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Neoadjuvant tamoxifen and aromatase inhibitors: comparisons and clinical outcomes☆

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Abstract

Neoadjuvant hormonal therapy for oestrogen receptor (ER) and/or progesterone receptor (PgR) positive large operable or locally advanced breast cancer is effective and a safe alternative to chemotherapy in postmenopausal women. A randomised trial has demonstrated that the response rate and the incidence and degree of downstaging with the aromatase inhibitor letrozole is significantly greater than with tamoxifen [J. Clin. Oncol. 19 (2001) 3808]. Tumours at all levels of ER appear to respond better to letrozole than tamoxifen but at low levels of ER responses are seen only with letrozole and not with tamoxifen. Patients most likely to benefit from neoadjuvant therapy and those who achieve the greatest reduction in tumour volume are those patients with tumours that express very high levels of ER (ALLRED category score 8). Both letrozole and anastrozole appear effective in both erbB2 positive and negative breast cancers. Three months of treatment is adequate to determine if a tumour will respond. Following breast-conserving surgery and radiotherapy, local recurrence rates appear satisfactory.

Keywords: Neoadjuvant tamoxifen; Aromatase inhibitors; ER and/or PgR positive

1. Introduction

Until recently neoadjuvant therapy of breast cancer has been used predominantly as cytotoxic chemotherapy [1–4]. Endocrine treatment is now emerging as an attractive alternative in hormone receptor positive postmenopausal women many of whom who could not tolerate the toxicities of chemotherapy. There have been few controlled studies of neoadjuvant endocrine therapy. In early studies, tamoxifen was used but patients were not selected on the basis of having oestrogen receptor (ER) or progesterone receptor (PgR) positive breast cancers to identify those most likely to respond [5].

1.1. Studies with tamoxifen

Randomised trials comparing primary endocrine therapy with tamoxifen alone with surgery±tamoxifen have all been in elderly patients [6–9]. Patients in these studies were not routinely selected on the basis of having ER or PgR positive breast cancer. In two of the studies, tamoxifen was compared with immediate surgery alone and in the other two, tamoxifen was compared with surgery and tamoxifen [6,7]. The time to relapse or first event was significantly shorter in the tamoxifen alone arm, as would be expected. A more recent combined analysis of these trials [10] showed that this translated to a significant reduction in breast cancer deaths in the immediate surgery group. However, none of these trials were designed to see whether there was a difference in survival between patients treated by neoadjuvant endocrine therapy before surgery or surgery followed by endocrine therapy.

In Edinburgh, small studies have been performed comparing neoadjuvant tamoxifen with aromatase inhibitors. Although patients were not randomised and the numbers were small, impressive results were achieved. Table 1 shows the number of patients who had reductions in tumour volume of more then 50% as assessed by ultrasound scan. As can be seen, 46% of patients treated with tamoxifen, 88% of patients treated with letrozole and 78% of patients treated with anastrozole had a reduction in tumour volume of greater than 50%. Of the whole group, only two patients progressed while on treatment.

There are no large randomised studies comparing neoadjuvant endocrine therapy with chemotherapy and little work has been done in this area since the patient populations who are most commonly treated with neoadjuvant chemotherapy tend to be premenopausal women with large ER negative tumours, in contrast those treated with endocrine therapy tend to be elderly postmenopausal women with ER positive tumours.

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Table 1
Median percentage in tumour volume as assessed by ultrasound

Drug	No.	No. >50% reduction	No. <50% reduction and <25% increase	No. >25% increase
Tamoxifen	65	30	34	1
Letrozole	24	21	2	1
Anastrozole	23	18	5	0

A potential problem with using tamoxifen as neoadjuvant therapy is the long time period required to reach steady state plasma levels—up to 5 weeks [11]. In contrast, the newer aromatase inhibitors build up rapidly reaching therapeutic concentrations within days.

1.2. Studies with letrozole

Initial studies performed in Edinburgh with letrozole, a highly selective aromatase inhibitor, suggested that there may be benefits of using aromatase inhibitors rather than tamoxifen in postmenopausal ER positive patients [12]. This led to randomised studies. The PO24 trial compared 4 months of neoadjuvant letrozole with tamoxifen in postmenopausal women with large breast cancers which required mastectomy or were locally advanced and inoperable and were ER or PgR positive [13]. This study demonstrated that letrozole achieved a significantly higher clinical response rate than tamoxifen (55% versus 36%; $P < 0.001$), enabling more patients treated with letrozole than with tamoxifen to undergo breast-conserving surgery (45% versus 35%; Table 2). Median time to response was 66 days in the letrozole group and 70 days in the tamoxifen group.

Modified WHO criteria was used to evaluate tumour response in the neoadjuvant setting as follows:

- *Partial response* (*PR*): Reduction in tumour size ≥50% from pre-treatment size.
- *Minor response* (*MR*): Reduction in tumour size ≥25 and <50% from pre-treatment size.
- *No change* (*NC*): <25% decrease or <25% increase in tumour size from pre-treatment size.
- *Complete response* (*CR*): No measurable tumour.
- *Progressive disease* (*PD*): 25% or more increase in tumour size from pre-treatment size.

Table 2
Primary and secondary efficacy end point results of trial P024 comparing 4 months of neoadjuvant letrozole vs. tamoxifen, in all study patients [12]

Efficacy end points	Letrozole (%) ($n = 154$)	Tamoxifen (%) ($n = 170$)	*P*-value
Primary end point			
Clinical response (palpation)	55	36	<0.001
Complete	10	4	
Partial	45	32	
Secondary end points			
Ultrasound response	35	25	0.042
Complete	3	1	
Partial	32	24	
Mammographic response	34	16	<0.001
Complete	4	0	
Partial	30	16	
Breast-conserving surgery	45	35	0.022

Table 3
Responses in trial P024 comparing 4 months of neoadjuvant letrozole vs. tamoxifen, relative to confirmed ER and/or PgR status [7]

Agent	Marker status	Response rate (%)	*P*-value
Letrozole	ER positive	60	0.005
	ER negative	19	
	PgR positive	63	0.018
	PgR negative	41	
Tamoxifen	ER positive	40	0.031
	ER negative	11	
	PgR positive	43	0.076
	PgR negative	28	

ER, oestrogen receptor; PgR, progesterone receptor.

There were fewer responses demonstrated by ultrasound and mammography but responses were significantly more common with letrozole than tamoxifen whether assessed by ultrasound or mammography (Table 2). The only other factor besides treatment which influenced the likelihood of patients being suitable for breast-conserving surgery was tumour size at presentation with patients with T2 tumours being more likely to be candidates for breast-conserving surgery than larger tumours ($P = 0.0001$). In this randomized study, letrozole was at least as well tolerated as tamoxifen.

Tumour response in this study was related to ER and PgR status [5]. There were significantly more responses in patients subsequently confirmed to have ER positive tumours than in patients who on subsequent testing had ER negative tumours (Table 3). In each of the ER categories, response rates were higher for letrozole than tamoxifen. There appeared to be a particular difference in response rates in tumours that were ER positive and also over expressed erbB1 and/or erbB2 with an 88% response rate in this group for letrozole versus a 21% response rate to tamoxifen $P = 0.0004$ [5].

1.3. Studies with anastrozole

In Edinburgh, a series of 24 patients have been treated with neoadjuvant anastrozole [14]. These tumours have recently been stained for erbB2 and a correlation between the erbB2 status response and change in proliferation in hormone receptor has been undertaken [15]. Twenty-two patients had sufficient tumour in all their specimens to allow us to assess erbB2 status prior to treatment and also to study changes in proliferation as assessed by Ki67 antibody and PgR as assessed by the DAKO antibody. There were 6 erbB2 3+ tumours with the other 16 tumours being either

Table 4
Response rates and changes in Ki67 and PgR in 22 patients treated by 3 months of preoperative anastrozole subdivided according to erbB2 status

erbB2	No.	Clinical		Ultrasound		Median Ki67		Fall in PgR
		CR/PR	S.D.	CR/PR	S.D.	Pre	Post	
0/>1	16	15	1	10	6	23.5	>5	13/13*
>3	6	6	0	5	1	22.5	~7.5	3/4*

* Five patients PgR 0 on first biopsy: (a) $P = 0.017$ and (b) $P < 0.0001$.

negative or 1+. Comparison has been made between these two groups. There was no difference in clinical response between the two groups (Table 4), and initial proliferation and changes in proliferation and PgR receptor did not differ between the different groups. These data demonstrate anastrozole is clinically and biologically effective in erbB2 positive tumours.

An ongoing multicentre, randomised, double-blind clinical trial, Immediate Preoperative Arimidex Alone or in Combination with Tamoxifen (IMPACT) has now completed recruiting. It compares anastrozole 1 mg daily versus tamoxifen 20 mg daily versus anastrozole plus tamoxifen. Three hundred and thirty postmenopausal patients with ER and/or PgR positive breast cancers if large or operable, or potentially operable but locally advanced, have been recruited. In this study, treatment was for 3 months and patients providing they respond continue on the same endocrine treatment as adjuvant therapy for 5 years. Primary endpoints are objective tumour response rates with secondary endpoints being breast-conserving rate and assessment of key biological markers including proliferation, hormone receptors and apoptotic rate.

1.4. Newer Edinburgh studies

In the Edinburgh Breast Unit, we have now treated 83 patients with neoadjuvant letrozole [16]. We have correlated clinical and ultrasound responses and change in tumour volumes in these patients in relation to the ER ALLRED score. Sixty of the tumours were ER category 8 and 23 were category 6 or 7 (Table 5). Response rates were similar in ER categories 8 and 6 + 7 but there was a greater percentage reduction in tumour volume in patients whose tumours had the highest ER level. This difference was significant ($P < 0.05$).

1.5. Selection of patients for neoadjuvant therapy

The data outlined indicate that selection for neoadjuvant endocrine therapy should be based primarily on ER status and to a lesser extent, PgR status [5]. Although PO24 suggested that one of the differences between tamoxifen and letrozole is that patients with lower levels of ER are more likely to respond to letrozole than tamoxifen, the numbers in these categories was small and it remains our policy to treat patients who are fit for surgery with neoadjuvant endocrine therapy only if their ER ALLRED score is 6 or over because these are the women who are most likely to respond and gain a clinical benefit.

1.6. Duration of neoadjuvant therapy

Standard practice with neoadjuvant chemotherapy is to administer between three and six cycles prior to surgery, a time period felt sufficient to delineate responders from non-responders [17]. The optimal duration of neoadjuvant therapy has never been investigated in detail. One study at the Edinburgh Breast Unit gave neoadjuvant tamoxifen to 100 consecutive patients over the age of 70 with ER rich breast cancers (>20 fmol/mg cytosol protein) [18]. It demonstrated that after 3 months 72 had responded (based on a greater than 25% reduction in tumour volume by ultrasound) and one patient had progressive disease. The remaining 27 continued on tamoxifen for a further 3 months during which 18 patients' disease remained static, four responded but five progressed. From these data, it can be concluded that if patients are not responding by 3 months they are unlikely to respond and there is the concern that if left on tamoxifen alone the disease may progress. Three months therefore appears sufficient to demonstrate whether the tumour is responsive. Maximal response may however take considerably longer than 3 months and the optimal duration of therapy depends on initial tumour size and the aim of the neoadjuvant therapy. If the aim is to downstage the tumour to allow breast-conserving surgery, then this can be achieved in the majority of patients with 3–4 months treatment.

1.7. Response and downstaging in breast cancer

Response rates to preoperative chemotherapy are generally around 80% regardless of the regimen used [19]. In appropriately selected patients, neoadjuvant endocrine

Table 5
Response in 83 patients treated with 3 months of neoadjuvant letrozole subdivided according to ALLRED ER score

ALLRED ER score	No. of patients	No. of responders	% Response	Median % reduction in tumour volume	
				Clinical	USS
8	60	48	80	76*	67*
6 + 7	23	17	74	63	48

* $P < 0.05$.

Table 6
Local recurrences after neoadjuvant endocrine therapy followed by surgery with or without radiotherapy, in series of breast cancer patients at the Edinburgh Breast Unit

Agent	No. of patients	No. with no XRT[a]	Number with local recurrence	Number with XRT[b]	Number with local recurrence	Median follow-up (months)
Tamoxifen	47	13	4	34	0	84
Letrozole	34	10	4	24	1	70
Anastrozole	21	0	0	21	1	51
Exemestane	10	4	1	6	0	42
Total	112	27	9	85	2	62

[a] Number of patients who, following 3 months of neoadjuvant therapy, underwent breast-conserving surgery without local radiation therapy (XRT).
[b] Number of patients who, following neoadjuvant therapy, underwent both breast-conserving surgery and local radiotherapy.

therapy also produces response rates of up to 80% (Table 5). In the Milan study, 16% of 227 cases having breast-conserving surgery had evidence of multifocality tumour within the wide excision specimen with the frequency being highest in larger tumours [20]. Following neoadjuvant chemotherapy in the Royal Marsden series 28% of patients who underwent breast-conserving surgery had involved margins [21]. In a series of patients with locally advanced breast cancer treated with neoadjuvant chemotherapy prior to surgery, 62.5% of patients had multiple foci of tumour remaining after wide local excision [22]. This contrasts with our own experience of surgery after neoadjuvant endocrine therapy of 47 patients who initially were treated by breast-conserving surgery after treatment with neoadjuvant tamoxifen where in only one case was there an incomplete excision in a patient with invasive lobular cancer [23].

In a subsequent series treated with neoadjuvant aromatase inhibitors, 65 patients had breast-conserving surgery and only two of these had an incomplete excision. When the residual tumour was evaluated histologically, the nature of the response to neoadjuvant endocrine therapy was somewhat different in that the whole tumour appears to shrink concentrically whereas with chemotherapy the extent of disease was often noted by our pathologist to have remained unchanged while the cellularity of the tumour was usually markedly reduced.

1.8. Local recurrence following neoadjuvant endocrine therapy followed by breast-conserving surgery

Several studies have examined the rates of tumour recurrence following neoadjuvant therapy followed by surgery. Veronesi et al. reported 12 cases of local recurrence in 203 patients with a median follow-up of 3 years after preoperative chemotherapy [24]. This was considerably better than the 22% recurrence rate among the patients who underwent mastectomy because after chemotherapy they were unsuitable for breast-conserving surgery. In another trial, the recurrence rates were similar for patients receiving initial chemoendocrine therapy with recurrence rates of 3.5% compared with patients treated in the standard manner (surgery followed by systemic therapy) where the recurrence rate was 2.7% [25]. The only data available on local recurrence after breast-conserving surgery in patients treated with neoadjuvant endocrine therapy are presented in Table 6. These are data from Edinburgh and demonstrate that the overall recurrence rate without radiotherapy was 33% at 5 years [23]. If patients who did not have radiotherapy are excluded, only two patients from a total of 85 have developed a local recurrence at a median follow-up of 5 years. These results indicate that breast-conserving surgery followed by radiotherapy achieves satisfactory local disease control in patients downstaged by neoadjuvant endocrine therapy.

The population of patients who are treated with neoadjuvant endocrine therapy tend to be elderly and these patients can have significant comorbidity. For many of these patients despite locally advanced disease they will die from causes other than breast cancer. For this reason, it is difficult to compare long term survival of these patients with a series treated with adjuvant endocrine therapy.

Both disease free survival and overall survival have been reported to be similar in patients treated with neoadjuvant chemotherapy preoperatively and in patients treated with systemic therapy after surgery [26–29]. A recently presented trial comparing preoperative ER directed neoadjuvant versus adjuvant therapy was presented and showed no difference in survival for patients treated with neoadjuvant endocrine or chemotherapy compared with patients having initial surgery and follow-up systemic therapy [30].

2. Conclusion

Neoadjuvant endocrine therapy does appear to be effective. Reductions in tumour volume using primary endocrine therapy in ER and/or PgR positive tumours are similar to those reported with neoadjuvant chemotherapy. In contrast, toxicity is much lower with neoadjuvant endocrine therapy and it is extremely well tolerated, with very few patients having to discontinue therapy because of side effects.

From a surgical perspective, the ability to perform less extensive surgery is an advantage especially considering the comorbidity and overall general health of the group of patients who tend to be treated with neoadjuvant endocrine therapy. The currently available data suggests that breast-conserving surgery followed by radiotherapy

produces adequate local disease control in patients downstaged by neoadjuvant endocrine therapy.

The patients who are most likely to respond to neoadjuvant endocrine therapy are those who have higher levels of ER (ALLRED score 6 and above). Response rates to neoadjuvant therapy in postmenopausal women have been shown to be higher when using aromatase inhibitors than with tamoxifen. This may partly be due to the fact that aromatase inhibitors are effective in both erbB2 positive and negative cancers while tamoxifen is less effective in erbB2 positive tumours and that the aromatase inhibitors produce responses in tumours with lower levels of ER whereas tamoxifen does not.

Results of the currently ongoing trails using neoadjuvant endocrine therapy are awaited with interest.

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