Irreversible aromatase inactivation: treatment for breast cancer

Stephen RD Johnston

Third-generation aromatase inhibitors extend treatment options for postmenopausal breast cancer patients refractory to initial antioestrogen therapy. This article reviews advances and recent developments in hormonal therapy, focusing in particular on exemestane, a new class of aromatase inactivator.

Once breast cancer has metastasized, it is incurable. As most available therapies have not been demonstrated to alter survival, the main goal of hormonal, cytotoxic and radiation therapies has largely been the palliation of tumour-related symptoms. However, the recent introduction of more potent and tolerable hormonal agents now offers the potential for improved survival as well as better palliative outcomes in advanced breast cancer, the second leading cause of cancer-related death in women.

A significant proportion of breast cancers are hormone dependent and are therefore amenable to endocrine therapy. Such therapy plays a pivotal role as first-line therapy for many women because it is generally well tolerated and has been reported to produce similar response rates compared with those produced by chemotherapy in patients who have hormone-receptor-positive disease. Durable responses with median durations of 12 months or more can be achieved with hormonal therapy. It is associated with less morbidity and therefore is preferred to cytotoxic treatment, if clinically appropriate.

EXTENDED TREATMENT OPTIONS

Tamoxifen, a competitive non-steroidal antioestrogen, is the hormonal agent of choice for first-line therapy of metastatic disease. In postmenopausal women with advanced breast cancer, tamoxifen induces objective responses (OR) in about one third of all patients and a high response rate in those with oestrogen receptor (ER)-positive tumours. However, since tamoxifen possesses partial oestrogenic activity, tamoxifen-treated patients may be exposed to a modest increased risk of endometrial cancer. Likewise, the partial agonist activity of tamoxifen can in some patients result in the development of acquired resistance whereby tamoxifen may stimulate tumour regrowth following prolonged therapy.

Although tamoxifen has been the mainstay of treatment for over two decades, new agents are now clinically available which have potentially superior activity together with an improved safety profile, extending the treatment options for postmenopausal patients who have failed anti-oestrogen therapy. After progression of disease on tamoxifen, second-line hormonal therapy traditionally included progestins, usually megestrol acetate (MA). In recent randomized trials, response rates to second-line MA treatment were between 8 and 16% (Thürlimann et al, 1997a; Dombernowsky et al, 1998; Buzdar et al, 1996, 1998). However, MA treatment is associated with troublesome side-effects, including the potential for substantial unwanted weight gain.

More recently, major strides in the management of hormone-sensitive breast cancer have been made with the introduction of orally active, potent and selective third-generation aromatase inhibitors. Data from randomized clinical trials have established their role as the treatment of choice following tamoxifen failure, with significant gains in clinical efficacy together with improved tolerability over progestins.

ENDOCRINE TREATMENT, AROMATASE INHIBITORS AND INACTIVATORS

Two general strategies have been developed for endocrine treatment of hormone-dependent breast cancer: blockade of ER action with antioestrogens, or inhibition of oestradiol biosynthesis with competitive enzyme inhibitors or enzyme inactivators.

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Oestrogen biosynthesis involves a series of steroid hydroxylation steps converting cholesterol to oestradiol. The most important of these involves aromatase, a cytochrome P450 enzyme, which catalyses the rate-limiting step in oestrogen biosynthesis, the conversion of androgens such as androstenedione and testosterone to oestrogens. Expression of ER remains the best determinant of endocrine response, although not all ER+ve tumours are known to be tamoxifen responsive. Recent studies have shown that ER or progesterone receptor (ER/PgR) expression is often maintained following tamoxifen failure, and that this may be an accurate predictor of response to aromatase inhibitors.

There are two classes of aromatase inhibitors: reversible non-steroidal competitive enzyme inhibitors and irreversible steroidal enzyme inactivators (*Figure 1*).

1. Reversible non-steroidal aromatase inhibitors (type II), such as aminoglutethimide, anastrozole, letrozole and vorozole, compete for the substrate on the enzyme's active site, bind reversibly to the haeme site of the enzyme and prevent product formation only as long as the inhibitor occupies this site. Because blockade is reversible, ongoing oestrogen deprivation requires the continued presence of the drug (Brodie and Njar, 1996; Harvey, 1996; Miller, 1996).
2. Irreversible steroidal aromatase inactivators (type I) such as exemestane, also known as 'suicide inhibitors', initially compete with the natural substrates (i.e. androstenedione and testosterone) for binding to the active site of the enzyme. The enzyme then specifically acts upon the inhibitor to yield reactive alkylating species which form covalent bonds at or near the active site of the enzyme, resulting in irreversible inactivation of the enzyme.

Aromatase inhibitor therapy provides complete oestrogen deprivation in postmenopausal women. The third-generation agents — anastrozole, letrozole and exemestane — are significantly more potent than the first-generation non-steroidal inhibitor aminoglutethimide and are highly effective in reducing serum oestrogen levels in postmenopausal women (Plourde et al, 1994; Iveson et al, 1993; Evans et al, 1992). They are also very selective for the aromatase enzyme without affecting mineralocorticoid or glucocorticoid synthesis.

Recent phase III trials have compared these agents with previously used second-line therapies such as progestins or aminoglutethimide in patients with metastatic breast cancer who failed tamoxifen. As well as demonstrating superior clinical activity in terms of response rate, time to progression and overall survival, these agents provide improved tolerability, possibly allowing a major impact on the natural history of endocrine-sensitive breast cancer.

CLINICAL TRIALS: EVALUATIONS AND FINDINGS

Clinicians acknowledge the continuing need to identify well-tolerated methods for controlling this life-threatening illness after failure of established first-line treatment. The aromatase inhibitors anastrozole, letrozole and exemestane have been compared with MA in four international, multicentre, randomized phase III trials as second-line therapy following tamoxifen failure in postmenopausal women with metastatic breast cancer. Also, more than 50% of the study population in all four trials had limited visceral disease.

Each of the randomized trials demonstrated the clinical superiority of the third-generation aromatase inhibitors over MA, with a better safety profile (*Table 1*). Each of these compounds showed some improvement in clinical endpoints over what was considered relatively standard second-line hormonal therapy for the treatment of postmenopausal breast cancer patients.

- In a combined analysis of two randomized studies involving a median follow-up of 31 months, it was found that anastrozole 1 mg daily revealed a significant improvement in overall survival (Buzdar et al, 1998)
- Letrozole 2.5 mg was associated with a significant improvement in response rate,

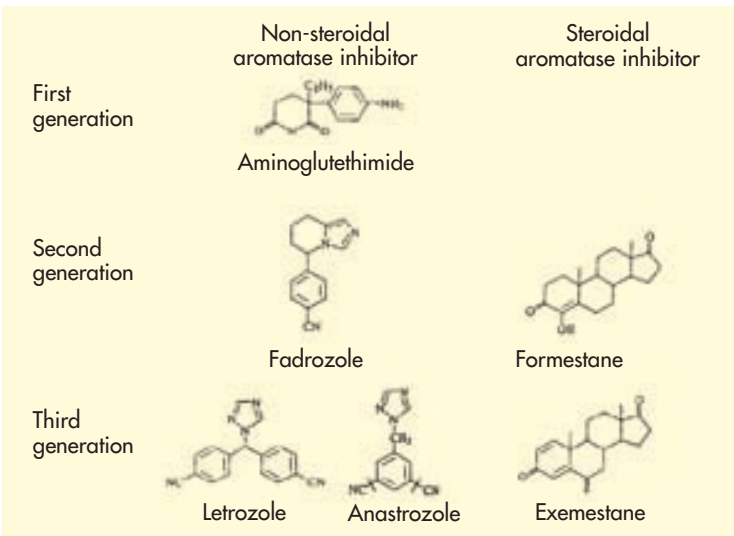

Figure 1. Structures of non-steroidal and steroidal aromatase inhibitors.

response duration and time to treatment failure (TTF), although there was no advantage of survival for letrozole in comparison with MA (Dombernowsky et al, 1998)

- In the study comparing exemestane with MA, time to disease progression, TTF and overall survival were all significantly better than MA (Kaufmann et al, 2000).

The overview analysis comparing anastrozole (1 and 10 mg once daily) with MA was based on a pooled analysis of two randomized trials including a total of 764 women. The trials comparing letrozole (0.5 mg and 2.5 mg respectively) with either MA or with the first-generation non-steroidal inhibitor, aminoglutethimide, involved 552 and 555 patients respectively.

The largest single trial was a double-blind, randomized, multicentre study, which evaluated the efficacy, pharmacodynamics and safety of 25 mg/day exemestane *vs* MA in 769 postmenopausal women with progressive advanced breast cancer who experienced failure of tamoxifen (Kaufmann et al, 2000).

EXEMESTANE: AN OVERVIEW

The results of this prospective evaluation demonstrate significantly improved overall duration of success, longer time to tumour progression (TTP) and TTF, and improved survival with the aromatase inactivator exemestane when compared with MA in the second-line therapy of metastatic breast cancer. The overall OR rates were higher in patients treated with exemestane than in those treated with MA (15.0% *vs* 12.4%); a similar trend was noted in patients with visceral metastases (13.5% *vs* 10.5%).

Median survival time was significantly longer with exemestane (median not reached) than with MA (123.4 weeks; P=0.039), as were the median duration of overall success (OR or stable disease ≥24 weeks; 60.1 *vs* 49.1 weeks; P=0.025), TTP (20.3 *vs* 16.6 weeks; P=0.037), and TTF (16.3 *vs* 15.7 weeks; P=0.042). Compared with MA, there were similar or greater improvements in pain, tumour-related signs and symptoms and quality of life with exemestane. Both drugs were well tolerated. Grade 3 or 4 weight changes were more common with MA (17.1% *vs* 7.6%; P=0.001).

Unlike the results reported with reversible non-steroidal aromatase inhibitors, this phase III study showed a significant prolongation in TTP and TTF with exemestane. With a median duration of follow-up of nearly 12 months, exemestane also demonstrated significantly improved survival times. Investigators reported that exemestane-treated patients had a 23% lower risk of death compared with MA-treated patients when treatment effect was adjusted by the stratification variables using Cox model analysis.

Tolerability was confirmed by the greater than 80% compliance by most patients treated with exemestane and the improvement in quality of life on a number of subscales. In general, this improvement was superior to that reported by women treated with MA. Patients receiving exemestane experienced significant improvements in sense of general wellbeing as well as improved physical and role functioning *vs* MA (P<0.001), significantly less fatigue, constipation and dyspnoea (P<0.001), and improvement in emotional symptoms, appetite loss, and pain, although improvements were even greater with MA (P≤0.01).

TABLE 1.
Clinical efficacy data of three randomized phase III trials each comparing either exemestane, anastrozole or letrozole with megestrol acetate (MA) as second-line hormonal therapy for postmenopausal patients with advanced breast cancer

	Treatment		
Characteristic	Exemestane 25 mg/day *vs* MA 40 mg four times daily	Anastrozole 1 mg/day *vs* MA 40 mg four times daily	Letrozole 2.5 mg/day *vs* MA 160 mg/day
Sample size (no. of patients)	366 *vs* 403	263 *vs* 253	174 *vs* 189
Overall OR* (%)	15.0 *vs* 12.4	12.5 *vs* 12.2	23.6 *vs* 16.4†
Median duration of OR (months)	17.5 *vs* 16.3	Not reported	NR *vs* 17.9†
Overall success‡ (%)	37.4 *vs* 34.6	42.2 *vs* 40.3	34.5 *vs* 31.7
Median duration of overall success (months)	13.8 *vs* 11.3†	Not reported	23.5 *vs* 14.5†
Median TTP (months)	4.7 *vs* 3.8†	4.8 *vs* 4.6	5.6 *vs* 5.5
Median TTF (months)	3.8 *vs* 3.6†	Not reported	5.1 *vs* 3.9†
Median survival (months)	NR *vs* 28.4†	26.7 *vs* 22.5†§	25.3 *vs* 21.5

From Kaufmann et al (2000). NR = not reached; OR = objective response; TTF = time to treatment failure; TTP = time to tumour progression. *complete response + partial response; †Difference is statistically significant (P≤0.05); ‡complete response + partial response + stable disease ≥24 weeks; §Based on data from a pooled retrospective analysis

This trial suggests that exemestane significantly delays tumour progression and prolongs survival compared with MA in postmenopausal patients who become refractory to tamoxifen therapy.

UNIQUE MODE OF ACTION AND LACK OF CROSS-RESISTANCE

Exemestane is the first oral aromatase inactivator for the treatment of postmenopausal women with advanced breast cancer whose tumours stop responding to tamoxifen therapy. Unlike agents currently available, exemestane is the first oral hormonal therapy that binds irreversibly to the aromatase enzyme, an action that interferes with the supply of oestrogen to the cancerous tumours that are dependent on the hormone.

The development of irreversible inactivators is of particular interest because evidence suggests a lack of cross-resistance between them and type II reversible non-steroidal inhibitors (Geisler et al, 1996a; Murray and Pitt, 1995). There have been two recent prospective studies which evaluated exemestane as third-line therapy following failure of a non-steroidal aromatase inhibitor. In a European multicentre study, exemestane 200 mg/day was administered to 78 patients previously exposed to aminoglutethimide. A substantial number, approaching 40% of patients, either achieved an OR or stable disease: study results demonstrated an overall response rate of 26%, and an additional 13% of patients achieved long-term stable disease (Thürlimann et al, 1997b).

Moreover, recently published results of a phase II trial evaluating the activity of exemestane in metastatic breast cancer after failure of non-steroidal aromatase inhibitors demonstrated the safety and antitumour activity of third- or fourth-line therapy with exemestane 25 mg once daily (Lønning et al, 2000). A total of 241 patients were enrolled; 56% had received aminoglutethimide, 19% anastrozole, 17% letrozole and 8% vorozole. Exemestane produced ORs in 6.6% of treated patients, including 8.1% and 4.8% of patients after failure of treatment with aminoglutethimide and other non-steroidal aromatase inhibitors, respectively, and an overall success rate (complete response+partial response+no change for 24 weeks or longer) of 24.3%.

Study authors argued that given the palliative goal of treatment in this setting, it is reasonable to consider disease stabilization (i.e. no change for 24 weeks or longer) as a clinical outcome. They noted that the 24.3% overall success rate suggests a meaningful percentage of patients in this series benefited from treatment with exemestane 25 mg daily. Notably, the duration of OR (median 58 weeks) as well as overall success (median 37 weeks) was substantial. While exemestane was more active in patients with soft tissue disease only, it also had some activity when the predominant disease site was the viscera.

These findings suggest a lack of complete cross-resistance between non-steroidal aromatase inhibitors and steroidal aromatase inactivators. Study investigators concluded that exemestane 25 mg once daily seems to be an attractive alternative to chemotherapy for the treatment of patients with metastatic breast cancer after failure of multiple hormonal therapies, especially for those patients with predominantly soft tissue disease.

Studies have revealed that the degree of total body aromatase inhibition was similar for exemestane (97.9%) (Geisler et al, 1998) compared with anastrozole (96%) (Geisler et al, 1996b) and letrozole (98.9%) (Dowsett et al, 1995). The findings that patients relapsing on potent non-steroidal inhibitors such as anastrozole and letrozole may benefit from therapy with exemestane suggest that alternative mechanisms may be involved other than superior total body aromatase inhibition. One possibility might involve a differential pharmacological influence on the intratumour aromatase enzyme by the different drugs. In particular, following failure of a reversible non-steroidal inhibitor, the aromatase enzyme may remain susceptible to complete inactivation with an irreversible steroidal inactivator such as exemestane. Alternatively, exemestane could also be working through hormonal mechanisms in addition to aromatase inhibition, such as local stimulation of the androgen receptor within the breast tissue.

In all conditions, exemestane maintained oestrogen suppression for at least up to 48 weeks, even when patients developed progressive disease. This suggests that progressive disease was not the result of a loss of oestrogen-suppressing activity of exemestane, but of other mechanisms at the tumour level. Dose escalation to 100 mg maintained but did not suppress oestrogen levels compared with the 25 mg dose, which is consistent with the results of previous studies which showed that maximal suppression occurs at a daily dose of 25 mg.

A lack of cross-resistance between steroidal and non-steroidal aromatase inhibitors may provide the option for their use sequentially in advanced breast cancer at the time of progression.

HORMONAL THERAPY IN BREAST CANCER AND PREDOMINANT VISCERAL DISEASE

The presence of visceral disease still represents a major challenge in the treatment of advanced breast cancer, and is usually an indication for treatment with cytotoxic chemotherapy. However, the latter may be associated with significant toxicity in some patients. Phase II and III clinical trials evaluating exemestane in postmenopausal advanced breast cancer patients suggest its efficacy in patients with visceral disease.

An exploratory analysis of the results of three clinical trials evaluating the efficacy of exemestane in a subset of postmenopausal patients with predominant visceral disease having progressed on antioestrogens suggest that exemestane is active in such patients (Tedeschi et al, 1999). A total of 626 patients received exemestane in two open phase II studies and one randomized, peer-reviewed phase III study; some 53.8%, or 337 patients, had at least once visceral site involved. One lesion in one visceral organ qualified a patient as having predominant visceral disease. Deep nodes were considered as visceral disease.

The overall response rate in the 130 patients enrolled in the phase II studies was 29.2% (95% confidence interval (CI)=21.6–37.8), and 13.5% (95% CI=9.2–19.0) in the 207 patients enrolled in the exemestane arm of the controlled phase III study. The response rate in patients with predominant visceral disease in the phase III study control arm (MA) was 10.5% (95% CI=6.9–15.1).

An analysis by selected measurable-only disease sites (lung and liver) indicated that a total of 27/65 measurable lung lesions (42%, 95% CI=29.4–54.4) responded to exemestane treatment in the phase II programme, as well as 8/55 measurable liver lesions (14%, 95% CI=6.5–26.7). In the phase III programme, the corresponding figures were 25% (95% CI=15.8–36.3) for lung and 19% (95% CI=11.0–29.4) for liver lesions with exemestane, while with the control treatment (MA) the corresponding figures were 17% (95% CI=11.0–29.4) and 11% (95% CI=5.4–18.3).

OR rates in women with predominant visceral metastases range from 32.8% to 13.5% in the three studies evaluated. It was also observed that OR rates in measurable disease sites were higher in women with metastases to the lung *vs* the liver. Also, the 1-year survival difference between exemestane and the control arm in the phase III study is similar in patients with predominant visceral disease and in the overall population (6% and 7% respectively, in favour of exemestane).

FUTURE FIRST-LINE DEVELOPMENTS

The most appropriate management strategy with regard to sequencing of aromatase inactivation remains the subject of much interest and ongoing clinical research, with large randomized trials in progress evaluating the use of these agents as potential first-line options challenging tamoxifen as the first-line agent of choice.

Preliminary data from the trials involving anastrozole in the first-line setting show that there was a significant improvement in TTF in favour of anastrozole in one trial, while there was no difference in primary efficacy endpoints to tamoxifen in the other. Data from the North American, first-line trial comparing anastrozole with tamoxifen in postmenopausal women with advanced breast cancer confirm that anastrozole is at least as effective as tamoxifen for the first-line treatment of advanced breast cancer in postmenopausal women. Both treatments were well tolerated, with a low number of withdrawals because of adverse events. In a recent combined analysis of ER-positive patients from both trials, anastrozole was associated with significantly longer median time to disease progression (10.7 *vs* 6.4 months, P=0.02) (Buzdar et al, 2000).

Full results from these studies will hopefully show whether complete oestrogen blockade provides greater control of tumour growth than tamoxifen and whether this impacts on survival. If they do, this could circumvent the problem of acquired tamoxifen resistance whereby a proportion of ER+ve tumours regrow following an initial response to tamoxifen (Johnston, 1997).

Furthermore, the unique mechanism of action of exemestane has prompted a cooperative cancer study group to begin further study of exemestane. The European Organisation for Research and Treatment of Cancer (EORTC) has recently conducted a randomized pilot phase II trial of exemestane *vs* tamoxifen as first-line hormonal therapy in postmenopausal breast cancer patients. The preliminary data from this trial were presented at the American Society of Clinical Oncology meeting in May 2000, and showed both a higher response and clinical benefit rate for exemestane compared with tamoxifen (Paridaens et al, 2000). The results of the large randomized phase III trial are eagerly awaited.

CONCLUSION

Results from several randomized controlled trials have established the superior efficacy and tolerability of third-generation aromatase inhibitors over progestins as preferred second-line hormonal therapy in postmenopausal women with metastatic breast cancer. Results of a phase II trial evaluating the activity of exemestane in metastatic breast cancer after failure of non-steroidal aromatase inhibitors demonstrate the safety and antitumour activity of third- or fourth-line therapy with exemestane 25 mg once daily. A lack of cross-resistance between steroidal and non-steroidal aromatase inhibitors may provide the option for their use sequentially in advanced breast cancer at the time of progression. Superior clinical activity, together with improved tolerability, offers the possibility of further prolonged benefit for patients.

Preliminary data confirm that aromatase inhibitors/inactivators may be considered as an alternative to tamoxifen as a first-line treatment for postmenopausal women with advanced breast cancer. Future insights from ongoing clinical trials, including randomized studies of first-line endocrine therapy *vs* tamoxifen both in advanced breast cancer and in the adjuvant setting for early breast cancer, will determine whether exemestane should be used earlier in the natural history of the disease and help further define the future role of steroidal aromatase inactivation (Johnston, 2000). HM

Conflict of interest: none.

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KEY POINTS

- Exemestane is the first oral irreversible aromatase inactivator and has a distinct mechanism of action.
- There is lack of cross-resistance between exemestane and reversible non-steroidal inhibitors such as anastrozole and letrozole.
- Following failure of tamoxifen, in a large randomized phase III trial exemestane was associated with significant improvement in several clinical efficacy endpoints compared with megestrol acetate, with improved response duration, time to disease progression and most importantly overall survival.
- Exemestane shows significant clinical activity in patients with visceral sites of metastases (i.e. liver and lung secondary disease sites).