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Neoadjuvant Chemotherapy in Operable Breast Cancer

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Primary chemotherapy in localised breast cancer may prevent tumour spread during surgical treatment and reduce proliferation of micrometastases. A randomised clinical trial, in 196 premenopausal and postmenopausal patients with operable (T2–3, N0–1b) breast cancer, was started in November 1983 at the Institut Curie to compare neoadjuvant and adjuvant regimens of chemotherapy with radiotherapy with or without surgery. The patients have been followed up for 35–70 months (median 54). A neoadjuvant group received two monthly cycles of intravenous doxorubicin/cyclophosphamide/5-fluorouracil before locoregional therapy and four cycles subsequently. Six monthly cycles following locoregional therapy were administered to the adjuvant group. Because of inclusion of postmenopausal and/or node-negative patients, compliance was less than optimal in 39 patients who were analysed separately according to actual dose received. Tumour response, evaluated after two cycles of neoadjuvant chemotherapy, was significantly associated with dose ($P = 0.003$). Survival showed a slight non-significant advantage for the neoadjuvant group. Survival plotted by actual dose was also similar. Neoadjuvant chemotherapy was safe and at least as effective as the adjuvant regimen. Patients have been accrued to a subsequent larger trial of chemotherapy as first-line treatment.
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INTRODUCTION

CHEMOTHERAPY AS a primary treatment in localised breast cancer has been advocated for a variety of theoretical reasons, based on both biological and clinical premises. Experimental systems suggest that non-curative reduction of tumour cell burden results in an increase in the proliferation of residual tumour cells, possibly due to the release of serum growth factors [1]. Clinical studies [2] have shown that cyclophosphamide, tamoxifen and radiotherapy, given prior to surgery, prevent an increase in metastatic tumour growth and prolong survival. According to the Goldie–Coldman hypothesis [3], the number of drug-resistant phenotypes generated by spontaneous mutation will increase concomittantly with tumour growth. The risk of generation and multiplication of resistant cells can therefore be minimised by initiating chemotherapy as soon as possible, thus preventing further cell proliferation.

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A randomised clinical trial involving 196 patients was initiated in November 1983 at the Institut Curie with the aim to compare neoadjuvant and adjuvant regimens in operable breast cancer. These patients have been followed up for 35–70 months (median 54) and the treatment efficacy as well as percentages of breast conservation have been evaluated.

PATIENTS AND METHODS

Patient presentation

Between November 1983 and March 1986, 196 patients were accrued in this study and randomised to receive either neoadjuvant ($n = 100$) or adjuvant (96) therapy. The criteria for inclusion were as follows: tumour size T2–T3, axillary nodes not involved clinically or involved but not adherent (N0, N1b) no prior cancer, no serious concomittant illness, and below 65 years of age. 15 patients were excluded due to errors of randomisation, poor patients' or physicians' complicance, or because treatment was at outside institutions. At the time this trial was conducted, the premise that surgically node-negative patients would benefit from adjuvant chemotherapy was not generally accepted and accordingly incomplete treatments (neoadjuvant) or treatment omissions (adjuvant) occurred not infrequently. For the purpose of this communication, patients were divided into four groups (Table 1) according to whether

Table 1. Patients' characteristics

	Neoadjuvant group		Adjuvant group		Patients excluded
	Ia	Ib	IIa	IIb	
Total	77	18	65	21	15
Randomised					Variable
Cycles	2 pre + 4 post	1–2 pre	6 post	0	Variable
Premenopausal	51 (66)	11 (61)	41 (63)	11 (52)	5 (33)
Age (median)	49	49	50	55	55
T2 N0	0	0	1	2 (9)	1
T2 N1b	33 (43)	10 (56)	21 (32)	5 (24)	5
T3 N0	22 (28)	2 (11)	17 (26)	7 (33)	2
T3 N1b	22 (28)	6 (33)	26 (40)	7 (33)	7
Grade (SBR)					
1	5 (6)	0	5 (8)	3 (14)	0
2	41 (53)	10 (55)	34 (52)	14 (67)	10
3	11 (21)	5 (28)	22 (34)	3 (14)	2
Not graded	15 (19)	3 (17)	4 (6)	1 (5)	3
ER positive	10/35 (29)	6/11 (54)	15/36 (42)	7/11 (54)	6/11 (54)
PR positive	19/57 (33)	7/13 (53)	25/58 (43)	8/20 (40)	7/14 (50)

No. (%).
SBR = Scarff, Bloom and Richardson, ER = oestrogen receptor, PR = progesterone receptor.

Table 2. Treatment protocol

Neoadjuvant (n = 100)	Adjuvant (n = 96)
Primary ACF : 2 cycles Secondary locoregional treatment Tertiary ACF : 4 cycles (good initial responders) AMVT : 4 cycles (poor initial responders)	Primary locoregional Secondary ACF : 6 cycles

ACF = doxorubicin, cyclophosphamide and 5-fluorouracil.
AMVT = doxorubicin, methotrexate, vindesine and thiotepa.

they received their treatment as planned (Ia+IIa) or whether the number of chemotherapy cycles was decreased (Ib) or chemotherapy was withheld (IIb). Group Ia represented 77 patients who underwent a neoadjuvant regimen (two cycles prelocal therapy and four cycles after therapy) and group IIa represented 65 patients who received 6 cycles of adjuvant treatment; both groups were treated on protocol. Group Ib represented 18 patients who received two cycles of neoadjuvant therapy only. Group IIb represented 21 patients randomised to receive adjuvant therapy, in whom chemotherapy was withheld. All data were analysed for the appropriately treated groups Ia (n = 77) and IIa (n = 65) only as well as for the groups as originally randomised (neoadjuvant = 95; adjuvant = 86). A second analysis according to the dose of chemotherapy received permitted us to evaluate all 181 patients.

Treatment

Chemotherapy was started either after the initial assessment was completed (neoadjuvant therapy) or within a few weeks of ending the locoregional therapy (adjuvant group). The median delay in the initiation of chemotherapy between these two groups was 72 days. All patients underwent irradiation either as primary treatment (adjuvant group) or between cycles 2 and 3 (neoadjuvant group) of chemotherapy. Radiation therapy was delivered with a cobalt-60 unit according to a technique which has been described previously [4]. The mean dosage to the breast was 55 Gy over 6 weeks, followed by a boost to the tumour bed to achieve a total dose of 75–80 Gy. This dose intensification to the tumour was withheld in those patients who did not show a significant tumour regression at 55 Gy. 55 Gy were delivered to the inferior axillary nodes and 45 Gy to the supraclavicular nodes and the internal mammary chain. Surgery was limited to those patients who presented with a persisting mass after the completion of irradiation (Table 2) and aimed to be as conservative as possible.

The neoadjuvant regimen (group I) consisted of doxorubicin at 25 mg/m^2 intravenously on days 1 and 8, cyclophosphamide intravenously at 400 mg/m^2 on days 1 and 8, 5-fluorouracil intravenously or intramuscularly at 500 mg/m^2 on days 1, 3, 5 and 8 (the ACF regimen). Cycles of chemotherapy were repeated at 28-day intervals or longer depending on recovery of bone marrow (absolute granulocyte count > 1500/μl and platelet count > 150000/μl). The dosage of ACF was reduced by 10 or 20% in subsequent cycles to permit correct timing. If the mucositis was worse than grade 2, the dosage of 5-fluorouracil was reduced by 20%.

Tumour response was evaluated after two cycles of chemotherapy. For patients with disease progression or stabilisation, the four cycles of chemotherapy postlocoregional treatment were changed to an AMVT regimen which consisted of doxorubicin at 20 mg/m^2 on days 1 and 8, methotrexate at 25 mg/m^2 on days 1 and 8, vindesine at 3 mg/m^2 on days 1 and 8 and thiotepa at 7 mg/m^2 on days 1 and 8. 8 patients received this alternative regimen in the adjuvant setting.

All patients who received adjuvant therapy only (group II) received six cycles of ACF. Methylprednisone at 80–120 mg intravenously (days 1 and 8) and 20–30 mg prednisone orally (10 days) were routinely associated.

Statistical methods

Survival curves wer drawn using Kaplan–Meier estimates. Comparison of survival distributions were made by logrank test [5].

RESULTS

Table 1 shows the clinical, pathological and biological characteristics of the different treatment groups. There was a tendency for the adjuvant group (II) to have a larger percentage of tumours classified T3N1b than the neoadjuvant group (I) but this difference did not reach statistical significance. The average tumour size in both these groups was 5 and 5.4 cm, with a variance of 3.6 and 3.2 cm, respectively.

Tumour response to dose of neoadjuvant chemotherapy

The total dose/m^2 received prior to locoregional therapy was analysed as the fraction of the planned treatment dose and the percentages of the different drugs were averaged to allow comparison. Table 3 shows a highly significant advantage in treatment response for those patients (in group Ia) who received > 75% of the planned dose (P = 0.003). This result also held true if all patients (95) were included (P = 0.002).

There were no treatment-related deaths. Undue haematological or mucosal toxicity were addressed by decreasing drug dosages by 10–20%.

Table 3. Tumour response according to dose of neoadjuvant chemotherapy

	Response		
	< 50	50–75%	75–100%
CR	0	0	10
PR > 50%	0	4	20
PR < 50%	2	12	20
Stable disease	0	3	4
Progressive disease	0	1	0
Total	2	20	54

$\chi 2 = 8.82$. $P = 0.003$.
CR = complete response, PR 50% = 50% tumour regression (partial response).

Patient survival

The median follow-up at the time of analysis was 54 months, with extremes at 35 and 70 months. 2 patients were lost to follow-up at 35 and 38 months. In the subgroup of patients whose treatment did not deviate from the planned protocol, the survival curve for the neoadjuvant group is above that for the adjuvant group; albeit did not reach statistical significance ($P = 0.3$). Since there was a slight bias towards removing good prognostic patients from the adjuvant setting, we analysed the survival of all patients according to their randomisation. There was no difference in the shape of the survival curve or in the P value when all patients remained in the analysis. The disease-free survival of groups I and II shows presently no difference ($P = 0.4$). No survival advantage without metastasis could be substantiated in either group I or II.

Since total chemotherapy dose and/or intensity [6] have been claimed to influence survival, we analysed groups Ia, Ib and IIa according to whether their total dose received over two to six cycles was above or below 75% of the planned 6-monthly course, and group IIb (in whom chemotherapy was withheld) separately. The average total dose of doxorubicin was 64%, of cyclophosphamide 75% and of 5-fluorouracil 71%. Median levels were 73, 82 and 84%, respectively. Figure 1 shows that the survival curve for the "good prognostic" group IIb was not superior to those treated with variable doses of chemotherapy ($P = 0.6$). Again,

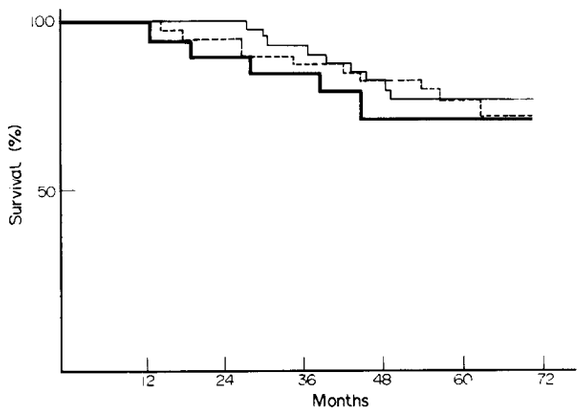

Fig. 1. Survival curves for all evaluable patients ($n = 181$) according to the actual dose received as a percentage of planned treatment dose. Patients who received no chemotherapy were more frequently node-negative and postmenopausal with well-differentiated tumours.

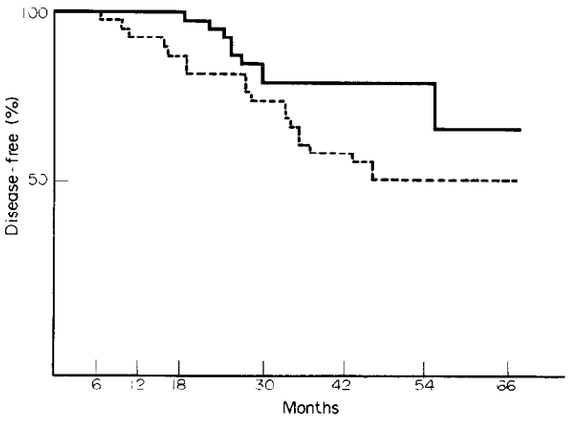

Fig. 2. Disease-free survival in the neoadjuvant group Ia according to tumour response after two cycles of chemotherapy. —— = > 50% tumour regression ($n = 35$), ---- < 50% tumour regression ($n = 42$). $P = 0.058$.

the group receiving less than 75% of the planned total dose included 18 patients who only had two neoadjuvant courses (at adequate dosage) and were judged not to need any further treatment after completion of their locoregional therapy. The small number of patients in the different groups did not allow the analysis of subsets according to the timing of chemotherapy as well as the total dose received.

When disease-free survival was analysed according to tumour response to primary chemotherapy, divergent results were seen whether group Ia was analysed alone or both groups Ia and Ib were included. A significant advantage (Fig. 2) ($P = 0.058$) existed for the responders in the group treated with six courses of chemotherapy (Ia), whereas the inclusion of group Ib (who received one to two cycles of chemotherapy only) confounded both curves ($P = 0.3$). Group Ib was considered not to "need" any further treatment after the completion of the locoregional therapy. A similar difference was obviated in survival curves (group Ia: $P = 0.07$, groups Ia+Ib: $P = 0.2$).

Local recurrence

Since not all patients had been operated on, local recurrence was defined by tumour presence at or after 9 months from the start of treatment. There was a small advantage towards a lower local recurrence rate in the good initial responders to chemotherapy (14% vs. 21% in the poor responders) but this difference was not significant ($P = 0.4$). Average local recurrence rates were 18% for group I and 20% for group II.

Breast preservation

Table 4 shows the surgical treatment received for the different subgroups. There was a tendency for patients treated with the neoadjuvant regimen to have a higher incidence for breast preservation. Only 22/95 (23%) patients treated with the neoadjuvant regimen required a mastectomy, whereas 31/86 (36%) patients in the adjuvant setting had their breasts removed. The lumpectomies being equally distributed, this difference reflects a higher "no surgery" rate in the neoadjuvant patients (43%), vs. 35% in the adjuvant setting.

DISCUSSION

In this study, the value of the timing of a systemic therapy in so-called operable breast cancer was assessed. Emphasis was made equally on treating patients conservatively and avoiding

Table 4. Surgical treatment (%)

	Group			
	Ia(n=77)	IIa(n=45)	Ia+b(n=95)	IIa+b(n=86)
Mastectomy	21	31	23	36
Lumpectomy	34	34	34	30
No surgical treatment	45	35	43	34

Group I represents patients randomised to neoadjuvant chemotherapy who (a) were treated as randomised or (b) received 1–2 cycles of primary chemotherapy, but no chemotherapy post locoregional therapy.
Group II represents patients randomised to adjuvent chemotherapy who (a) were treated as randomised or (b) received no chemotherapy.

mastectomy whenever possible. Although patients were randomised to either start with systemic therapy or to have adjuvant chemotherapy at the end of their locoregional treatment, multiple deviations from this initial plan forced us to regroup the patients into four treatment categories for analysis, where only groups Ia and IIa were treated according to randomisation. At the time this study was designed, the value of adjuvant chemotherapy in node-negative patients was not well established and the treatment compliance not optimal. Another weakness of this study was the inclusion of a large number of postmenopausal patients who were not infrequently given adjuvant hormone therapy instead of chemotherapy. These problems are addressed in a current randomised trial (S6) which was initiated in 1986 and for which the accrual of the 414 premenopausal patients was completed in June 1990.

Here, we hoped to observe a better tumour response with a higher drug dosage, but were unable to observe any statistically significant survival advantage. Our numbers were too small to analyse subsets of patients according to both timing and total dose received. However, in the neoadjuvant group, those patients who responded to chemotherapy (> 50% reduction) as primary treatment had less metastasis (P = 0.1) and an improved disease-free survival (P = 0.058, Fig 2) compared to those who had a minimal (< 50%) or no objective tumour shrinkage.

There appeared to be a slight advantage towards breast preservation in the neoadjuvant group. Similar results have been published by two separate European trials [7, 8]. Moreover, prolonged postoperative chemotherapy (in addition to neoadjuvant treatment) resulted in a significant survival advantage [7]. We did see an improved disease-free survival (P = 0.058) for the responders to primary chemotherapy who had an additional four courses of adjuvant chemotherapy (group Ia) but this advantage disappeared (P = 0.3) when all patients (Ia+b) were included. These results suggest that group Ib (one to two cycles of neoadjuvant chemotherapy only) was insufficiently treated. Our study design with a systematic assocation of radiation treatment did not allow to assess potential advantages of chemotherapy alone. There was no major toxicity resulting in treatment-related death, and minor haematological and mucous membrane toxicity, as well as alopecia, were equal in both groups.

In conclusion, we felt that neoadjuvant therapy is a safe and certainly not less effective treatment than adjuvant chemotherapy. It may prove superior, but we are unable to determine a significant difference in survival between both arms in the present study. A selected "good prognosis" group of patients who received no further drug treatment did not have an improved survival (Fig. 1) as compared to the treated higher risk patients, although the numbers were too small to reach statistical significance. The importance of optimal drug dosage in order to achieve a complete response (P = 0.003) is visualised in the neoadjuvant setting and equally reflects a prolonged disease-free survival (P = 0.058). A more recent trial designed to randomise premenopausal patients (only) into either neoadjuvant or adjuvant courses of chemotherapy has concluded and will enable us to reassess more effectively the value of chemotherapy as primary treatment for breast cancer patients in the near future.

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