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Anastrozole as Neoadjuvant Therapy for Patients with Hormone-dependent, Locally-advanced Breast Cancer

A. MILLA-SANTOS[1], L. MILLA[2], N. CALVO[2], J. PORTELLA[3], L RALLO[1], J.M. CASANOVAS[4], M. PONS[3] and J. RODES[3]

[1]*Medical Oncology Service and*
[3]*Gynecology Service, Sanitas Hospitales, Barcelona;*
[2]*CRC Radiological Department, University Hospital S Juan, Reus, Tarragona;*
[4]*Medical Oncology Service, Clınica Carmelitana, Barcelona, Spain*

Abstract. *Background: We investigated the efficacy and safety of anastrozole as neoadjuvant therapy in a group of postmenopausal patients with locally-advanced breast cancer. Patients and Methods: This was an open-label trial, which recruited patients with histopathologically-confirmed unilateral, locally-advanced, estrogen-receptor-positive breast cancer (stage III A/B). All patients received anastrozole 1 mg/day for 3 months, after which the clinical response was evaluated. All patients with a complete or partial clinical response (cCR or cPR) underwent surgery (radical modified mastectomy), after which patients continued with the same therapy for two years or until progression. Primary end points were clinical response rate (cCR + cPR), surgery rate, pathological complete response rate and tolerability profile. Results: cCR and cPR were seen in 61/112 (54.5%) and 32/112 (28.6%) patients (n=112), respectively, giving an objective response rate of 93/112 (83%) patients. Following surgery in responding patients, 14/61 patients (23%) had a pathological CR and 47/61 (77%) patients had a pathological PR. Conclusion: Neoadjuvant anastrozole treatment was highly effective and well-tolerated in postmenopausal women with hormone-dependent locally-advanced breast cancer.*

The current attractiveness of neoadjuvant therapy for locally-advanced breast cancer lies in its ability to downstage both the primary tumor and the axilla and increase the number of patients who are eligible for surgery. In the neoadjuvant setting, endocrine therapy is superior to chemotherapy in patients with estrogen-receptor-positive (ER+) tumors (1), and also has theoretical and practical advantages. For example, the inhibition of estrogen-stimulated enzyme release may reduce tumor cell shedding, while estrogen withdrawal reduces growth factor synthesis and disrupts the function of several growth factors and hormone receptors and their second messenger signaling pathways (2-4). Drugs that reduce the availability of estrogen, either by acting as estrogen receptor antagonists, such as tamoxifen, or by inhibiting estrogen synthesis, such as the aromatase inhibitors anastrozole and letrozole, represent the major hormonal options for neoadjuvant therapy of postmenopausal patients with large ER+ tumors (5-6).

Despite the potential benefits of neoadjuvant endocrine therapy, there is widespread use of neoadjuvant chemotherapy and to date only a few trials have evaluated the role of endocrine therapy in this setting. The majority of these studies involved older patients who received tamoxifen, aminoglutethimide, 4-hydroxyandrostenedione or, more recently, the newer aromatase inhibitors letrozole and anastrozole (7-11).

We have previously performed an independent, prospective, randomized, double-blind trial to evaluate the role of anastrozole as first-line therapy for advanced breast cancer (12). In this study, anastrozole (1 mg/day) was superior to tamoxifen (40 mg/day) in terms of clinical benefit, median duration of clinical benefit and survival. We initiated a prospective, non-randomized trial to evaluate anastrozole as neoadjuvant therapy in a group of postmenopausal women with hormone-dependent, locally-advanced breast cancer. The results of this study are provided in the present paper.

Patients and Methods

Eligibility criteria. The patients included in this trial were postmenopausal with histopathologically-confirmed large unilateral breast tumors (confirmed by a biopsy that was performed before enrolment) (stage III A/B); positive ER status; ECOG (Eastern

Correspondence to: Dr A. Milla-Santos, Medical Oncology Service, Sanitas Hospitales, 111 Balmes St. 08008, Barcelona, Spain. Tel: 34 93 650 27 13, Fax: 34 93 451 10 79, e-mail: drmilla@inicia.es

Key Words: Anastrozole, breast cancer, postmenopausal, hormone-dependent tumors.

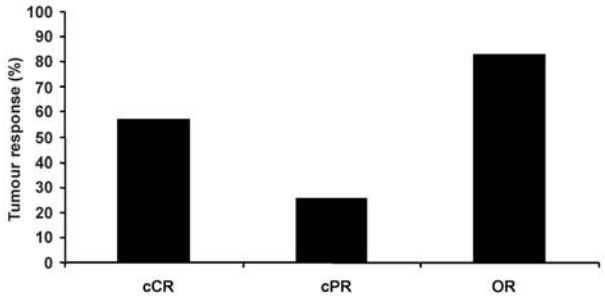

Figure 1. *Clinical tumor response in postmenopausal patients with locally-advanced breast cancer following three months of treatment with anastrozole (1 mg/day).*

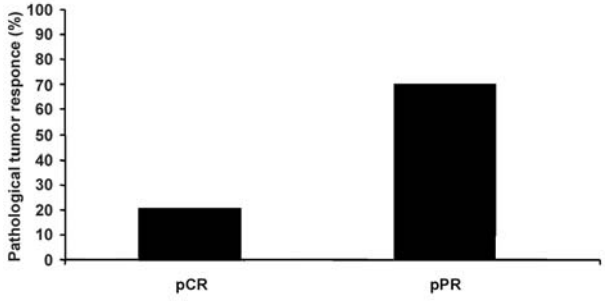

Figure 2. *Pathological tumor response (pCR and pPR) post-surgery in postmenopausal patients receiving anastrozole (1 mg/day) treatment.*

Cooperarative Oncology Group) performance status of 0-1 and adequate organ function. Patients who had received any previous therapy for breast cancer were not eligible for inclusion.

Study design. Eligible patients received anastrozole 1 mg/day for three months. After this time, objective response (OR) to therapy (complete clinical response [cCR] + partial clinical response [cPR]) was assessed by repeating the staging procedures, following WHO guidelines (13). Response was defined as the best response recorded from the start of anastrozole therapy. A cCR indicated clinical and radiological evidence of a 100% regression of the tumor, whereas cPR was defined as a >50% reduction in tumor size compared with baseline measures. A cCR and cPR were confirmed by two evaluations of the disease by means of mammography, ultrasonography and caliper assessment (using the Kenny and colleagues formula, in which V is tumor volume and D is the mean diameter (14)).

$$V = \frac{D^3 \times \Pi}{6}$$

All patients showing an OR underwent radical modified mastectomy. Breast-conserving surgery was not permitted as the breast tumors at enrolment were very large. Pathological specimens of the primary lesion and axilla were then assessed for evidence of pathological CR (pCR) (total histopathological disappearance of the tumor following analysis of the specimens of the primary lesion and axilla) and pathological PR (pPR) (any tumoral evidence in the specimens of the primary lesion and axilla). Following surgery, all patients showing a pCR or pPR received anastrozole 1 mg/day for a further two years. Patients who did not show an OR following neoadjuvant anastrozole therapy underwent radiotherapy. Side-effects were evaluated according to WHO criteria (15).

The procedures followed were in accordance with the standards of the responsible Institutional Committee on Human Experimentation and with the Helsinki Declaration of the World Medical Association amended in 1975 and 1983. All patients gave signed informed consent.

Results

Recruitment into the study began in June 1998 and, by the cut-off date (September 2001), data from 74 patients were available. Median age was 64.7 (range 56-73) years; 29 (39%) and 45 patients (61%) had stage III A and stage III B breast cancer, respectively.

Tumor responses following treatment are illustrated in Figure 1 and were as follows: 13/74 patients (18%) did not respond to neoadjuvant anastrozole treatment and thus underwent radiotherapy; 42/74 patients (57%) showed a cCR and 19/74 patients (26%) showed a cPR. Thus OR (cCR + cPR) was seen in 61/74 patients (83%).

All patients showing an OR (61/74 (83%) patients) underwent a radical modified mastectomy. Following surgery, 14/61 patients (23%) had a pCR and 47/61 patients (77%) had a pPR (Figure 2). All 61 patients with an OR therefore received anastrozole treatment for a further two years.

By the cut-off date, the status of the patients recruited into the study was as follows: a total of 54/74 patients (73%) remain in the trial and are continuing adjuvant anastrozole therapy; 8/74 patients (11%) have stopped treatment due to disease progression (bone metastases n=7; lung metastases n=1); 11/74 patients (15%) have died and the status of one patient is unknown (lost to follow-up) (Figure 3).

Throughout the study anastrozole treatment was well-tolerated, with a low incidence of side-effects (Figure 4): leucorrhea (5% of patients), vaginal bleeding (5%), fluid retention (4%), hot flashes (5%), sweating (1%) and somnolence (5%).

Discussion

Subsequent to our previous demonstration (12) that anastrozole is a highly effective drug in postmenopausal patients with hormone-dependent advanced breast cancer, we initiated a trial to investigate the role of anastrozole as neoadjuvant therapy in postmenopausal patients with large hormone-dependent breast tumors.

In this study, 83% of patients obtained a cCR or cPR. These figures are in accordance with those of other investigators using similar strategies (7-11). After neoadjuvant

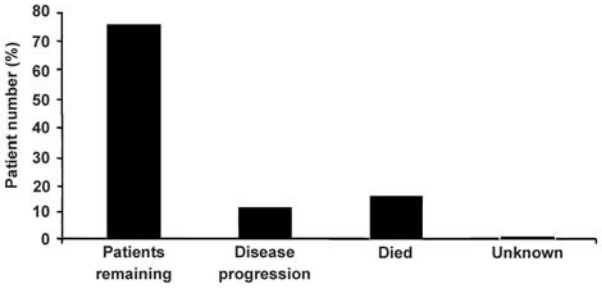

Figure 3. *Patient status post-surgery (assessed September 2001).*

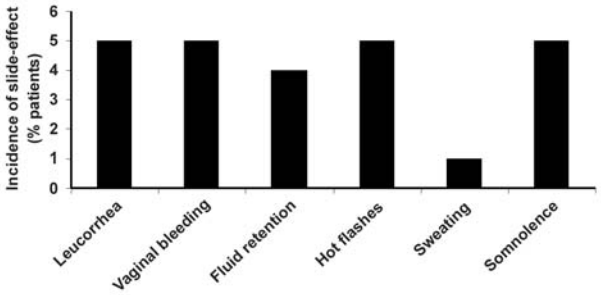

Figure 4. *Side-effects reported by patients during treatment with anastrozole (1 mg/day) in postmenopausal patients with locally-advanced breast cancer.*

treatment, all responding patients were suitable for surgery and underwent a modified radical mastectomy. No adjuvant radiotherapy was required after this surgery and no local relapses have been observed to date. By contrast, in the majority of the previous studies, elderly patients were treated with radiotherapy as many patients were not suitable for surgery. In many instances in these neoadjuvant studies with endocrine treatment, adjuvant radiotherapy was also used after surgery (7-11). All of our patients underwent an adequate surgical procedure and histology of the wide excision specimens demonstrated that all tumors were completely removed.

We found that, in patients who had a clinical OR to neoadjuvant endocrine therapy, pathological assessment demonstrated a pCR in 23% of patients. In the remaining patients, a clear decrease in tumor cellularity and increased fibrosis was evident. The extent of tumor reduction following neoadjuvant endocrine therapy correlated with outcome: 73% of patients remain in our trial and are continuing with adjuvant anastrozole treatment, whereas 15% of patients have died. These figures are encouraging considering that this patient subset generally has a very poor outcome. The low incidence of side-effects observed is also of note, with no severe events being seen.

It has been shown that neoadjuvant endocrine therapy is potentially superior to neoadjuvant chemotherapy in patients with hormone-dependent, locally-advanced breast cancer (1). Tamoxifen and the newer aromatase inhibitors, anastrozole and letrozole, represent the main therapeutic options for postmenopausal patients with ER+, locally-advanced breast cancer. Substantial reduction of tumor size following three months' treatment has been recorded with the use of such therapies. Several studies have reported CR rates ranging from 8-68% and PR rates from 15-75% following neoadjuvant endocrine therapy, with over 80% of patients then being suitable for surgery and showing a high level of pathological responses, both complete and partial (11,17-19). Tamoxifen is currently the most important therapeutic option for postmenopausal patients with large ER+ breast tumors. Of particular note is that responses following neoadjuvant anastrozole are at least as good as those with tamoxifen. This was shown in our previous trial, comparing anastrozole with tamoxifen in advanced breast cancer (12), and by the combined analysis of the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability) and the North American studies (20).

Table I. *Patient baseline characteristics.*

	Anastrozole (1mg) n=74
Median age (years)	64.7
Age range	56-73
Breast cancer stage	
Stage III A (no. [%])	29 (39)
Stage III B (no. [%])	45 (61)

An exciting aspect of neoadjuvant endocrine treatment in the multidisciplinary management of locally advanced breast cancer is the potential for rapid evaluation of promising novel cancer treatments in patients with a very poor prognosis. Other studies have documented the activity of neoadjuvant tamoxifen in patients with hormone-dependent, locally advanced breast cancer (2-6, 21, 22), demonstrating an OR rate of 40-60%. The efficacy of letrozole as neoadjuvant hormonal therapy was investigated in a study by Dixon *et al.* (23). A small number of patients (24) were treated with two different letrozole doses (12 patients with 2.5 mg and 12 with 10 mg) with a response rate of 81%. Furthermore, in a study including 337 patients as primary systemic therapy, letrozole (2.5 mg od) was reported to be significantly superior to tamoxifen with regards to OR rate (20 mg od) ($p<0.001$) (24). A further trial by Dixon *et al.* (11) investigated 24 postmenopausal patients who were treated with anastrozole 1

mg or 10 mg. The median reduction in tumor volume on ultrasound was 75.5% (95% CI 51-79) (data for both doses combined) and the authors concluded that the results were almost identical to those seen with letrozole.

The results of the current trial show that anastrozole is highly effective as neoadjuvant endocrine therapy for patients with hormone-dependent, locally-advanced breast cancer and is a reasonable alternative to the traditional and more aggressive neoadjuvant chemotherapy. The benefits of anastrozole included good efficacy and a low incidence of side-effects. Our initial results are very encouraging and longer-term follow-up is continuing to evaluate the effects of neoadjuvant anastrozole on overall outcomes.

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