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Original Paper

Pre-operative Chemotherapy and Radiotherapy in Breast Cancer

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Primary systemic treatment of breast cancer with cytotoxics yields a high response rate and allows conservative surgical procedures in bulky tumours. In order to maximise local control of disease, two innovations were introduced in a pilot study. The first was to identify the good responders after three cycles of chemotherapy and to treat them with three additional cycles. The second was to also give this group of patients a full dose of radiotherapy before surgery with the aim of verifying the rate of pathological complete remissions in view of a possible treatment of breast primary with chemo-radiotherapy only. Patients were treated with doxorubicin 60 mg/m^2 and cyclophosphamide, 600 mg/m^2 both intravenously on day 1, every 21 days for three courses. Partial or complete responders received three more courses followed by radiotherapy (50 Gy plus a 10 Gy boost). The others underwent immediate surgery. A total of 32 patients (median age, 50 years; range 28–69 years); performance status, 0–1; T_2 22, T_3 8, T_4 2) were enrolled and were evaluable for response and side-effects. 9 patients had only three cycles of chemotherapy due to absence of response and 23 patients had six cycles of chemotherapy. Overall, 7 patients had a complete remission, 16 a partial remission and 9 had stable disease, for an overall response rate of 72% (95% confidence interval 53–86%). In the group of patients that completed the programme, two complete pathological remissions were observed and 5 patients had only microfoci of tumour. No toxic death or grade III–IV toxicities were observed. Mild or moderate side-effects included mucositis, nausea/vomiting and leucopenia. In conclusion, our results indicate that the addition of radiotherapy to pre-operative chemotherapy did not significantly enhance the incidence of pathological complete remissions. New primary treatment approaches should be explored in this subset of patients in order to improve outcome.

Key words: neoadjuvant, chemotherapy, radiotherapy, breast cancer
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INTRODUCTION

THERE ARE several possible advantages in the use of systemic chemotherapy as a primary medical treatment before surgery. Originally primary chemotherapy was introduced to make locally advanced tumours (T_4) operable [1]. This early experience showed a limited advantage in terms of long-term survival, but a very high regression rate of the primary breast carcinoma. This finding encouraged clinicians to extend the indications of primary chemotherapy to make cases candidates for mastectomy with breast conserving surgery, by reducing the size of the tumour [2, 3]. Breast conservation was described in approximately 60–90% of patients included in studies exploring this subject [4–7]. A second objective of primary cytotoxic therapy was to improve systemic disease control by eradication of distant micrometastases. Chemotherapy administered before surgery in animal models showed a reduction in neoplastic cell proliferation and suppression of tumour growth [8]. It was also hypothesised that the risk of chemoresistance could be reduced by the early use

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of chemotherapy [1, 8, 9]. Reported data indicate a high rate of responses after primary chemotherapy [10–14], but results on disease-free survival were inconclusive on whether this modality should be offered as a standard treatment [5, 15–17].

The aim of this pilot study was to explore the efficacy of chemotherapy as an effective treatment of primary breast carcinoma, combining chemotherapy and radiotherapy pre-operatively to obtain a complete pathological remission of the primary carcinoma, thus avoiding surgery, at least in some subgroups of patients. The theoretical advantage of combining chemotherapy with radiotherapy in the pre-operative setting is that the latter may increase therapeutic results by suppressing those cancer cells which survive cytotoxics. In a previous investigation by our group, it was shown that the addition of pre-operative radiotherapy was able to increase the rate of complete pathological remissions [18]. Moreover, a synergistic effect of chemotherapy and radiotherapy was observed in clinical trials investigating breast conservation [14, 19].

The original concept of this pilot study was to identify patients with very chemosensitive tumours, i.e. with a high response after three cycles of chemotherapy and to prolong their treatment up to six cycles with the objective of obtaining maximum tumour cell kill. In this group of patients, full dose radical radiotherapy was administered to evaluate the possibility of destroying completely the primary tumour and so open the way to further studies to identify subgroups of patients to be treated with chemoradiotherapy and avoiding surgery.

PATIENTS AND METHODS

Patients

Patients with biopsy-proven T_2–T_4, $N_{0–2}$ breast cancer were considered eligible for the study. Other inclusion criteria were: non-metastatic tumours; < 75 years of age; largest tumour diameter > 2.5 cm; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; white blood cell count > 4000 mm^3 and platelet count > 100 000; serum creatinine < 1.2 mg/dl; bilirubin < 3 mg/dl; aspartate and alanine aminotransferase < 2.5 times the upper limit. Patients with evidence of cardiac disease (congestive heart failure, history of myocardial infarction within the previous 3 months), severe vascular disease or uncontrolled concomitant infections were excluded.

Patients had baseline liver and renal function tests, electrolyte studies and complete blood count carried out within 2 weeks of inclusion in the study. Also, bilateral mammography and echography, chest X-ray, abdominal ultrasound, bone scan, CA 15.3 and electrocardiography were performed within 2 weeks of treatment start. Written informed consent was mandatory.

Treatment

Chemotherapy consisted of doxorubicin (60 mg/m^2 dissolved in 100 ml of 5% glucose solution administered intravenously) followed by cyclophosphamide (600 mg/m^2 dissolved in 100 ml of normal saline solution) administered for three courses every 21 days. Patients had a complete blood count 7 and 14 days after treatment. Liver and renal function tests, electrolyte studies, complete blood count and a visit were performed every 3 weeks. Dose modifications were made for granulocyte and platelet counts on day 1 of each course. In the case of the platelet count < 100 000 mm^3 and/or the neutrophil count < 1500 mm^3, treatment was delayed for 1 week. In the case of no recovery after 1 week of delay, doses were adjusted as follows: in the case of the platelet count > 75 000 mm^3 but < 100 000 mm^3 and/or the neutrophil count > 1000 but < 1500, 50% of the doxorubicin and cyclophosphamide doses were administered. In the case of the platelet count < 75 000 mm^3 and/or the neutrophil count < 1000 mm^3, treatment was delayed for 1 additional week, and in the case of no further recovery, no further chemotherapy was given. The dose of doxorubicin and cyclophosphamide was reduced to 75% of the baseline dose in the case of grade III mucositis or diarrhoea.

Tumour response was evaluated by clinical measurement of the two largest diameters of the primary tumour after each course, and immediate surgery was planned in patients with clinically progressive disease. After three and six courses, patients underwent breast ultrasound and mammography for assessment of response. Patients with stable disease after three courses were offered surgery, whereas responding patients received three additional courses of chemotherapy followed by radiation.

High-voltage radiotherapy was given to the involved breast starting 3–4 weeks after the last course of chemotherapy, at the dose of 50 Gy with two opposite tangential fields and with a 10 Gy boost applied to the tumour nodule [14].

Surgery consisted of a quadrantectomy as described by Veronesi and colleagues [19] and an axillary node dissection, which was always performed through a separate incision. Total mastectomy was performed in all cases where breast conservation was not considered feasible.

Responses were graded according to the standard WHO criteria. A complete response was defined as the disappearance of all parameters of disease. A partial response was defined as a 50% or more reduction in the products of the perpendicular diameters of the lesion. Stabilisation of disease was defined as a less than 50% reduction in the

Table 1. *Major patient characteristics*

	No. of patients
Entered/assessable	32/32
Median age, years (range)	50 (28–69)
Premenopausal/postmenopausal	16/16
Tumour size*	
T_2	22
T_3	8
T_4	2
T < 3.5 cm	17
T > 3.5 cm < 4.5 cm	5
T ≥ 4.5 cm	10
Node status*	
N0	8
N1	24
ER and PgR status	
ER+ PgR+	13
ER+ PgR−	8
ER− PgR−	9
Undetermined	2
Expression of Ki-67	
≤ 20%	12
> 20%	17
Undetermined	3

*At baseline. ER+ ≥ 20%; PgR+ ≥ 20% (immunohistochemical assessment).

Table 2. Outcome of patients

	No. of patients (%)
Entered/evaluable	32/32
Stable disease/progressions	9
Partial remissions	16
Complete clinical remissions	7
Complete pathological remissions	2 (6)
Tumoral microfoci	5 (16)
Overall pathological remissions	7 (22)
Overall objective remissions	23 (72)
Quadrantectomy	25
Mastectomy	7
No. positive nodes (at surgery)	
0	11
≤ 3	10
> 3	11

products of the perpendicular diameters of the lesion without any evidence of new lesions. Side-effects were scored according to WHO criteria.

RESULTS

32 patients entered the study and were assessable for clinical and pathological response and side-effects. Major patient characteristics are given in Table 1. Approximately a third of the cases were $T \geq 3$, with 10 patients presenting a tumour larger than 4.5 cm in diameter. A total of 165 courses of therapy was administered.

No toxic deaths were observed, and side-effects related to chemotherapy were manageable, generally mild or moderate and reversible. The most frequently encountered side-effect was nausea and vomiting (grade I–II in 20 patients). Haematological side-effects included mild or moderate neutropenia, which was observed at the time of recycling in 23% of the patients. Nadir grade III–IV neutropenia was observed in 34% of patients. Grade I–II mucositis was registered in only 5 cases, whereas alopecia was universal.

Of the 32 patients assessed after three courses, 9 had stable disease (Table 2) and were offered surgery. Of the other 23 responding patients, 7 achieved a radiological and clinical complete remission and 16 had a partial remission (although 1 patient developed progressive disease at the 6th cycle). The overall response rate was 72% (95% confidence interval, 53–86%). In 23 assessable patients who completed six cycles of chemotherapy, 2 complete pathological remissions were observed. Moreover, 1 patient had a single microfoci of invasive tumour and 4 had multiple microfoci (Table 2). In this group, 3 patients did not receive radiotherapy after completion of chemotherapy (1 progressive disease and 2 patient requests).

As shown in Table 3, responses seemed to be correlated with baseline characteristics. Interesting is the observation that complete clinical remissions, as well as pathological remissions, were observed only in the subgroup of 17 patients with elevated baseline Ki-67, whereas most non-responding patients were observed in the subgroup of patients whose primaries expressed ER but not PgR. In the group of 22 patients with disease classified as T_2, the response rate was 82%. Moreover, in the subgroup of patients with disease classified as T_2 and elevated baseline Ki-67 (11 cases), the response rate was 91% and 2 complete pathological remissions were observed. No other correlation between baseline characteristics and response was detected in patients with T_2 tumours.

Quadrantectomy was possible in 80% of patients while 7 patients required mastectomy. As shown in Table 2, 70% of cases had positive nodes at surgery, with 11 cases presenting more than three nodes. Postoperative complications were frequent. 5 patients developed grade II–III infections that required prolonged antibiotic therapy, and in 4 cases, wound dehiscence was observed.

DISCUSSION

The use of pre-operative chemotherapy, first described by Horthobagy and colleagues [20], De Lena and associates [21] and others [22] to make locally advanced tumours operable, had more extensive indications in the 1980s with the aim of increasing breast conservation [1–3, 14]. Breast-saving surgery has been possible in 57–97% of cases submitted to pre-operative chemotherapy and is usually dependent upon initial tumour diameter and other features which allow this approach (e.g. breast size) [18, 23]. Clearly, chemotherapy plays an important role as one of the components of treatment of primary breast cancer while in the past it was confined to the control of distant metastases.

In spite of the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-18 that did not show any disease-free survival advantage for pre-operative chemotherapy as compared with the same treatment given

Table 3. Response according to baseline features

	Patients	Number (%) of CR	PR	Total response (%)	SD (%)	Pathological remissions (%)*
Receptor status						
ER + Pgr +	13	2 (15)	8 (62)	10 (77)	3 (23)	2 (15)
ER + PgR –	8	1 (13)	2 (24)	3 (38)	5 (63)	1 (13)
ER – PgR –	9	4 (44)	4 (44)	8 (89)	1 (12)	4 (44)
Ki-67 expression						
$\leq 20\%$	12	—	7 (58)	7 (58)	5 (42)	—
$> 20\%$	17	7 (41)	7 (41)	14 (82)	3 (18)	7 (41)
Size of tumour						
T_2	22	4 (18)	14 (64)	18 (82)	4 (18)	4 (18)
T_3	8	3 (38)	2 (25)	5 (63)	3 (38)	3 (38)
T_4	2	—	—	—	2 (100)	—

*Includes complete pathological remissions plus tumoral microfoci. CR, complete remission; PR, partial remission; SD, stable disease; ER+ $\geq 20\%$; PgR+ $\geq 20\%$.

postoperatively [17], an argument could be made that response to pre-operative chemotherapy may serve as a marker of prolonged survival. In fact, in a group of 11 patients with pathological complete remission out of a total of 434, only 1 recurrence was observed within 5 years, while the estimated 5-year relapse-free survival rates of 63% and 31% were observed in patients who obtained a partial response or stable disease, respectively [3]. The present study was initiated to explore the maximum efficacy of the association of chemotherapy and radiotherapy with the objective to isolate subgroups who could potentially be treated with this combination without the need of surgery.

The results of the combined treatment in our study, leading to 2/20 complete pathological remissions, is less impressive than those of others who used chemotherapy alone. Smith and colleagues [10], with the combination of epirubicin, cisplatin and 5-fluorouracil, administered as a continuous infusion, reported a pathological complete remission rate of 27% in 50 evaluable patients, whereas other authors achieved a rate ranging between 13 and 23% [9, 10, 14, 23]. However, our pilot series was composed of patients with fairly advanced primary carcinomas. In fact, in the subgroup of 22 patients with disease classified as T_2, the response rate was 82% (Table 3).

The low number of complete pathological responses achieved may be at least partially attributable to the limited efficacy of the chemotherapy regimen in a group of patients with locally fairly advanced disease. It is noteworthy that of 32 evaluable patients 21 (66%) had positive nodes at surgery, and 10 had more than three nodes involved. Although these results are similar to those of others [1–3, 13–18], they indicate that prolonged chemotherapy with doxorubicin and cyclophosphamide is insufficient to eradicate the tumour in its primary site for many of the patients. Other reasons for the high proportion of residual disease in the definitive pathological specimen might be the particularly meticulous histopathological examination and the fact that its early timing after radiation therapy may have led to an underestimation of responses. In fact, surgery might have been performed prematurely, not giving all the tumour cells the time to undergo apoptosis.

Radiotherapy given before surgery was correlated with significant postsurgical side-effects. 5 patients had prolonged postoperative infections and 4 patients had wound dehiscence. Such data have not been reported after pre-operative chemotherapy alone [24]. There are few reports in the literature concerning pre-operative chemotherapy plus radiotherapy. Rilke and associates [25] reported on 73 patients with pre-operative chemotherapy, 42 of whom also received pre-operative radiotherapy. Patients included in the study had small carcinomas less than 2.5 cm in diameter and, therefore, differed from the patients included in our present study. Although the patients received only a dose of 15 Gy, and the chemotherapy regimens were heterogeneous, the percentage of complete remission was similar to ours.

One of the major issues related to the choice of primary systemic treatment is the prospective identification of subsets of patients most likely to benefit. There is some evidence of decreased response to chemotherapy related to several factors, including DNA ploidy, S-phase fraction, p53 product accumulation and *bcl*-2 expression [26–28]. More recently, a trend for a better response to neoadjuvant chemoendocrine therapy was observed for tumours classified as ER-positive, PgR-positive and *bcl*-2-positive, whereas a significantly increased response rate was observed for patients with c-erbB-2-positive tumours [29]. The expression of c-erbB-2 in tumour cells was, in fact, associated with several observations on resistance and sensitivity to adjuvant therapies. The Cancer and Acute Leukemia Group B (CALGB) investigators found that higher doses of a doxorubicin-containing combination were more effective than lower doses in c-erbB-2-positive tumours [30]. The International Breast Cancer Study Group (IBCSG) observed that CMF (cyclophosphamide, methotrexate, fluorouracil) adjuvant chemotherapy was more effective for c-erbB-2-negative tumours as compared with c-erbB-2-positive tumours [31]. c-erbB-2 expression is, thus, a good candidate for prospective exploration of factors related to the degree of response to primary cytotoxic therapy. This factor may be integrated with Ki-67 and hormone receptor expression to allow a finer tailoring of a preoperative chemotherapy regimen.

In conclusion, the results of our preliminary study do not support, at this time, the addition of radiotherapy to preoperative chemotherapy with doxorubicin and cyclophosphamide in breast cancers greater than 2.5 cm. However, in order to improve results, future trials should explore new regimens in this setting and should evaluate pretherapy prognostic and predictive features in order to select subsets of patients who may benefit from this treatment modality. It appears, in particular, that tumours with a diameter between 2 and 5 cm, with a high proliferative rate according to Ki-67 should be considered for further trials.

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