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Original article

Neoadjuvant endocrine therapy in breast cancer patients

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ABSTRACT

Background: The aim of this study is to evaluate if the extension of neoadjuvant endocrine therapy (NET), beyond the conventional time, allows additional downstage of the tumour, in order to perform a breast conservative surgery (BCS), and to analyze if it is a good option for long-term control in patients who refuse or are unfit for surgery.
Patients and methods: We retrospectively reviewed a database containing all patients treated in our institution with NET. All included patients were post-menopausal with primary local disease. The type of response obtained was assessed using modified RECIST criteria.
Results: Thirty-three patients were included. Two patients had tumours with 90% expression of oestrogen receptors and all the others had 100%. The tumour size in the largest diameter was 6.51 cm before treatment and 5.18 cm after. Eighteen patients achieved a partial response after 10.28 months of therapy. Patients that were proposed to downstage the tumour performed 9.71 months of therapy until surgery and all were submitted to BCS. Progression occurred after 27.5 months.
Conclusion: Endocrine therapy is a feasible option for a longer time to allow additional downstage of the tumour and is a good solution in patients who refuse or are unfit for surgery.

Introduction

Breast cancer (BC) is the most common type of cancer in women.[1,2] Its incidence is expected to increase with ageing of the population.[1,2] As estrogens have a major impact in BC development and progression, endocrine therapy is an increasingly used treatment option both as adjuvant (after surgery) or neoadjuvant (alone or before surgery).[3–5] Currently used drugs are tamoxifen and aromatase inhibitors (AIs): letrozole, anastrozole and exemestane.

In what concerns pre-menopausal women, neoadjuvant endocrine therapy (NET) is contra-indicated[3,6,7] because studies are lacking to take conclusions, and for the moment, the ones that exist are contradictory.[8,9] On the other hand, regarding post-menopausal patients, in the most important international Guidelines[3,6,7,10] there are no precise orientations related to NET.

For many years tamoxifen was validated as initial sole treatment for frail elderly women, with overall response rates achieving 73%.[11] A study from Nottingham randomized women with estrogen receptor (ER)-positive cancers for mastectomy plus 5 years of tamoxifen versus tamoxifen alone for 5 years.[12] The update of the phase III GRETA trial did the same but there were no data concerning ER expression.[13] Some results of the studies mentioned are shown in Table 1.

Nevertheless, the group in which there is more controversy is that of young and fit postmenopausal women with inoperable locally advanced tumour in whom breast conservative surgery is not possible.[3,9,14–18] In luminal cancers, the pathologic complete response (pCR) rate to chemotherapy is much lower and, consequently, neoadjuvant chemotherapy is of limited benefit.[3,9,14–17] Actually, there are some studies that compare hormonal therapy to chemotherapy before surgical treatment in strong ER expression tumours.[9,15,19] The major results of those studies are shown in Table 2.

Besides the controversy over the effectiveness of NET, there is also no consensus on how long the treatment should last. The conventional treatment period is 3–4 months.[16,17,20,21] However, recent trials have reported better results with the extension of the treatment's duration.[17,18]

Dixon et al. conducted a study in which patients with locally advanced ER-positive cancers were submitted to neoadjuvant letrozole.[21] More recently Llombart-Cussac et al. published a small phase II trial with letrozole and the goal was to establish mean time to maximum response.[22] Until the 4th month those who progressed or had stable disease were excluded, 37.1% women improved after

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Table 1
Results of the Nottingham study and the update of the phase III GRETA trial.

	Nottingham[12]		Update of phase II GRETA trial[13]	
	BC-specific survival (%)	Local progression (%)	Death related to BC (%)	Local progression (%)
Tamoxifen + mastectomy	66	2	36.3	11.2
Tamoxifen alone	64	43	39.4	47.6

Table 2
Results of the studies of Alba, Palmieri and Semiglazov.

	Neoadjuvant hormonal therapy (%)	Neoadjuvant chemotherapy (%)
Overall response rates		
Alba[9], Palmieri[15], Semiglazov[19]	58–77.3	60–90.6
Breast conservation Semiglazov[19]	43	24
Breast conservation Alba[9]	56	47

Table 3
Results of the studies of Dixon, Llombart-Cussac, Allevi and Carpenter.

	Dixon[21]	Llombart-Cussac[22]	Allevi[18]	Carpenter[17]
Overall response rate (%)				
3rd month	69.8			
4th month			49.6	55
8th month			85.3	
12th month		76	95.0	72
24th month	83.5			
Breast conservation rate (%)				
3rd month	60			
12th month				69
24th month	72			
Median time to response (months)				
Median time to maximum response (months)	3.9			
Median time to enough response for breast conservation (months)	4.2			7.5
Progression (patients)	7 out of 63			

the 6th month but none after the 8th month.[22] In 2013, Allevi et al. created three cohorts with 40 patients each, that took letrozole for 4, 8 and 12 months.[18] All women were older than 65 years old, with luminal BC and unfit for chemotherapy.[18] Carpenter et al., in 2014, conducted a study with post-menopausal women not eligible for breast conservation, that took letrozole for 12 months.[17] The most important results of the studies mentioned above are described in Table 3.

Given that there are no standardized guidelines on how long NET should be performed, there is a real need for more studies focusing on this matter. Therefore, the aim of this study is to evaluate whether the extension of NET, beyond the conventional time of[3–4] months, allows additional downstage of the tumour, in order to perform a breast conservative surgery (BCS), and to analyze if it is a good option for long-term control in patients who refuse or are unfit for surgery.

Patients and methods

We retrospectively reviewed a database containing all patients with BC, from January 2007 until October 2015, who were treated with NET (with or without surgery) in our institution. All included patients were post-menopausal women with primary local disease, who had been submitted to NET with tamoxifen or AIs. Patients excluded were those with metastatic disease, inflammatory BC, previous radiation directed to the chest or chemotherapy for other concurrent cancer during the period of study.

We collected data concerning age; indication to endocrine therapy; multifocality; tumour size (T) and status of axillary nodes (N), according to TNM staging system for BC; tumour histologic subtype and grade; status and percentage of expression of ER and progesterone receptors (PR); HER2Neu amplification; drug used; response to treatment; time to response and surgery. Positive ER expression is defined as >1% of expression and positive PR expression as >20% of expression.

Tumour size before treatment was assessed through mammography and ultrasound in all patients. Post-treatment size was measured in the surgical specimen in one patient and obtained through clinical observation in two patients; all the others were measured by mammography and ultrasound. The efficacy of the treatment was evaluated using modified RECIST criteria: (1) total response: the tumour is no longer palpable or visible in images; (2) partial response: sustained reduction of at least 30% of the tumour size; (3) progression: an increase of 20% or a new lesion, axillary node or metastasis; and (4) partial response followed by progression: reduction of at least 30% of the tumour size followed by an increase of 20% or a new lesion, axillary node or metastasis.[2,23]

Immunohistochemistry was carried out to assess: HER2 status, using the anti-Her-2/neu (4B5) rabbit monoclonal antibody; ER, with the anti-estrogen receptor (SP1); PR, with the anti-progesterone receptor (1E2); using the Bench Mark ULTRA. Number of copies of the HER2/neu gene was obtained through Silver-enhanced in situ hybridization (SISH), using the BenchMark XT and the probe INFORM TM. The equipment is commercialized by Ventana® Medical Systems (Tucson, EUA).

Statistical analysis was performed using the SPSS® software version 23.0 (SPSS Inc., Chicago, IL). For categorical variables data was presented as absolute frequencies and percentages. For continuous variables, data was presented as mean ± standard deviation. Categorical variables were compared using chi-squared test while continuous variables were compared using independent samples *t*-test. The size of the tumour before and after treatment was analyzed using a Wilcoxon Test. Differences were considered statistically significant if the corresponding *p*-value was ≤ 0.05.

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