Lessons from the use of aromatase inhibitors in the neoadjuvant setting

J M Dixon, C D B Love, L Renshaw, C Bellamy¹, D A Cameron, W R Miller and R C F Leonard

Edinburgh Breast Unit, Western General Hospital, Edinburgh, UK
¹Department of Pathology, Western General Hospital, Edinburgh, UK

Abstract
Postmenopausal patients with oestrogen receptor-positive locally advanced T_4b, N_0-1, M_0 and large operable breast cancers T_2>3 cm, T_3, T_4, N_0-1 and M_0 have been treated with 2.5 mg letrozole (12 patients), 10 mg letrozole (12 patients), 1 or 10 mg anastrozole (24 patients) and 20 mg tamoxifen (65 patients). There was no apparent difference in response rate between 2.5 and 10 mg letrozole. Only 17 patients with anastrozole have so far completed the 3-month treatment period. Median clinical, mammographic and ultrasound reductions in tumour volumes for patients treated with letrozole were 81% (95% confidence interval (CI) 66-88), 77% (95% CI 64-82) and 81% (95% CI 69-86) respectively and for anastrozole, values were 87% (95% CI 59-97), 73% (95% CI 58-82) and 64% (95% CI 52-76) respectively. This compares with a median reduction in tumour volume for tamoxifen-treated patients as assessed by ultrasound of 48% (95% CI 27-48). There were seven complete clinical responses (CR), sixteen patients who achieved 50% or greater reduction in tumour volume (PR) and one no change (NC) for letrozole and four CRs, twelve PRs and one progressive disease for anastrozole. Best radiological responses were one CR, twenty PRs and three NCs for letrozole and one CR, fifteen PRs and one NC for anastrozole. This study has shown that the new aromatase inhibitors, letrozole and anastrozole, are highly effective agents in the neoadjuvant setting and they should now be compared with tamoxifen as first-line treatment in a randomised study.

Introduction
Neoadjuvant therapy has been used to treat large operable and locally advanced breast cancers (Anderson et al. 1989, Hortobagyi et al. 1996, Fisher et al. 1997). Studies to date have concentrated mainly on the use of chemotherapy. Few centres have evaluated neoadjuvant endocrine therapy in hormone-sensitive large operable and locally advanced breast cancer (Anderson et al. 1989). Studies published using primary hormone therapy have demonstrated high response rates in oestrogen receptor-positive tumours (Anderson et al. 1989, Keen et al. 1997). Although responses appear slower than those with chemotherapy, substantial reductions in volume over a 3-month period have been recorded (Keen et al. 1997) which have allowed tumour downstaging.

In premenopausal women the luteinizing hormone-releasing hormone analogue Zoladex has been assessed (Anderson et al. 1989). In postmenopausal women the most common neoadjuvant endocrine agent used has been tamoxifen (Keen et al. 1997). As part of a study to assess the effects of letrozole and anastrozole on intratumoral aromatase, the present study has investigated the effectiveness of letrozole and anastrozole given as primary medical therapy (neoadjuvant) for patients with newly diagnosed oestrogen receptor-positive locally advanced and large operable breast cancer.

Patients and methods
Three groups of patients have been studied. All were postmenopausal patients with oestrogen receptor-positive breast cancers (>20 fmol/receptor per mg per cytosol protein) or a histoscore of >80 (histoscore calculated by multiplying the percentage of cells staining by the intensity of staining graded from 0 to 3 (McCarty et al. 1997).
1985). Only patients with large operable or locally advanced breast cancers without evidence of metastases were included in this study, $T_2 > 3\, \text{cm}$, $T_3\, T_4a$, $N_0\, -1$ and $M_0$. Patients were $M_0$ on the basis of normal biochemistry and no metastases on a chest X-ray or bone scan. Patients with inflammatory cancers, extensive peau d’orange and satellite nodules were excluded.

**Letrozole patients**

Twenty-four postmenopausal patients (age range 53-84 years) were treated in sequence, the first twelve received 2.5 mg letrozole and the second twelve were treated with 10 mg letrozole. Oestrogen receptor levels varied from 40 to 890 and histoscore levels ranged from 140 to 300 in these twenty-four patients.

**Anastrozole patients**

Twenty-four postmenopausal patients (age range 63-86 years) have been or are currently being treated with anastrozole, either 1 or 10 mg, in a randomised study. As this is an ongoing study only seventeen patients have currently completed the 3-month study period. Histoscore levels ranged from 120 to 300 in these seventeen patients. It is not yet known which patients received 1 or 10 mg anastrozole.

**Tamoxifen patients**

Sixty-five patients have been treated as part of an identical protocol in our Unit with tamoxifen and data on these patients have been published (Keen et al. 1997). All patients gave written informed consent. Protocols for all studies were passed by the local ethics research committee. At the outset of the study all tumours were measured clinically in four different directions, 45° apart and the volume calculated using the following formula (Forouhi et al. 1994):

$$V = (D^2 \times d \times \pi)/6$$

where $V$ is volume, $D$ is mean diameter and $d$ is mean thickness.

They also had mammograms and using the measurements on the oblique and cranio-caudal views four diameters were obtained. The mean diameter was calculated and tumour volume calculated using the formula (Forouhi et al. 1994):

$$V = (D^3 \times \pi)/6$$

where $V$ is volume and $D$ is mean diameter.

Patients also had an ultrasound and four scans were performed at 45° apart and tumour volume was estimated according to the following formula (Forouhi et al. 1994):

$$V = (D^2 \times d \times \pi)/6$$

where $V$ is volume, $D$ is mean diameter and $d$ is mean thickness.

As part of this study patients receiving aromatase inhibitors had a radioactive infusion of 20 MBq $[^3H]$ androstenedione and 1.0 MBq $^{14}$C-labelled oestrogen in 50 ml 95% plasma protein solution and 5% ethanol 18 h prior to surgery for assessment of peripheral and intratumoral oestrogen production. Prior to institution of any treatment an open biopsy was performed removing approximately 1 g tumour for confirmation of oestrogen receptor positivity and to provide tumour for biological studies. Samples of tumour from patients treated with letrozole or anastrozole were also removed for estimation of intratumoral aromatase activity.

Patients were treated with drugs for a 3-month period. During this time, patients were monitored at monthly intervals and had clinical and ultrasound tumour volumes calculated at each visit. A second mammogram was performed at 3 months and mammographic volumes at 3 months were calculated. Percentage change in volume was used to assess response. UICC criteria for response demands a 50% increase in reduction, the product of the two diameters of the tumour persisting for 1 month. This is impractical in a period of treatment which lasts only 3 months. Modified WHO criteria for response have therefore been utilised (WHO Handbook for Reporting Results of Cancer Treatment 1979), partial response (PR) being defined as a 50% or greater reduction in tumour volume and a complete response (CR) being no measurable tumour. Progression of disease (PD) is defined as a greater than 25% increase in tumour volume with a no change (NC) being defined as a volume decrease of less than 50% or a volume increase of greater than 25%.

**Results**

**Letrozole (2.5 mg)**

There were five clinical CRs and seven PRs. Results based on the best imaging response were one CR, ten PRs and one NC.

**Letrozole (10 mg)**

There were two CRs, eight PRs and two NCs. Best imaging responses were eleven PRs and one NC.

When comparing the results of 2.5 mg and 10 mg letrozole, there were no apparent differences between these groups when responses based on clinical mammographic and ultrasound changes in tumour volume were compared. For the purposes of future comparisons, patients treated with the two doses of letrozole have been combined. Median clinical, mammographic and ultrasound reductions in tumour volume were 81% (95% confidence interval (CI) 66-88), 77% (95% CI 64-82) and 81% (95% CI 69-86) respectively.

**Anastrozole (1 or 10 mg)**

This is an ongoing study and to date seventeen patients have completed the 3-month protocol. Clinically there were four CRs, twelve PRs and one PD. Best radiological response was one CR, fifteen PRs and one NC. Median
clinical, mammographic and ultrasound reductions in tumour volume were 87% (95% CI 59-97), 73% (95% CI 58-82) and 64% (95% CI 52-76) respectively.

Table 1 compares the data of patients treated with letrozole or anastrozole. The two drugs produced similar percentage reductions in tumour volume. The small numbers of patients in this study does not allow assessment of whether one agent is superior.

Data were available on 65 patients treated in an identical protocol with tamoxifen (20 mg daily). Figure 1 shows the median percentage reduction in tumour volume at 3 months in patients treated with tamoxifen, letrozole and anastrozole. Although this was not a randomised study both letrozole and anastrozole appear to produce greater reductions in tumour volume than tamoxifen.

Surgical treatment of patients following treatment by letrozole or anastrozole

Letrozole

Nine patients were suitable for breast conservation at the outset of the treatment but by the end of the 3-month course of letrozole all patients were eligible for treatment by breast conservation. Histology demonstrated that all the cancers were completely excised. There was one complete pathological response in a patient treated with 2.5 mg letrozole and three patients had residual microscopic disease only, two in the 2.5 mg and one in the 10 mg group.

Anastrozole

At the outset of the study fourteen out of seventeen patients would have required a mastectomy. After anastrozole, sixteen were suitable for breast conservation. Histologically there were two patients who had microscopic foci only and no patient had a complete pathological response.

Discussion

Neoadjuvant endocrine therapy has been shown previously to produce significant reductions in tumour volume over a 3-month period (Keen et al. 1997). This is the first time that the new specific aromatase inhibitors have been used in this setting. The present study has demonstrated high response rates with significant numbers of patients achieving complete clinical responses within 3 months. Such have been the reductions in tumour volume that this short period of treatment has allowed the majority of women to be treated with less extensive surgery. As many of these patients are elderly and, in this elderly population, mastectomy is associated with a 1% mortality (Hunt et al. 1980), this is an important issue.

Results appear similar with letrozole and anastrozole although the study does not have the power to assess whether one agent is more effective than the other. Data from our unit on a series of patients treated with tamoxifen in an identical protocol indicate that the new aromatase inhibitors appear to produce responses at least as good as tamoxifen, with the suggestion of a greater percentage reduction in tumour volume with these new aromatase inhibitors when compared with tamoxifen. These data indicate that it is time formally to assess these new aromatase inhibitors as first-line treatment for patients.

Table 1 Comparison of reduction in clinical, mammographic and ultrasonographic volume of patients treated with a three month course of letrozole or anastrozole

<table>
<thead>
<tr>
<th>Aromatase inhibitor</th>
<th>No. of patients</th>
<th>Median % reduction clinical volume (95% CI)</th>
<th>Median % reduction mammographic volume (95% CI)</th>
<th>Median % reduction ultrasound volume (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole (2.5 mg or 10 mg)</td>
<td>24</td>
<td>81 (66-88)</td>
<td>77 (64-82)</td>
<td>81 (69-86)</td>
</tr>
<tr>
<td>Anastrozole (1 mg or 10 mg)</td>
<td>17</td>
<td>87 (59-97)</td>
<td>73 (58-82)</td>
<td>64 (52-76)</td>
</tr>
</tbody>
</table>
with large operable or locally advanced oestrogen receptor-positive breast cancers.

There are potential weaknesses with the current study. All patients had a wedge biopsy which may have reduced the volume of the tumour, it may have interfered with tumour blood supply and can make early assessment of response difficult. All surgery was, however, performed by a single individual (J M D) who removed approximately 1 g tissue at the initial biopsy. Any swelling associated with the wedge biopsy did settle apart from one patient who developed a haematoma. This patient was the second patient treated with letrozole (2.5 mg); she developed considerable scarring and distortion following the haematoma which made ultrasound assessment of the tumour difficult. This patient was recorded as having a 0% reduction in tumour volume on ultrasound but pathologically she had a complete response. In no other patient was there a problem imaging the tumour on the monthly or 3-monthly assessments. Mammography proved particularly useful in this elderly age group because most elderly patients have radiolucent breasts and the tumour can be clearly visualised. In this study there was good agreement between all three assessments of response indicating that 3-month percentage reduction in tumour volume is a robust endpoint.

The superiority of letrozole and anastrozole over conventional second-line endocrine agents in metastatic breast cancer surprised a number of oncologists (Dombernowsky et al. 1998). Our data suggests that it is possible that these new agents might prove to be better in the first-line situation than the current standard treatment, tamoxifen. The lessons we have learned from using these new aromatase inhibitors in the neoadjuvant setting are that they are extremely powerful agents, they produce significant response rates with large reductions in tumour volume permitting less extensive surgery. Studies of these drugs as first-line therapy are now indicated.

References


