Primary chemotherapy with sequential docetaxel followed by docetaxel and epirubicin in large operable breast cancer

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Summary

Primary chemotherapy is increasingly used in patients with large operable breast cancer. Docetaxel and epirubicin are the most active agents in breast cancer treatment.

Purpose: To evaluate clinical response rate, breast conserving surgery and pathological response rate in patients with large operable breast cancer treated with docetaxel followed by docetaxel and epirubicin as primary chemotherapy.

Patients and Methods: Patients with operable breast cancer more than 3 cm in the longest diameter with T2N0, T2N1 and T3N0 disease were enrolled. Patients were treated with three cycles of docetaxel 100 mg/m² followed by three cycles of docetaxel 75 mg/m² and epirubicin 90 mg/m² prior to surgery.

Results: Sixty-five patients were enrolled between 09/2002 and 12/2005. The median age was 48.9 years and 72.3% were premenopausal. Median tumour size was 4.26 cm, 10.8% were T3 tumours and 38.5% had clinical positive lymph nodes. Of the tumours 58.5% were grade 1/2, 33.9% ER positive and 21.5% c-erb negative. All six cycles were administered to 62 patients; six cycles were delayed and five had dose reductions. Complete clinical response occurred in 41.5% of patients and partial response in 49.2%. Breast conserving surgery was performed in 30% of patients however it was feasible in 57%. Complete pathological response occurred in both primary tumour and nodes in 28%, and in 34% just in the primary tumour. Nine percent of cases had neutropenia and 7.7% febrile neutropenia, and two cases had a hypersensitivity reaction to docetaxel. One associated treatment death occurred.

Conclusion: Docetaxel followed by epirubicin and docetaxel as primary chemotherapy results in a high clinical and pathological response rate. The majority of adverse events were predictable and manageable.

Key words: Operable breast cancer; Primary chemotherapy.

Introduction

Breast cancer mortality is decreasing in many countries despite the rising incidence. Treatment options tend to be more tailored to the individual patient.

Primary chemotherapy (PC) is indicated before tumour removal in patients with advanced disease and is also being used increasingly in the management of patients with large operable breast cancers to produce tumour shrinkage and potential breast conservation [1]. Moreover, PC may theoretically improve survival through elimination of systemic micrometastasis and it also identifies individual chemosensivity, as the activity of chemotherapy agents may be tested *in vivo* [2, 3]. Axillary clearance and pathological complete response in the breast after PC have been considered established prognostic factors [4].

In the current study, an analysis was proposed of patients with large operable breast cancer that were submitted to primary chemotherapy with three cycles of docetaxel followed by three cycles of docetaxel and epirubicin to allow breast conservation, and to evaluate pathologic response. The primary endpoints of this study were to determine clinical response rate, breast conserving surgery (BCS) rate and pathologic response rate.

The study was presented with only 35 cases at the 29th ESMO Congress, 29 October-2 November 2004, Vienna (Austria).

Revised manuscript accepted for publication February 26, 2007

Patients and Methods

Patients with operable breast cancer with at least 3 cm in the longest diameter were evaluated by physical examination with T2N0, T2N1 and T3N0 disease of TNM clinical classification. Mammography and ultrasonography were performed before any biopsy was done. Patients with multifocal lesions were excluded.

The diagnosis was usually established by punch biopsy of the primary tumour. Immunohistochemical staining for estrogen and progesterone receptors as well as for HER status were routinely determined.

In order to enable preoperative localisation of the initial tumour bed, all tumours were tattooed on the first visit. Axillary lymph node involvement was clinically recorded.

The staging workup included a complete history and physical examination, complete blood cell and platelet counts, blood chemistry analysis and CA15.3, electrocardiography, chest radiograph, abdominal ultrasonography, bone scan and cardiac scintigraphy.

Written informed consent was given by every patient involved.

Treatment modalities

Chemotherapy consisted of intravenous (IV) infusion of 100 mg/m² docetaxel for one hour every three weeks for three cycles, followed by three cycles of 90 mg/m² epirubicin IV for 15 minutes and 75 mg/m² docetaxel IV for one hour, every three weeks. Corticosteroid premedication was done with 8 mg of dexamethasone or 40 mg of methylprednisolone administered six times over three days, starting the day before each cycle. Antiemetic premedication was offered according to hospital protocol. G-CSF support (5 mcg/kg/day, SC) was given as secondary prophylaxis from days 2 to 8.

BCS was proposed to the patient whenever it was applicable. Patients that were considered inappropriate for or did not desire BCS, underwent mastectomy. All patients were submitted to axillary lymph node dissection.

Four cycles of adjuvant chemotherapy with FEC (fluorouracil - 750 mg/m²; epirubicin - 100 mg/m²; cyclofosphamide - 600 mg/m²) were administered to pN+ patients.

Patients were evaluable for toxicity if they received one or more cycles of chemotherapy.

Every patient submitted to breast conserving surgery also had whole breast irradiation. The breast was treated with standard medial and lateral tangent fields using 6 to 15 MV photons to a total dose of 50 cGy delivered in 25 fractions. Subsequently, the tumour bed was treated with an additional 10 Gy in five fractions with electrons. Hormone therapy for hormone receptor-positive tumours was prescribed.

Clinical and pathological response criteria

Breast examination with tumour measured in the longest dimension was done on the third and sixth cycle; ultrasonography and mammography were repeated after the sixth cycle, before surgery.

Clinical response was classified according to the RECIST criteria [5]: complete clinical response in the absence of clinical evidence of tumour; partial clinical response when the reduction of the largest diameter of the tumour was greater then 30%; progressive clinical disease if the largest diameter increases more than 20%; stable disease whenever none of the previous criteria were met.

Pathological response was evaluated according to the following criteria: pathological complete response (pCR) - complete disappearance of the primary tumour or presence of *in situ* lesions with negative axillaries nodes; partial pathological response (pPR) – residual tumour modified by chemotherapy; no change or stable disease (NC/SD) – tumour with no histological changes.

All specimens of breast conserving surgery were oriented by the surgeon and sent to the pathology suite. The pathologist grossly examined the specimen to identify suspicious areas and their proximity to margins to decide whether additional margins should be obtained or not.

The resection specimen was inked and permanent paraffin sections of the suspicious areas and margins were obtained. The number of sections taken was based on gross inspection. In general, for nonpalpable lesions (complete clinical response), at least 10-15 blocks of specimen were examined to assess the presence of microscopic disease. In cases with a residual palpable mass (partial clinical response or non response) the specimen was sectioned into 3-5 mm slices. The pathologist determined the tumour size.

All axillary lymph nodes were carefully evaluated by serial gross sectioning. One or two representative histologic sections were evaluated for lymph nodes that contained grossly identifiable metastatic carcinoma. Lymph nodes that did not show grossly identifiable tumour were submitted for histologic evaluation in their entirety, and were sliced if bigger than 1 cm.

Results

According to the inclusion criteria 65 patients were included in this study. All were evaluable for toxicity analysis but only 63 were evaluable for pathological response as one treatment-related death was registered and one patient had progressive disease and was submitted to radiotherapy before surgery. This patient survived ten months.

Patient median age was 48.9 ± 10.6; most of them were premenopausal (72.3%) and all had WHO performance status 0 (Table 1).

Table 1. — *Patients and tumour characteristics.*

Number of patients (n = 65)	
Median age	48.9 ± 10.6
WHO PS 0	100%
Hormonal status	
Premenopause	47 (72.3%)
Postmenopause	18 (27.7%)
Median tumour size	4.26 cm
Median tumour size	
3-5 cm	58 (89.2%)
> 5 cm	7 (10.8%)
Clinical lymph node status	
N0	40 (61.5%)
N1	25 (38.5%)
Clinical stage	
T2N0	33 (50.7%)
T2N1	25 (38.5%)
T3N0	7 (10.8%)
Pathological characteristics	
Ductal invasive	64
Lobular invasive	1
Grade	
1	8 (12.3%)
2	30 (46.2%)
3	16 (24.6%)
unknown	11 (16.9%)
ER positive	41 (63%)
ER negative	22 (33.9%)
ER unknown	2 (3.1%)
c-erb pos	14 (21.5%)
c-erb neg	44 (67.7%)
c-erb uknown	7 (10.8%)

Diagnosis was made by core biopsy in all patients. Median tumour size was 4.26 cm, with just 10.8% of T3 tumours; only 38.5% of patients had clinical positive lymph nodes (Table 1). All but one tumour were ductal type, 58.5% were grade 1/2, 33.9% were estrogen receptor (ER) negative and 21.5% were c-erb positive (Table 1).

All six cycles of chemotherapy were administered to 62 patients. One patient received only five and two received three cycles. Six chemotherapy cycles were delayed and five dose reductions were done.

Clinical tumour response was complete in 41.5% of the patients and partial in 49.2%, with an overall response rate of 90.7% (Table 2). All but one clinically positive lymph node became negative after chemotherapy.

Table 2. — *Clinical response.*

Clinical response (n = 65)	
cCR	27 (41.5%)
cPR	32 (49.2%)
cCR+cPR	59 (90.7%)
cSD	4 (6.2%)
cPD	2 (3.1%)

cCR (clinical complete response); cPR (clinical partial response); cSD (clinical stable disease); cPD (clinical progression of disease).

BCS was performed in 30% of patients but it was feasible in 57%, as 17 patients decided not have the surgery (Table 3).

Table 3. — *Surgical treatment.*

	n = 63	CI
Breast conserving surgery (BCS)	19 (30%)	30.16 % (18.73 - 41.58)
Mastectomy	44 (70%)	69.84 % (58.42 - 81.27)
– physician option	27/63 (42.8%)	
– patient option	17/63 (27.2%)	
BCS possible (BCS + mastectomy – patient option)	36 (57%)	

Complete pathological response was considered only if there was no residual tumour or if there were only *in situ* lesions and no node disease. Hence a complete response was found in both primary tumours and nodes in 28% of patients and in 34% of primary tumours. Fourteen of 25 (56%) patients with clinically positive lymph nodes became pathologically negative after chemotherapy.

Of clinical complete response in primary tumours 55.5% were associated with pathological complete response; 59.4% of partial clinical response were associated with partial pathological response; 21.8% of patients classified as having partial clinical response had indeed complete pathological response (Table 4).

Table 4. — *Clinical response in breast and pathological correlation.*

	pCR	pPR	pSD	Total
cCR	15 (55.5%)	11 (40.7%)	1	27
cPR	7 (21.8%)	19 (59.4%)	6	32
cSD	1	1	2	4
cPD	–	1	–	1
total	23	32	8	63

cCR (clinical complete response); cPR (clinical partial response); cSD (clinical stable disease); cPD (clinical progression of disease); pCR (pathological complete response); cPR (pathological partial response).

Tumour characteristics of complete response in primary tumours were: median size 4 cm, 37.5% were c-erb positive, 52.4% were ER negative and 33.3% were grade 3 (Table 5). No significant difference in tumour characteristics between complete and partial response was found.

Haematological toxicity was the most frequent complication of therapy and 9% of grade 3 neutropenia and 7.7% of grade 3 febrile neutropenia were recorded. There was no case of grade 3 or 4 thrombocytopenia. There were two cases of hypersensitivity reaction to docetaxel but after recovery it was possible to resume treatment (Table 6).

Table 5. — *Tumour characteristics of pCR in the breast and comparison with pPR.*

	pCR	pPR	Chi-square test
Median tumour size	4.03 cm	4.06 cm	NS
SBR grade 3*	(5/15) 33.3%	(9/23) 39%	NS
ER negative**	(11/21) 52.4%	(10/32) 31.3%	NS
c-erb positive***	(9/19) 37.5%	(4/28) 14.3%	NS

*11 unknown; ** 2 unknown; *** 7 unknown.

Table 6. — *Toxicity grade 3/4.*

	No. of patients = 65
Hypersensitivity reaction	2 (3%)
Neutropenia	6 (9%)
Febril neutropenia	5 (7.7%)
Anemia	2 (3%)
Stomatitis	2 (3%)
Death	1
No. of chemotherapy delays	6 (9%)
No. of dose reductions	5 (7.7%)

One associated treatment death occurred. The patient was 42 years old with a history of diabetes. She developed peripheral neuropathy and toxicodermia following the third docetaxel course and died two months later with hepatitis and lung interstitial infiltration.

Discussion

Primary chemotherapy has been evaluated in a large number of clinical studies. The National Adjuvant Breast and Bowel Project (NSABP)-B18 trial compared preoperative with postoperative doxorubicin and cyclophosphamide and found that primary chemotherapy resulted in a clinical complete response rate of 36% and a partial clinical response rate of 44%, for an overall clinical response of 80% [2]. Patients randomised to primary chemotherapy demonstrated a pathologic complete response rate of 13% and a significant improvement in the rate of breast conserving surgery (68% *vs* 60%) [2, 6]. In the phase 3 Aberdeen University trial, patients received primary chemotherapy with four cycles of the doxorubicin containing regimen CVAP (cyclofosfamide, doxorubicin, vincristine, prednisolone). Those demonstrating a partial or complete clinical response to CVAP were assigned to either four cycles of CVAP or four cycles of docetaxel and those who did not respond were treated with four cycles of docetaxel [7]. Four cycles of docetaxel sequential to CVAP resulted in a higher overall clinical response rate and pathologic complete response rate compared with four additional cycles of CVAP.

The NSABP-B27 trial compared doxorubicin-cyclofosfamide (AC) as the primary chemotherapy followed by docetaxel administered either before or after surgery compared to preoperative AC alone. Treatment with AC followed by docetaxel resulted in a significant increase in clinical complete response rate compared with AC alone (63.6% *vs* 40.1%) as well as higher overall clinical response rate (90.7% *vs* 85.5%) and pathologic complete response rate (26.1% *vs* 13.7%), and a decrease in the rate of histologically-positive axillary nodes (41.8% *vs* 49.2%) [7, 8]. However, some comparative studies of the same regimen given before and after surgery did not show significant differences in disease-free and overall survival between the approaches [3].

In this study, PC consisted of a sequential regimen of docetaxel followed by epirubicin and docetaxel. There is limited data to support the use of sequential instead of

concurrent schedules. Sequential regimens permit the use of full doses of each agent. A phase II trial with docetaxel, doxorubicin and cyclophosphamide (DAC) showed inferior activity and more toxicity than sequential AC-docetaxel, based on historical controls [9]. Moreover, the sequential use of antracyclines and docetaxel has been the most successful approach in primary chemotherapy randomised trials [8, 10].

On the other hand, doxorrubicin and docetaxel are among the most effective agents in the treatment of advanced disease [11, 12] and there is evidence that these two agents are only partially cross-resistant [13, 14].

In this study BCS was carried out in 30% of patients but it was feasible in 57%, as 17 patients preferred being submitted to mastectomy. However, all patients would have undergone mastectomy if PC had not been done. Mauriac *et al.* randomized 138 patients to mastectomy and axillary clearance and 134 to PC followed by surgery; in this group, BCS was possible in 63% of patients [15]. Makris *et al.* demonstrated a significant improvement in BCS in the group receiving PC compared with those receiving adjuvant chemotherapy [16]. However, the breast conservation rate may decrease over time after initial surgery because of local recurrence. In the Mauriac study, BCS decreased from 63% to 45% after a follow-up of 124 months [15]. If local recurrence rate after PC is compared with that associated with postoperative chemotherapy as was done in the NSABP-B18 trial, a non-significant increase in local recurrence between those receiving PC (11%) and those receiving postoperative chemotherapy (6%) [8] is found.

Primary chemotherapy provides the ideal scenario for the investigation of prognostic factors and predictive factors of response to chemotherapy in breast cancer. Axillary clearance and pCR have been considered established prognostic factors, while for clinical response the evidence is less solid [4]. The identification of reliable predictive factors of response to chemotherapy could lead to optimal individualization of treatment and avoidance of unnecessary toxicity in patients unlikely to respond to a given regimen [4]. Some potential predictive factors have been inconsistently reported, namely Her2- overexpression [17, 18], lack of Her2-overexpression [19], ER/EP expression [19] and lack of ER/EP expression [20, 21].

In our study none of these factors were predictive of pathological response.

It could be stated as a final comment that PC with sequential docetaxel followed by docetaxel and epirubicin provides a good rate of complete pathological response in both primary tumours and lymph nodes with predictable and manageable adverse events.

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