table IV). Care should be taken when comparing agents across studies, as these comparisons are fraught with bias and may not be accurate. Based on method of administration alone, formestane would not be an optimal choice because of the inconvenience of an injection. Exemestane has the least data to date and is currently not widely available. Fadrozole appears to be similar in terms of response rates to megestrol and tamoxifen; there are concerns regarding the inhibition of cortisol and aldosterone production by fadrozole, but the clinical relevance of this inhibition is not yet evident. From the current data comparing fadrozole with letrozole, there appears to be little advantage of fadrozole over letrozole. Anastrozole and letrozole are very similar agents and choosing between them is difficult in the absence of a direct comparative trial. There are no definitive data to show that either anastrozole or letrozole is superior in terms of efficacy or tolerability. Both agents are superior to megestrol and have longer time to progression (letrozole and anastrozole) and/or survival (anastrozole) compared with megestrol. Ongoing trials comparing anastrozole and letrozole with tamoxifen may help to differentiate between the 2 aromatase inhibitors, but until those data are available both agents should be considered of equal value.

Once the selective aromatase inhibitors have been studied in the adjuvant setting, more data will be available to address the issues of risks and benefits in this patient population. The use of these agents as chemopreventives for breast cancer is also being investigated, but may be less than optimal in light of the long term detrimental effects of total estrogen suppression such as osteoporosis, cardiovascular disease and urogenital atrophy.[52]

These are exciting times, and the aromatase inhibitors hold great promise of positively affecting the lives of postmenopausal women with breast cancer in all stages of the disease.

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