Pergamon

European Journal of Cancer Vol. 33, No. 6, pp. 862–866, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00038-5

Original Paper

Clinical and Pathological Response to Primary Chemotherapy in Operable Breast Cancer

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Neoadjuvant chemotherapy is used to improve patients' survival in locally-advanced and inflammatory breast cancer and to increase conservative surgical procedures in bulky tumours. Pathological complete responses are unusual. The aim of this pilot study was to assess the clinical and pathological response rates and to evaluate toxicity with a new protocol of primary chemotherapy in 50 high-risk breast cancer patients. All tumours were >3 cm and had at least one other adverse prognostic factor: lymph node involvement (32 N1, 6 N2), SBR grade III (20), aneuploidy (29), negative hormonal receptors (19). Patients were treated by 3-week cycles of THP–doxorubicin 20 mg/m^2 D1 to 3, vinorelbine 25 mg/m^2 D1 and 4, cyclophosphamide 300 mg/m^2 and 5-fluorouracil 400 mg/m^2 D1 to 4 (TNCF). 38 patients received G-CSF or GM-CSF support. After 4–6 cycles, all underwent surgery (39 conservative, 11 modified radical). Tumour response was assessed clinically, by mammography and echography and on pathological specimens. An objective clinical response was observed for 43 patients: 26 complete (51%) and 18 partial (37%). After pathological review, 11 patients (22%) were devoid of any tumour cells, 4 others (8%) had only *in situ* carcinoma. From 253 evaluated cycles, grade III–IV toxicity occurred, 81% with neutropenia, 25% with anaemia, and 20% with thrombocytopenia. All patients recovered. This regimen induced a severe but not life-threatening haematological toxicity and resulted in a high pathological response rate (30%). © **1997 Elsevier Science Ltd.**

Key words: neoadjuvant (induction) chemotherapy, breast cancer, vinorelbine

Eur J Cancer, Vol. 33, No. 6, pp. 862–866, 1997

INTRODUCTION

IT HAS been many years since systemic therapy was introduced as primary treatment in locally advanced or inflammatory breast cancer. This strategy has led to a substantial improvement in patient survival [1, 2]. The application of "neoadjuvant" chemotherapy has been extended to operable large breast cancers so as to reduce tumour volume and increase conservative surgical procedures [3–7]. However, little or no information exists to indicate whether pre-operative therapy results in better patient outcome. In most series, residual tumour has been found on pathological examination after surgery [8–10]. However, Feldman and associates [11] showed that achievement of a surgical specimen free of residual disease is the best prognostic factor.

In order to increase the response rate, a new cytotoxic regimen (TNCF, THP–doxorubicin, vinorelbine, cyclophosphamide and 5-fluorouracil (5-FU)) has been used for several months in our centre. TNCF is based on our previous experience with doxorubicin, vincristine, cyclophosphamide and 5-FU (AVCF), used by our group as adjuvant [12, 13] and neoadjuvant [14] chemotherapy. However, to lower cardiac toxicity, the analogue THP–doxorubicin was chosen instead of doxorubicin [15], and following publication of better results obtained with vinorelbine in metastatic breast cancer (40% response as first-line treatment), this drug was chosen to replace vincristine [16]. Moreover, we chose to apply this schedule at the maximally tolerated dose. Haematopoietic growth factors were used to reduce antici-

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Received 17 Jul. 1996; revised 15 Nov. 1996; accepted 15 Jan. 1997.

Table 1. Patient characteristics (n = 50) in the TNCF study

Characteristics	Number of patients	%
T		
T2	35	70
T3	15	30
N		
N0	12	24
N1	32	64
N2	6	12
Pathology		
Invasive ductal	43	86
Invasive lobular	4	8
Unspecified invasive carcinoma	3	6
SBR grading		
I	2	4
II	21	42
III	20	40
Not done	7	14
Hormonal receptors		
ER– PgR–	19	38
ER– PgR+	4	8
ER+ PgR+	8	16
ER+ PgR–	4	8
not done	15	30
Cell kinetics		
Presence of an aneuploid population	29	58
S phase ⩾5%	28	56
Not done	13	26

ER, oestrogen receptor; PgR, progesterone receptor.

pated neutropenia and avoid hospitalisation as much as possible.

The purpose of this non-randomised study was to evaluate clinical and particularly pathological response rates obtained with this cytotoxic regimen as primary therapy for high-risk breast cancer.

PATIENTS AND METHODS

From April 1991 to June 1996, 50 patients were treated and are evaluable for toxicity and response.

The eligibility criteria of this study were as follows: pathological proof by surcut biopsy of invasive adenocarcinoma, no prior specific treatment, no metastatic spread. Induction chemotherapy was required for non-inflammatory bulky tumours, potentially operable, but which would require mastectomy due to tumour size >3 cm (Milan criteria): 50 cases. Furthermore, patients had at least one other adverse prognostic factor (Table 1): clinical lymph node involvement (32 N1, 6 N2), high Scarff–Bloom–Richardson (SBR) grading (20 grade III), aneuploidy (29 cases), negative hormonal receptors (19 cases).

Initial staging comprised complete and detailed clinical examination, bilateral mammography and echography, cytological or pathological diagnosis for primary tumour and nodes. Every patient was proven to be devoid of metastases by chest X-ray, liver echography and bone scintigraphy. Biological assessment comprised blood cell count, electrolytes and serum creatinine, alkaline phosphatases and gamma glutamyl transferase, CEA and CA15.3.

When invasive adenocarcinoma was proven by pathological examination and, when material was sufficient (i.e. in most cases), a determination of prognostic factors was made: SBR grading [17], hormone receptors by radioimmunology [18], flow cytometry DNA analysis with EPICS V (Coulter) and cycle software program.

Treatment

Induction chemotherapy. All patients received TNCF chemotherapy:

—D1, D2 and D3: THP–doxorubicin (20 mg/m^2).
—D1 and D4: vinorelbine (25 mg/m^2).
—D1 to D4: cyclophosphamide (300 mg/m^2).
—D1 to D4: 5-FU (400 mg/m^2).

This treatment was scheduled for six cycles. To increase dose intensity, the interval between day 1 of each cycle was 21 days only. The dose per week of each drug was:

—vinorelbine, 17 mg/m^2/week;
—THP–doxorubicin, 20 mg/m^2/week;
—5-FU, 533 mg/m^2/week;
—cyclophosphamide, 400 mg/m^2/week.

The first 12 patients treated with this regimen did not receive haematopoietic growth factors, bue due to notable haematological toxicity, the other 38 had support with either GM-CSF (7.5 μg/kg) or G-CSF (5 μg/kg) subcutaneously, once daily, for 7 to 10 days from cycle 1. Peripheral haematological values were assessed twice weekly. In case of severe (grade IV) leuconeutropenia associated with febrile episode, the dose of the next cycle was reduced by approximately 20%. If neutrophils were <1500/mm^3 or platelet <100 000/mm^3 at day 21, treatment was delayed for one week.

Locoregional treatments. After induction chemotherapy, all patients underwent surgery: lumpectomy with axillary dissection if the residual tumour size was less than 3 cm and modified radical mastectomies (MRM) in other cases (tumour greater than 3 cm, extended intracanalar disease). Radiotherapy was applied following conservative surgical procedures or in the case of axillary node involvement with extracapsular invasion.

Adjuvant therapy. When important residual disease remained, adjuvant chemotherapy was considered for each case: conventional, even intensive chemotherapy with ABMT (autologous bone marrow transplantation). Adjuvant hormonotherapy (tamoxifen) was given to patients who were postmenopausal and had oestrogen receptor-positive tumours.

Assessment of response

Before treatment, during induction chemotherapy after 2 and 4 cycles and before surgery, clinical, echographic and mammographic measurements were carried out. Clinical, echographic and mammographic responses were evaluated by the decrease of the tumour and nodes volumes (product of two main diameters) and were classified as follows: 100% disappearance, complete response (CR); >50% <100% reduction, partial response (PR); <50% reduction, minor or no change (MR/NC).

Pathological response was independently evaluated after surgical resection of the remaining tumour and nodes. After macroscopic inspection, microscopic examination comprised at least 15 sections per breast specimen and the whole axillary dissection. The pathologic responses were classified as follows, according to Chevallier [19]:

Class 1. Disappearance of all tumour on microscopic examination = pCR.

Table 2. Haematological toxicity (WHO grades III and IV). Frequency after TNCF

Cycle number	1	2	3	4	5	6	Total cycles (1–6)
	Number of patients						Events (No.)
Evaluated patients	47	50	48	43	36	29	253
WBC							
Grade 3	7	9	3	8	7	3	37
Grade 4	31	35	39	26	19	17	167
ANC							
Grade 3	5	3	1	5	7	1	22
Grade 4	37	39	40	28	16	19	179
HB							
Grade 3	2	6	17	15	9	5	54
Grade 4		1	3	4	1	1	10
Platelets							
Grade 3	4	8	8	10	2	3	35
Grade 4		3	7	3	3	1	17

WBC, white blood count; ANC, absolute neutrophil count; HB, haemoglobin.

Class 2. Presence of *in situ* carcinoma, but no invasive tumour in the breast and no tumour found in the lymph nodes.

Class 3. Presence of invasive carcinoma with alteration of stroma or cells considered to be related to therapy.

Class 4. No or few modifications of the tumour appearance.

RESULTS

Patient characteristics are listed in Table 1. Median age of the 50 patients was 44 years (range 27–69). All had a good performance status (WHO = 0). 40 patients were premenopausal. The median diameter of the tumour was 43 mm (range 30–80 mm).

Treatment management

A total of 253 cycles of neoadjuvant chemotherapy were infused. The average number of coursees was 5.3 with a dose intensity of 88% for THP–doxorubicin, 81% for vinorelbine, 84% for cyclophosphamide and 87% for 5-FU. Due to high haematological toxicity, dose reduction was necessary in 20 patients. The treatment was delayed at least once in 21 patients for short haematological recovery and was discontinued after 4 courses in 12 cases because of severity and duration of neutropenia.

After induction chemotherapy, all patients underwent surgery: 39 conservative and 11 MRM. 5 patients had had axillary dissection before, 37 after chemotherapy. Radiotherapy was applied in 46 cases. 3 patients received conventional adjuvant chemotherapy and 4 responding patients received an intensive course with ABMT. 7 patients had adjuvant tamoxifen.

Toxicity of induction chemotherapy

Haematological toxicity was severe. The degree of myelotoxicity is detailed in Table 2. 266 cycles of treatment were administered with a median of five cycles per patient (six cycles initially projected). From 253 completely evaluated cycles, leucopenia (grade IV) occurred in 167 (66%) episodes. Thrombocytopenia was less severe, with grade IV occurring in only 17 cycles (7%), requiring 12 platelet transfusions. Severe anaemia (grade IV) appeared in 10 cycles (4%) and 34 packed red blood cells were administered to these patients. Neutropenia was associated with febrile episodes in 54% of patients during cycle 1; details are shown in Table 3. All these patients required broad-spectrum antibiotherapy, but there was no septic shock and no toxic death.

Other toxicities included: constant but reversible complete alopecia; mild to moderate myalgias and arthralgias (3 patients), exacerbated during CSF administration; nausea and vomiting, effectively palliated by 5-HT_3 antagonists. Diarrhoea and mucositis were rare and mild, and no immediate cardiac toxicity with clinical and electrocardiographic examinations, nor significant changes in renal or hepatic parameters, were observed.

Responses (Tables 4 and 5)

Objective responses were observed in 43 (88%) of the 49 evaluable patients. After clinical evaluation, at the end of chemotherapy there were 25 complete responses (51%), 18 partial responses (37%), and in 6 cases (12%) there was no significant change (one was not examined clinically).

Echographic and mammographic assessments confirmed clinical results, although these more sensitive methods

Table 3. Febrile episodes with TNCF chemotherapy

Cycle number	1	2	3	4	5	6	Total cycles (1–6)
No. of patients at risk	50	50	50	46	38	32	266
No. of patients with fever	27	22	22	12	7	2	92
Median duration of febrile episode (days) (range)	4 (1–9)	3 (1–8)	4 (1–12)	2 (1–8)	3 (2–6)	1 (1–2)	
No. of patients requiring hospitalisation	22	15	17	12	2	3	70
Median duration of hospitalisation (days) (range)	6 (2–11)	5 (2–10)	6 (2–13)	5 (2–7)	6 (4–9)	3 (3)	5

showed lower response rates: echographic 85%, mammographic 80%. We also observed that tumour reduction was quickly obtained: out of 25 complete clinical remissions, 20 were obtained after 4 cycles.

All patients underwent surgery and pathological response was as follows: 11 cases were class 1, without residual tumour or tumour cells on microscopic examination. In four cases we found *in situ* carcinoma only (class 2). 12 patients had tumour persistance or tumour cells with alterations (class 3). 23 cases had apparently unmodified tumour remaining after chemotherapy (class 4). Among these patients, 2 had positive axillary nodes with no residual tumour in the breast. For patients who had pCR, the mean tumour size before chemotherapy was 48 mm (range 30–65 mm).

When a complete clinical response was obtained after full staging before surgery, a residual pathological tumour was found in half these patients, and among 24 patients showing incomplete clinical response, only two had pCR.

Survival

The median follow-up of this study is 31 months (range 9–58). Three women have died. Eight recurrences were observed:

—two in the lymph node areas; one axillary with plurimetastases (the patient died) and one supraclavicular;

—one local in the breast;

—one in both breasts after conservative surgery;

—four with distant metastases: two had pulmonary recurrence and died, two other have been treated for pulmonary and liver metastases.

Of these 8 patients with recurrence, following primary chemotherapy, 4 had shown clinical complete response and 2 pathological complete response (1 liver metastases, 1 supraclavicular recurrence).

DISCUSSION

The goal of this pilot study was to assess clinical and pathological response rates of TNCF as induction chemotherapy for high-risk breast cancer. Responses were assessed clinically, by ultrasound and X-rays, and on pathological examination.

We observed a high degree of tumour reduction allowing breast conservation in 78% of the patients. In our study, patients with primary or residual tumour >3 cm were considered unsuitable for breast conserving surgery [4], but there are differences in the criteria used by different groups. The NSABP may choose breast conservation for tumours 5 cm in diameter. TNCF produced an 88% clinical response rate, although this was slightly lower with echographic/mammographic examinations. However, the results indicate greater efficacy than that of our previous regimen AVCF plus or minus methothrexate [14]. Furthermore, responses were rapidly obtained: 20/25 complete responses were obtained after 4 courses. Careful microscopic examination found 30% of patients without residual invasive carcinoma in the surgical specimen (class 1: 22%, class 2: 8%). Neoadjuvant chemotherapy generally results in less than 10% tumour disappearance on pathological examination [8–10, 20]. Only one study with "FEC high dose" protocol has given comparable data in inflammatory breast cancer [19] and one in operable breast cancer [21]. Another team has reported a preliminary study with the Chevallier protocol in non-inflammatory breast cancer [22].

Table 5. Pathological response after induction chemotherapy by TNCF (n = 50) [14]

Response	No. of patients	Percentage
Class 1: no tumour	11	22%
Class 2: *in situ* carcinoma alone	4	8%
Class 3: invasive carcinoma with alteration	12	24%
Class 4: invasive carcinoma	23	46

Growth factor administration has been proven to be particularly effective in reducing the length of the granulocyte depression and to allow a higher chemotherapy dose intensity [23]. In our study, tolerance was evidently improved with haematopoietic growth factors, but 20 patients required dose reduction. Moreover, CSF retained their efficacy and there was no evidence of delayed depletion of the haematopoietic pool. This administration has proven particularly effective, improving the compliance to this aggressive chemotherapy with an acceptable cost and avoiding serious side-effects.

In conclusion, the clinical and pathological response rate observed in this study seems promising. Several teams have suggested that the achievement of surgical specimens, free of residual tumour was the most significant factor in predicting a prolonged disease-free survival and overall survival [11, 24]. However, the ability of neoadjuvant chemotherapy to improve patient outcome remains unresolved. Results from large controlled trials such as NSABP B-18 will give important scientific information in this regard [25].

Using the primary tumour as a target could indicate the efficacy of systemic drugs [6]. New antineoplastic agents such as taxanes could be evaluated in the pre-operative setting subsequent to standard chemotherapy. Other studies could determine the possible benefit of non-cross-resistant regimens given postoperatively. Such a strategy may thereby

Table 4. Clinical, echographic and mammographic responses after TNCF induction chemotherapy (n = 50)

Response	Method of assessment		
	Clinical	Echographic	Mammographic
Complete (CR)	25 (51%)	14 (35%)	23 (51%)
Partial (PR)	18 (37%)	20 (50%)	13 (29%)
Minor or no change (MR + NC)	6 (12%)	6 (15%)	9 (20%)
Not done	1	10	5

For each method of assessment, the percentage was calculated from the number of evaluable patients.

allow optimisation of chemotherapy to improve patient survival.

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