Role of aromatase inhibitors in advanced breast cancer

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Abstract
A number of potent and selective non-steroidal aromatase inhibitors are now available for treatment of advanced breast cancer in postmenopausal women, of which anastrozole and letrozole, in particular, represent a significant advantage over the earlier agents in terms of both efficacy and tolerability. These agents are rapidly becoming established as the second-line therapy of choice in postmenopausal women with advanced disease, progressing on tamoxifen, and data on their efficacy as first-line treatment compared with tamoxifen will be available in the near future. Exemestane, a new, steroidal aromatase inhibitor which potentially lacks cross-resistance with non-steroidal agents is still in clinical development. The full potential of the new-generation aromatase inhibitors in the treatment of breast cancer is currently being investigated in a large program of clinical trials evaluating their use as adjuvant treatment following surgery in postmenopausal patients with early disease.

Introduction
It is well established that at least one-third of all breast cancers are estrogen dependent and will regress following estrogen deprivation (Miller 1989). In the postmenopausal woman, ovarian steroid production declines with age and the production of estrogens takes place mainly in the peripheral tissues, such as adipose tissue and the adrenal glands, where the adrenal steroid, androstenedione, is converted to estrone and, subsequently, estradiol (Roseman et al. 1997, Brodie & Njar 1998). This peripheral conversion is carried out by aromatase, an enzyme complex consisting of a cytochrome P450 hemoprotein and a flavoprotein, which catalyzes the conversion of androgens to estrogens via three enzymatic hydroxylations (Roseman et al. 1997). In addition to aromatase activity in peripheral tissues, approximately two-thirds of breast tumors also exhibit aromatase activity, apparently providing a local source of estrogens within the tumor itself (Boluffer et al. 1992). The inhibition of aromatase, therefore, is more likely to accomplish a ‘complete’ estrogen blockade than surgical removal of the endocrine glands (Roseman et al. 1997), and the new-generation aromatase inhibitors are rapidly becoming established as the second-line therapy of choice in postmenopausal women with advanced breast cancer, whose disease has progressed or recurred whilst on tamoxifen treatment (Blamey 1997, Wyld et al. 1998).

Aromatase inhibitors first became available for the treatment of advanced breast cancer in postmenopausal women in the early 1980s, with the introduction of aminoglutethimide. A number of studies have demonstrated the efficacy of aminoglutethimide as first- or second-line treatment compared with tamoxifen or progestins in this patient population (Congdon et al. 1991, Coombes et al. 1992, Garcia-Giralt et al. 1992, Gale et al. 1994), but it is not specific for the aromatase enzyme and also inhibits the adrenal synthesis of both glucocorticoids and mineralocorticoids, thus requiring the co-administration of hydrocortisone (Roseman et al. 1997). This, together with the significant side-effects associated with the standard daily dose of 1000 mg, e.g. lethargy, depression and morbilliform skin rash, has severely limited its use (Garcia-Giralt et al. 1992, Brodie & Njar 1998). A second, more selective, steroidal aromatase inhibitor, formestane (4-hydroxyandrostenedione), became available in 1993. A second, more selective, steroidal aromatase inhibitor, formestane (4-hydroxyandrostenedione), became available in 1993. Whilst it has shown major advantages over aminoglutethimide in terms of both specificity for the aromatase enzyme and a more favorable tolerability profile, formestane is administered as a fortnightly intramuscular injection, which makes it inconvenient to use and, furthermore, it has been...
associated with injection-site reactions (Coombes et al. 1992).

The late 1980s/early 1990s, therefore, saw a continued search for better-tolerated aromatase inhibitors with more convenient dosage regimens. This resulted in the development of the new-generation triazole analogues, which are orally active, non-competitive, selective inhibitors of the aromatase enzyme. This class of drugs includes anastrozole (Arimidex), the first of these agents to become commercially available as a treatment for advanced breast cancer in postmenopausal women, failing on tamoxifen therapy; letrozole (Femara), also now commercially available; fadrozole (Afema), which is available only in Japan; and vorozole (Rivizor) which has not progressed beyond phase III clinical development. Over the past 2-3 years, each of these drugs has been assessed versus established endocrine treatment in large, randomized clinical trials in patients failing on tamoxifen. The aim of this presentation is to review the available data on these new agents, with major emphasis on their clinical efficacy in the treatment of advanced breast cancer.

Non-steroidal inhibitors

Two large phase III studies have been conducted to compare anastrozole (1 and 10 mg daily) with megestrol acetate (160 mg daily) as second-line therapy in postmenopausal women with advanced breast cancer, failing on tamoxifen. Each trial was of the same protocol design which allowed a combined analysis to be performed on data from a total of 764 patients (Buzdar et al. 1996). At a median duration of follow-up of 6 months, approximately one-third of patients in each group showed clinical benefit from treatment (complete or partial response, or stable disease for at least 6 months). Both anastrozole and megestrol acetate were well tolerated but there was significantly less weight gain in those patients treated with anastrozole, at either dose (Buzdar et al. 1996a). In addition, patients on megestrol acetate were continuing to gain weight at 9 months, whilst with both doses of anastrozole bodyweight continued to remain at, or around, baseline values (Buzdar et al. 1998). A further safety analysis after 12 months confirmed the favorable tolerability profile of anastrozole compared with that of megestrol acetate (Buzdar et al. 1998).

Updated, mature results for this combined analysis are now available, with a median follow-up of 31 months (Buzdar et al. 1996b, 1998, Howell et al. 1997). Objective tumor response data are summarized in Table 1.

Although there were no statistically significant differences between the three treatment arms, approximately 40% of patients in each group gained clinical benefit from treatment.

There was, however, a significant improvement in both median survival and 2-year survival rates for anastrozole (1 mg) compared with megestrol acetate in the combined analysis (hazard ratio 0.78; P<0.025). Additionally, the two studies were consistent when analysed individually, each demonstrating a lower risk of death for anastrozole (both 1 and 10 mg) compared with megestrol acetate.

A subgroup analysis of the combined data compared the 2-year survival in patients with complete or partial response with that of those achieving stable disease for at least 24 weeks (Robertson & Lee 1997). This demonstrated that for each treatment arm, patients with

Table 1 Anastrozole vs megestrol acetate: objective tumor response data from the combined analysis of two independent phase III trials at a median follow-up of 31 months

<table>
<thead>
<tr>
<th>Objective response</th>
<th>Anastrozole 1 mg (n=263)</th>
<th>Anastrozole 10 mg (n=248)</th>
<th>Megestrol acetate (n=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit*</td>
<td>111 (42.2%)</td>
<td>99 (39.9%)</td>
<td>102 (40.3%)</td>
</tr>
<tr>
<td>CR</td>
<td>11 (4.2%)</td>
<td>10 (4.0%)</td>
<td>11 (4.3%)</td>
</tr>
<tr>
<td>PR</td>
<td>22 (8.4%)</td>
<td>21 (8.5%)</td>
<td>20 (7.9%)</td>
</tr>
<tr>
<td>SD ≥ 24 weeks</td>
<td>78 (29.7%)</td>
<td>68 (27.4%)</td>
<td>71 (28.1%)</td>
</tr>
<tr>
<td>SD &lt; 24 weeks†</td>
<td>1 (0.4%)</td>
<td>6 (2.4%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Progression</td>
<td>151 (57.4%)</td>
<td>143 (57.7%)</td>
<td>150 (59.3%)</td>
</tr>
</tbody>
</table>

*Clinical benefit = complete response (CR) + partial response (PR) + stable disease (SD) ≥24 weeks.
†Patients lost to follow-up. No identifiable patients were still on study with SD <24 weeks.

The material quoted here was adapted from Buzdar et al. (1998).
stable disease of 24 weeks or longer had comparable overall survival to those achieving an objective tumor response. The subgroup analysis, therefore, confirms the clinical value of stable disease in this study and supports previous findings with both megestrol acetate and tamoxifen that long-term stable disease is an important remission criterion in advanced breast cancer patients (Robertson et al. 1996).

Although the 10 mg dose of anastrozole did not produce any additional clinical benefit compared with the 1 mg dose, the tolerability profile was very similar, thus providing an excellent therapeutic margin for tolerability and selectivity over the clinically recommended daily dose of 1 mg (Jonat 1997, Brodie & Njar 1998). Thus the important survival benefit, together with the favorable tolerability profile, further supports the role of anastrozole (1 mg) as a valuable replacement for progestin therapy as second-line treatment in this patient population (Buzdar et al. 1998, Wyld et al. 1998).

Another of the new-generation aromatase inhibitors, letrozole, is also becoming more widely available. The recent publication of phase III trial results comparing letrozole (0.5 and 2.5 mg daily) with megestrol acetate (160 mg daily) in 551 postmenopausal women with advanced disease reported a significant improvement in both objective response rate ($P=0.04$) and duration of response ($P=0.02$) for letrozole (2.5 mg) over megestrol acetate (Dombernowsky et al. 1998). Objective response data are summarized in Table 2.

Letrozole (2.5 mg) was also superior to megestrol acetate in terms of time to treatment failure ($P=0.04$), although there was no significant difference in time to progression ($P=0.07$) or overall survival ($P=0.15$). In addition, patients receiving letrozole (2.5 mg) had significantly fewer serious adverse events than those on megestrol acetate.

In a similar study comparing the same two doses of letrozole with aminoglutethimide (500 mg daily) in 555 postmenopausal advanced breast cancer patients (Gershovanich et al. 1998), letrozole (2.5 mg) was shown to be superior to aminoglutethimide in terms of both time to progression ($P=0.008$) and overall survival ($P=0.002$), although there were no statistically significant differences between treatments in objective response. As might be expected, significantly more patients on aminoglutethimide experienced drug-related adverse events than did those on letrozole (2.5 mg). Both of the phase III studies demonstrated a dose-effect relationship for letrozole and showed 2.5 mg to be the clinically superior dose (Brodie & Njar 1998, Dombernowsky et al. 1998, Gershovanich et al. 1998).

Anastrozole and letrozole, therefore, have both shown superiority in terms of efficacy and tolerability over existing endocrine agents as second-line therapy for postmenopausal women with advanced breast cancer and are rapidly becoming established as the treatments of choice in such patients (Wyld et al. 1998). Currently there are no data available which directly compare the two agents.

When first reviewing the data, it may appear that the objective response rate of 23.6% observed for letrozole (2.5 mg) in the study versus megestrol acetate

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### Table 2 Letrozole vs megestrol acetate: overall tumor response data at a median follow-up of 33 months

<table>
<thead>
<tr>
<th>Objective response</th>
<th>Letrozole 0.5 mg (n=188)</th>
<th>Letrozole 2.5 mg (n=174)</th>
<th>Megestrol acetate (n=189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Clinical benefit*</td>
<td>51 (27.1)</td>
<td>60 (34.5)</td>
<td>60 (31.7)</td>
</tr>
<tr>
<td>CR</td>
<td>6 (3.2)</td>
<td>12 (6.9)</td>
<td>8 (4.2)</td>
</tr>
<tr>
<td>PR</td>
<td>18 (9.6)</td>
<td>29 (16.7)</td>
<td>23 (12.2)</td>
</tr>
<tr>
<td>NC ≥6 months</td>
<td>27 (14.4)</td>
<td>19 (10.9)</td>
<td>29 (15.3)</td>
</tr>
<tr>
<td>Progression</td>
<td>105 (55.9)</td>
<td>93 (53.4)</td>
<td>106 (56.1)</td>
</tr>
<tr>
<td>Not assessable†</td>
<td>32 (17.0)</td>
<td>21 (12.1)</td>
<td>23 (12.2)</td>
</tr>
</tbody>
</table>

*Clinical benefit = complete response (CR) + partial response (PR) + no change (NC) ≥6 months; †Patients with incomplete documentation of tumor lesions, patients judged by peer review not to have evidence of malignant disease, or patients who had PRs or NC that was not confirmed at least 4 weeks later.

The material quoted here was adapted from Dombernowsky et al. (1998).
(Dombernowsky et al. 1998) is high alongside the 12.6% response seen with anastrozole, in a similar study versus the same comparator (Buzdar et al. 1998) (see Table 3). The numbers of patients with progressive disease, however, are similar for both treatment groups in each study. This suggests that the apparent differences in objective response may be explained by the different response criteria used in the two studies. Indeed, in the anastrozole versus megestrol acetate study, the assignment of a partial response was not permitted for patients with non-measurable disease, an important consideration as approximately 30% of patients in this study had disease which was not measurable (Buzdar et al. 1998). For these patients, any response other than complete tumor regression could only be categorized as stable disease. In the study of letrozole (2.5 mg) versus megestrol acetate, however, patients with non-assessable, non-measurable lesions could be assigned a partial response (Dombernowsky et al. 1998). Such differences in assessment of response emphasize the value of clinical benefit as an important criterion for advanced breast cancer patients (Robertson & Lee 1997).

Whilst anastrozole and letrozole have shown clear evidence of benefit over existing agents, the data regarding fadrozole and vorozole are more equivocal. Two large phase III trials of fadrozole (1 mg, twice daily) versus megestrol acetate (160 mg daily) as second-line treatment for advanced breast cancer, in a total of 683 postmenopausal women failing on antiestrogen therapy (Buzdar et al. 1996c), showed no significant differences between treatment groups for objective response, time to progression or survival, in either trial. There were no statistically significant differences between groups in the incidence or severity of adverse events; however, weight gain, fluid retention and dyspnea were observed more frequently with megestrol acetate, whilst fadrozole was associated with a higher frequency of nausea and vomiting.

Two further trials have also investigated fadrozole as an alternative to tamoxifen as first-line therapy in postmenopausal women with advanced disease (Falkson & Falkson 1996, Thuerlimann et al. 1996). The larger study (n=212) showed no significant differences between treatments in terms of efficacy, although there was a trend in favor of tamoxifen for time to treatment failure. Fadrozole, however, was significantly better tolerated, in particular with respect to cardiovascular adverse events (Thuerlimann et al. 1996). A second, smaller study (n=38) had slightly conflicting conclusions; again, efficacy was similar for both treatments, but there were no differences in either time to treatment failure or toxicity (Falkson & Falkson 1996). Overall, therefore, whilst fadrozole may have tolerability advantages over existing endocrine therapies, it has not shown the efficacy advantages of the other new-generation aromatase inhibitors as a second-line therapy, or proven superior to tamoxifen as a first-line agent (Cocconi 1996).

With regard to vorozole, it appears that this agent has been withdrawn from clinical development in the US. Phase III trials versus both megestrol acetate (Goss et al.
Endocrine-Related Cancer (1999) 6 219-225

1997) and aminoglutethimide (Houston 1997), as second-line therapy for postmenopausal women with advanced disease, have not shown any statistically significant differences in favor of vorozole for any of the clinical endpoints studied, although it was shown to be superior to aminoglutethimide for quality of life (Houston 1997).

Although anastrozole and letrozole remain the only new-generation, non-steroidal aromatase inhibitors to have demonstrated significant efficacy benefits over existing endocrine therapies, the tolerability profile of all these new agents appears to be fairly similar, the main adverse events generally being those pharmacological effects that might be anticipated as a result of estrogen withdrawal (Table 4).

Although such detailed data are not available from the published literature for vorozole, the main adverse event in the study versus megestrol acetate was reported to be hot flashes (Goss et al. 1997).

Steroid inhibitors
In contrast to the new-generation, non-steroidal agents discussed above, exemestane is a second-generation steroidal aromatase inhibitor, with the advantage of improved oral activity over formestane (the latter normally being given intramuscularly), allowing once daily, oral dosing. Exemestane interacts covalently with the aromatase enzyme during the first oxidation cycle, causing potent, selective, irreversible inhibition of aromatase (Lonning et al. 1997), and may lack cross-resistance with the non-steroidal aromatase inhibitors (Thuerlimann et al. 1997). At a dose of 200 mg daily, it has shown promising activity as third-line therapy in postmenopausal patients progressing on aminoglutethimide, confirming the lack of cross-resistance when a steroidal aromatase inhibitor is sequenced after a non-steroidal aromatase inhibitor (Thuerlimann et al. 1997). A second phase II study has investigated the much lower dose of 25 mg daily as second-line therapy following tamoxifen (n=134) (Kvinnsland et al. 1997). The overall objective response rate to exemestane was 22%, with an additional 31% of patients achieving no change for at least 24 weeks. The drug was well tolerated, the main adverse events being hot flashes and nausea. Exemestane is currently being evaluated in a large, double-blind phase III study versus megestrol acetate in this patient population (Kvinnsland et al. 1997).

Conclusions
A number of potent and selective non-steroidal aromatase inhibitors are now available, of which anastrozole and letrozole, in particular, represent a significant advantage over the earlier agents in terms of both efficacy and tolerability. These agents are rapidly becoming established as the second-line therapy of choice in postmenopausal women with advanced disease, progressing on tamoxifen, and data on their efficacy as first-line

| Table 4 Indirect comparison: adverse events with new-generation aromatase inhibitors in studies vs megestrol acetate |
|------------------|-----------------------------|-----------------------------|
| Adverse event    | Anastrozole (1 mg)* (n=263) | Letrozole (2.5 mg)† (n=174) | Fadrozole (n=196; n=152) |
| Headache         | 14%                         | 13%                         | 7.7%, 15.1%               |
| Hot flashes      | 13%                         | 6%                          | 11.7%, 14.5%              |
| Nausea           | 18%                         | 11%                         | 21.9%, 36.2%              |
| Vomiting         | 10%                         | 8%                          | 9.2%, 18.4%               |
| Diarrhea         | 9%                          | 6%                          | 9.9%, 11.2%               |
| Weight gain      | 3%                          | 2%                          | NA                        |
| Rash             | 6%                          | 6%                          | 5.6%, 11.8%               |
| Dyspnea          | 11%                         | 9%                          | 7.7%, 14.5%               |
| Asthenia         | 18%                         | NA                          | 6.6%, 11.2%               |
| Fatigue          | NA                          | 11%                         | 16.3%, 20.4%              |

*Commonly reported adverse events, irrespective of causality.
†Adverse experiences in >5% of patients irrespective of trial-drug relationship.
Anastrozole data, see Buzdar et al. (1998); letrozole data, see Dombernowsky et al. (1998); fadrozole data, see Buzdar et al. (1996c).
treatment compared with tamoxifen will be available in the near future (Blamey 1997). A new, steroidal aromatase inhibitor with a potential for lack of cross-resistance with non-steroidal agents is still in clinical development. The full potential of the new-generation aromatase inhibitors in the treatment of breast cancer is currently being investigated in a large program of clinical trials evaluating their use as adjuvant treatment following surgery in postmenopausal patients with early disease (Blamey 1997).

References
Houston SJ 1997 ‘Rivizor’ versus aminoglutethimide (AG) in the second-line endocrine treatment of postmenopausal patients with advanced breast cancer (ABC) following tamoxifen failure. *Breast* 6 244 (Abstract 0-72).


Robertson JFR & Lee D 1997 Static disease (SD) of long duration (>24 weeks) is an important remission criterion in breast cancer patients treated with the aromatase inhibitor ‘Arimidex’ (anastrozole). *Breast Cancer Research and Treatment* **46** 54 (Abstract 214).


