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# Neo-adjuvant exemestane in elderly patients with breast cancer: a phase II, multicentre, open-label, Italian study

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**Background:** The steroidal aromatase inhibitor exemestane has demonstrated efficacy for the treatment of breast cancer in the metastatic and adjuvant settings. Smaller trials have also reported efficacy in the neo-adjuvant setting.
**Patients and methods:** This phase II, open-label, multicentre study examined the efficacy and safety of neo-adjuvant exemestane in women aged >70 years with operable, receptor-rich breast cancer. Consecutive eligible patients received exemestane 25 mg/day for 6 months before planned surgery. The primary end point was clinical response.
**Results:** Overall, 117 patients were recruited (median age 80 years). The objective response rate in 112 assessable patients (85 with clinical and mammographic evaluation; 27 with clinical evaluation only) was 69.6% (two complete responses; 76 partial responses). In patients who responded, median tumour size reduced from 4.81 to 2.12 cm. Seventy-seven patients (68.7%) continued to surgery. Of the 40 patients eligible for breast-conserving surgery, 34 (85%) deemed unfit for this procedure at baseline. Exemestane-related adverse events were unremarkable except for grade 3 allergic skin reactions in two patients (1.8%).
**Conclusion:** Neo-adjuvant exemestane given for 6 months appears to be effective for receptor-rich breast cancer in older patients. There may now be sufficient evidence to support the use of neo-adjuvant in this patient population.
**Key words:** aromatase inhibitor, breast cancer, endocrine therapy, exemestane, neo-adjuvant



## introduction

There is an increasing amount of evidence supporting the potential for primary neo-adjuvant endocrine treatment of breast cancer, particularly for older patients who account for ~20% of breast cancers [1]. Neo-adjuvant endocrine treatment alone may avoid the need for surgery [2] and constitute a better early predictor of both local and long-term outcome than adjuvant treatment [3, 4].

Tamoxifen, a selective oestrogen receptor (ER) modulator, has been the principal adjuvant therapy for pre- and postmenopausal women with hormone receptor-positive breast cancer for ~20 years. In one phase III, randomised trial in older women with early breast cancer who underwent surgery (radical or minimal) followed by adjuvant tamoxifen therapy, overall survival or death was not significantly different from that observed in women receiving tamoxifen alone [2]. Tamoxifen alone was also shown to be an adequate alternative to surgery in very old/frail patients [5].

Following their introduction, aromatase inhibitors have changed the standard of care in breast cancer. The European Society for Medical Oncology Expert Panel updated recommendations describe these agents as: 'Well-established in the neo-adjuvant endocrine treatment of postmenopausal women with hormone-responsive tumours'[6]. In two phase III, randomised trials comparing 3 months of primary neo-adjuvant treatment with tamoxifen or anastrozole, no significant differences observed between the two agents in terms of objective response rate. However, in both studies anastrozole was associated with significant improvements compared with tamoxifen with respect to the proportion of patients eligible for breast-conserving surgery [7, 8]. In a 4-month, phase III, randomised trial, neo-adjuvant treatment with letrozole was associated with a significantly superior response rate compared with tamoxifen [9]. The steroidal aromatase inhibitor exemestane has demonstrated superiority to tamoxifen in randomised clinical trials in both the metastatic [10] and adjuvant settings [11]. In small, open-label, phase II trials in the neo-adjuvant setting, exemestane treatment resulted in response rates of 45–80% [12, 13], with 5.5% of patients in one study achieving a complete pathological response [13]. A phase II multicenter study with neo-adjuvant exemestane given for 4 months achieved on 80 patients 41% response rate [14]. In a recent open-label, phase II trial ($n = 44$) of neo-adjuvant exemestane, a clinical response was seen in 66% of 41 assessable

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patients; pathological partial responses (PRs) were seen in 43% of patients [15]. In a separate 3-month, randomised, phase II trial ($n = 151$) comparing neo-adjuvant exemestane with tamoxifen, patients receiving neo-adjuvant exemestane achieved both a superior objective response rate and a superior rate of conversion to breast-conserving surgery [16].

Here we report the results of a study investigating the efficacy and safety of neo-adjuvant exemestane in older patients with operable, receptor-rich breast cancer.

## patients and methods

### study design

In this multicentre phase II, open-label trial, patients aged >70 years with ER and/or progesterone receptor (PgR)-positive tumours were treated with primary exemestane 25 mg/day for 6 months before surgery. The study had the approval of the ethics committees of participating centres and all patients provided written informed consent.

### inclusion criteria

For inclusion in the study, patients were required to be aged >70 years with histological evidence of invasive breast cancer. Tumours with >10% staining nuclei were defined as ER and/or PgR positive. Operable disease was defined as T1, T2, T3a; N0 or N1; absence of distant metastases was assessed by clinical examination, chest X-ray, bone scan and liver ultrasound. Patients were required to be fit for surgery and available for follow-up. Patients with a history of previous or concomitant malignancy (except treated skin cancer or *in situ* carcinoma of the cervix), or prior chemotherapy and/or hormone therapy, were excluded from the study.

### study end points

The primary end point was the clinical response rate [complete response (CR) + PR] to exemestane. Secondary end points were the mammographic/ultrasound response rate, conversion to breast-conserving surgery rate and safety assessments. Biological characteristics assessment of cellular proliferation (Ki-67 antigen determined by immunochemistry by MIB-1) and HER-2/neu status [by immunochemistry (IHC)] were also recommended.

### statistical analysis

In phase II/III neo-adjuvant trials, patients receiving tamoxifen for 6 months achieved a response rate (PR + CR) of 39%–50% [2–5, 17, 18]. Patients receiving neo-adjuvant letrozole for 4 months in a phase III trial achieved a 34% mammographic response rate versus 16% with tamoxifen [9]. In the present study, we expected at least a similar response rate than that observed with letrozole in the latter study: i.e. between 35% and 40%. We also estimated ~25% of probability of protocol violations, therefore, if eight CR + PR were observed in the first 20 patients, a further 30 patients would be treated; if ≥20 CR + PR were observed in these 50 patients, a further 50 patients would be recruited, making a total of 100 patients.

### tumour response and toxicity evaluation criteria

Local tumour response was assessed by caliper and mammography, in accordance with the Eastern Cooperative Oncology Group criteria, adopted also for toxicity evaluation [19]. (Complete Response: disappearance of all the known manifestations of the disease; Partial Response: 50% or more reduction in the total size of the cancerous lesions that have been measured; Stable Disease: tumour reduction less than 50%.)

Clinical and instrumental (mammography ± ultrasound) examination was planned at entry, after 3 and 6 months. Follow-up after surgery (or refusal of surgery) was recommended but was not a study end point.

## results

### baseline characteristics and disposition

An observed response rate of 66% in first 20 and 50 patients meeting the study inclusion criteria [20] met the predetermined criteria for further recruitment, and a total of 117 patients were enrolled from July 2001 to December 2006. The median age was 80 years (range 65–92). Only one patient was aged <70 years. Median baseline tumour size at baseline was 4 cm (range 1.2–20) and only 12 patients were suitable for breast conservative surgery. The median value for ER status was 90% (0%–100%) and for PgR status 55% (0%–95%). Overall, 72% of tumours were ER/PgR positive, 27.2% were ER positive/PgR negative and one tumour (0.9%) was ER negative/PgR positive. Main patients and basal tumour characteristics are shown in Table 1.

Five patients (6.1%) were not assessable for response evaluation due to early refusal (one patient) or withdrawal as a result of toxicity (one patient); three patients were lost to follow-up. Thus, 112 patients were assessable for response (85 with both clinical and mammographic evaluations, 27 with clinical evaluation only).

### response rates

The overall clinical response rate was 69.6% (76 PR; two CR). Twenty-six of the 112 patients (23.2%) had stable disease (SD) and eight (7.1%) experienced local progression. The two patients achieving a CR had clinical evaluation data only (Table 2).

Among the 85 patients with both mammographic and clinical response evaluation, the response rate at 6 months was 73% (73% PR; 0 CR); 22.3% had SD. Overall response rate at 3 months was 44.7% and at 6 months 72.9%, with an odds ratio of 0.32 (95% confidence interval 0.16–0.63, $P = 0.0003$)

**Table 1.** Main patient and basal tumour characteristics

| | *n* (%) |
|---|---|
| Median age, years (range) | 80 (65–92) |
| Clinical stage | |
| T <2 cm | 13 (11.6) |
| T 2.1–5 cm | 86 (76.9) |
| T >5 cm | 13 (11.6) |
| N0 | 59 (52.6) |
| N1 | 33 (29.4) |
| N2 | 20 (17.8) |
| ER, median % (range) | 90 (0–100) |
| PR, median % (range) | 55 (0–95) |
| ER+ PgR+[a] | 81 (72.3) |
| ER+ PgR−[a] | 30 (26.7) |
| ER− PgR+[a] | 1 (0.9) |

[a]Tumours with >10% staining nuclei were defined as ER and/or PgR positive.

ER, estrogen receptor; PR, progesterone receptor.

**Table 2.** Efficacy end points (basal versus 6 months)

| | Clinical evaluation only (palpation/caliper), $n = 27$ | Mammographic evaluation, $n = 85$ | $P$ value | Overall, $n = 112$ |
|---|---|---|---|---|
| CR | 2 (7.41%) | 0 | n.s. | 2 (1.8%) |
| PR | 13 (48.1%) | 62 (72.9%) | n.s. | 76 (67.8%) |
| Stable disease | 8 (29.6%) | 19 (22.3%) | n.s. | 27 (24.1%) |
| Progressive disease | 4 (14.8%) | 4 (4.7%) | n.s. | 8 (7.1%) |
| Overall RR (CR + PR) | 15 (55.5%) | 62 (72.9%) | n.s. | 78 (69.6%) |

CR, complete response; PR, partial response; RR, response rate; n.s., not significant.

**Table 3.** Efficacy end points (3 versus 6 months), only patients with mammographic evaluation

| | 3 months ($n = 85$) | 6 months ($n = 85$) | Odds ratio (95% CI) | $P$ value |
|---|---|---|---|---|
| CR | 0 | 0 | | n.s. |
| PR | 39 (44.7%) | 62 (72.9%) | 0.32 (0.16–0.63) | 0.0003 |
| Stable disease | 42 (49.4%) | 19 (22.3%) | 3.33 (1.67–7.00) | 0.0002 |
| Progressive disease | 4 (4.7%) | 4 (4.7%) | | n.s. |
| Overall RR (CR + PR) | 39 (44.7%) | 62 (72.9%) | 0.32 (0.16–0.63) | 0.0003 |

CR, complete response; PR, partial response; RR, response rate; n.s., not significant.

(Table 3). Tumour size and change over time by type of evaluation is shown in Table 4. In the same population, no significant difference was observed between mammographic and clinical evaluations (72.9% versus 64.1% PR, $P = 0.6$). The median final tumour size in patients who responded to exemestane treatment was 2.5 cm (range 0–10). Median time to the best response was 7.75 months (range 3.8–23.6).

### surgical outcomes

Thirty-five patients did not progress to surgery due to refusal ($n = 25$) (SD 4 of 25, PR 17 of 25, not assessable 4 of 25), presence of comorbidities ($n = 8$) or achievement of clinical CR ($n = 2$). Of the remaining 77 patients (68.7%), 29 (37.6%) underwent modified radical mastectomy, eight (10.3%) underwent simple mastectomy, 28 (36.3%) underwent quadrantectomy and 12 (15.6%) underwent lumpectomy. Thus, a total of 40 patients (52%) were assessed as suitable for breast-conserving surgery interventions. Thirty four of these patients (85%) have been assessed as unfit for breast-conserving surgery at baseline. Pathological median tumour size was 2 cm (0.1–6) and no pathogical complete response (pCR) was reported.

### biological characteristics

Baseline and posttreatment biological characteristics were available for 74 of 77 patients who underwent surgery. Ki67 values decreased significantly regardless of local response (Table 5) with no correlations between baseline Ki67 value and local response or between Ki67 decrease and response.

HER2 status was available for 71 patients by IHC. Seven cases were 3+. Among the 23 IHC 2+ cases, FISH is available only in 12, with three cases showing gene amplification. Thus, HER2 certainly positive tumours are 10. Seven had a PR, two SD and one progressive disease, with a response rate similar to the overall population. No significant variation in ER status was noted. However, PgR levels showed a significant nine-fold increase ($P = 0.02$) in patients with local progression and a significant decrease in patients with SD ($P = 0.01$) or a PR ($P = 0.01$) (Table 5).

### safety

Treatment-related adverse events were rare and mild. Adverse events observed included three patients (2.6%) with grade 2 hot flashes and one patient (0.9%) each with grade 2 asthenia, grade 3 asthenia, grade 1 nausea, grade 3 muscle pain and grade 2 allergic skin reaction. Only one of these patients withdrew from the trial (grade 2 allergic skin reaction).

## discussion

The present study demonstrated the efficacy and tolerability of exemestane for the neo-adjuvant treatment of endocrine-sensitive breast cancer in elderly women with operable but large tumours. In view of the age of the patients and the size of the tumours, the high response rate obtained is particularly interesting and probably due to the very high hormone receptor expression, which is related to an higher probability of response to neo-adjuvant treatment, in particularly with aromatase inhibitors [7, 26].

Another important issue is the optimal neo-adjuvant treatment duration: in previous studies with tamoxifen it was 6 months [2, 5, 17, 18]. In studies comparing neo-adjuvant anastrozole and tamoxifen, anastrozole did not demonstrate a higher response rate compared with tamoxifen at 3 months [7, 8]. Letrozole demonstrated a significantly higher response rate than tamoxifen at 4 months (34% versus 16% mammographic response rate; 45% versus 35% conversion rate to breast-conserving surgery) in the P024 study, although the response rates in both arms were quite low [9]. Exemestane given for 4 months obtained a 41% response rate [14]. A recent report noted that prolonging primary endocrine treatment in responders beyond 3 months improved response rates [21, 22]. Compared with the results of shorter duration studies, our findings, in patients with relatively large tumours, support this research. Best ever response was reached by 3 months in 33% of patients and by 6 months in the remaining 66%, leading to a final response rate of 70% with 23% of patients having SD. As

**Table 4.** Tumour size changes from baseline to 3 and 6 months, only patients with mammographic evaluation

| $n = 85$ | Baseline evaluation | 3 months | 6 months | Basal versus 6 months ($P$ value) |
|---|---|---|---|---|
| Median tumour size (range, in cm) | | | | |
| Overall clinical | 4 (1.2–20) | 3 (0–10) | 2.5 (0–10) | 0.00001 |
| Overall mammography | 3 (1.3–20) | 2 (0.7–7) | 2 (0–5) | 0.0001 |
| T size variation (% patients) | | | | |
| <2 cm | 11.6 | 34.2 | 44.3 | 0.001 |
| 2.1–5 cm | 76.9 | 59.2 | 52.5 | 0.01 |
| >5 cm | 11.6 | 6.4 | 3.09 | 0.05 |

**Table 5.** Baseline and final Ki67 and PgR values (%), by local response

| | Basal median value % (range) | Final median value % (range) |
|---|---|---|
| Ki67 | | |
| PD | 23.6 (7.1–40.0) | 12.3 (−4.2–28.9) ($P = 0.02$) |
| SD | 14.2 (9.3–19.1) | 6.7 (3.3–10.0) ($P = 0.02$) |
| PR | 17.2 (13.9–20.5) | 6.7 (4.4–9.0) ($P = 0.05$) |
| PgR | | |
| PD | 5 (0–30) | 45 (20–70) ($P = 0.02$) |
| SD | 80 (0–90) | 2 (0–90) ($P = 0.01$) |
| PR | 50 (0–95) | 15 (0–90) ($P = 0.02$) |

PgR, progesterone receptor; PD, progressive disease; SD, stable disease; PR, partial response.

shown in Table 3, a longer treatment more than doubles the probability of response.

In the present study, Ki67 significantly decreased in 72% of patients following treatment with exemestane and increased in 28.3%. In contrast with a multivariate analysis of the recent IMPACT trial, where increases in Ki67 levels were significantly associated with shorter disease-free survival [23, 24], no correlation between changes in Ki67 level and tumour response was found in the present study. There was, however, a highly significant correlation between an increase in PgR levels and local disease progression and, conversely, between decreases in PgR levels and tumour response. According to a recent paper by Miller [25], the predictive value of ER/PgR changes is still under discussion. Nevertheless, our findings are intriguing and warrant further investigation. HER2 positive cases are too few in order to give a reliable information, by the way response rate is consistent with data of other authors reporting similar efficacy of aromatase inhibitors in HER2 positive or -negative, endocrine-sensitive tumours [26]. In our study, because of the small sample size and lack of information about the HER2 evaluation method among different Centres, no conclusion can be drawn on this topic.

The efficacy of aromatase inhibitors in HER2 positive tumours is controversial, but data from a phase II study with exemestane recently suggested no relationship between the HER2 status and tumour response [14].

No patient in our study achieved a pCR; however, primary endocrine treatment is known to have a low pCR rate compared with chemotherapy (approximately < 5% versus 20%, respectively). Adjuvant endocrine treatment is the gold standard for endocrine-responsive tumours in postmenopausal women [27] and there is evidence that chemotherapy has little effect in the majority of these patients [27, 28], based on both older [29–31] and more recent data [32–35] from primary chemotherapy trials.

Different molecular subtypes of tumours respond to chemotherapy, with a high response rates in receptor-negative tumours and evidence of relative resistance in endocrine-sensitive tumours [36]. Primary endocrine treatment with tamoxifen showed no difference versus primary chemotherapy in a small randomised trial [37] and also in locally advanced disease [38]. Similarly, a lack of difference between anastrazole and exemestane versus chemotherapy was reported more recently in a small randomised, phase II trial [39], in which pCR was achieved in 7.4%, 3.3% and 6.8% of patients receiving chemotherapy, anastrozole and exemestane, respectively. Similarly, a recent Austrian phase II study reported with exemestane for 4 months 3% pCR [14].

## conclusions

As expected from published phase III trials in patients with breast cancer in the metastatic and adjuvant settings, exemestane also appears to be active and well tolerated in the neo-adjuvant setting. In elderly, frail patients, exemestane could be considered the only treatment required. There may now be sufficient evidence to consider exemestane for neo-adjuvant treatment in patients with receptor-rich tumours. However, further phase III trials would be useful to understanding whether primary endocrine treatment would be a suitable alternative to chemotherapy in younger patients.

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