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Neoadjuvant Versus Adjuvant Chemotherapy in Premenopausal Patients With Tumours Considered Too Large for Breast Conserving Surgery: Preliminary Results of a Randomised Trial: S6

S.M. Scholl, A. Fourquet, B. Asselain, J.Y. Pierga, J.R. Vilcoq, J.C. Durand, T. Dorval, T. Palangié, M. Jouve, P. Beuzeboc, E. Garcio-Giralt, R.J. Salmon, A. de la Rochefordière, F. Campana and P. Pouillart

The aim of this study was to assess a potential advantage in survival by neoadjuvant as compared to adjuvant chemotherapy. 414 premenopausal patients with T2-T3 N0-N1 M0 breast cancer were randomised to receive either four cycles of neoadjuvant chemotherapy (cyclophosphamide, doxorubicin, 5-fluorouracil), followed by local-regional treatment (group I) or four cycles of adjuvant chemotherapy after primary irradiation ± surgery (group II). Surgery was limited to those patients with a persisting mass after irradiation, and aimed to be as conservative as possible. 390 patients were evaluable. With a median follow-up of 54 months, we observed a statistically significant difference ($P = 0.039$) in survival in favour of the neoadjuvant chemotherapy group. A similar trend was seen when the time to metastatic recurrence was evaluated ($P = 0.09$). At this stage, no difference in disease-free interval or local recurrence between these two groups could be observed. The mean total dose of chemotherapy administered was similar in both groups. On average, group I had more intensive chemotherapy regimes (doxorubicin $P = 0.02$) but fewer treatment courses ($P = 0.008$) as compared to the treated patients in group II. Haematological tolerance was reduced when chemotherapy succeeded to exclusive irradiation. Breast conservation was identical for both groups at the end of primary treatment (82 and 77% for groups I and II, respectively). Of the 191 evaluable patients in the neoadjuvant treatment arm, 65% had an objective response (>50% regression) following four cycles of chemotherapy. The objective response rate to primary irradiation (55 Gy) was 85%. Improved survival figures in the neoadjuvant treatment arm could be the result of the early initiation of chemotherapy, but we cannot exclude that this difference might be attributable to a slightly more aggressive treatment. So far, the trend in favour of decreased metastases was not statistically significant. The local control appeared similar in both subgroups.
Eur J Cancer, Vol. 30A, No. 5, pp. 645–652, 1994

INTRODUCTION

LIMITED INFORMATION exists to support timing decisions in treating human neoplasms. In animal models, survival is optimised when systemic chemotherapy precedes the surgical resection of transplantable tumours, and better results are achieved with a shorter time interval between tumour implantation and start of therapy [1–9].

In pilot studies, locally advanced breast tumours have been shown to regress following pre-operative chemotherapy [10–13], and a complete pathological response could be achieved in 36%

of 76 patients [13] in one of the more aggressive treatment regimes. A controlled trial, the Scandinavian Multicenter Trial [14], exploring peroperative single-agent alkylating chemotherapy, reported a 10.5% reduction in death rates at 10 years for those patients receiving a 6-day course of cyclophosphamide starting on the day of surgery as compared to untreated controls. Similarly, the Ludwig Breast Cancer Study Group reported a prolonged disease-free survival for node-negative patients treated with a single peri-operative course of combination chemotherapy as compared to controls receiving no adjuvant treatment [15]. Both these trials reported a benefit of early chemotherapy as compared to no chemotherapy. In node-positive patients, a single peri-operative course of chemotherapy proved less effective than prolonged therapy, and the start of chemotherapy at surgery versus 4 weeks later proved no different [16]. These results are in agreement with Skippers mathematical model [17] according to which multiple courses of treatment beyond the point of remission induction are needed, in order to achieve a cure. Multiple course neoadjuvant chemotherapy in operable breast cancer was pioneered by Jacquillat [18] and by the Milan group [19], and has since been adopted by many centres [13, 20, 21]. Clinical response rates following four to six cycles of doxorubicin-containing combined chemotherapy regimes ranged between 70 and 87% [22].

Comparisons of survival figures with historical control groups (treated with adjuvant chemotherapy) seemed to show a survival advantage for patients treated by induction chemotherapy [19, 23]; but so far confirmation from mature controlled trials is still awaited. A slight advantage in survival in favour of neoadjuvant chemotherapy could initially be observed in a randomised trial at Fondation Bergonié (Bordeaux, France) [20], but this advantage disappeared at a later evaluation [24]. Again, no difference in outcome as regards relapse rates or survival in both arms was shown in a previous similar pilot trial (S5) from our institute [21].

Primary radiotherapy to tumours not amenable to wide excision has been largely used in our institute as well as by other investigators, and allowed breast preservation in large subsets of patients [25–28].

The present study was conducted to assess whether prolonged (four cycles) neoadjuvant chemotherapy, improved survival, as compared to the same chemotherapy scheduled to follow the local-regional treatment in clinically node-positive or node-negative, premenopausal patients. 414 premenopausal breast cancer patients were included and treated with either induction chemotherapy followed by locoregional treatment, or induction radiotherapy (± surgery) followed by systemic treatment. The median follow-up was 54 months. Recurrence, survival and breast conservation were evaluated, as well as tumour response to primary chemotherapy or to primary irradiation.

PATIENTS AND METHODS

Patient presentation (*Table* 1)

414 patients were accrued in this study between October 1986 and June 1990, and randomised to receive either neo-adjuvant (group I) or adjuvant chemotherapy (group II). The criteria for inclusion were as follows: non-metastatic operable breast tumours, largest tumour diameter between 3–7 cm (patients with smaller tumours were not eligible and treated with limited surgery), axillary nodes not involved clinically, or involved but not adherent (N0, N1b), no prior cancer, no serious concomitant illness. Pathological diagnosis of invasive breast cancer was performed in all patients on drill biopsy specimen. In an attempt to assure an optimal homogeneity of the study population and avoid interference with hormonal treatments, we did not include postmenopausal patients into this trial. Bilateral, inflammatory or locally advanced breast cancers (>7 cm) were also not eligible. 24 patients opted out of this treatment protocol and 390/414 (94%) patients are thus evaluable, 200 in group I, 190 in group II. Protocol violations or errors of randomisation occurred in 7 patients (3.5%) in group I and 12 patients (6%) in group II, and the data were analysed both with and without these exclusion patients. All deaths were due to disseminated cancer with the exception of 3 patients: 1 patient committed suicide and 2 died of sudden deaths in the absence of clinically evident metastatic disease.

Table 1. *Patients' characteristics*

Timing of chemotherapy	Neoadjuvant chemotherapy	Adjuvant chemotherapy	*P*
No. of patients	200	190	
Mean age (years)	45.16	45.08	NS
T2	141	145	
T3	59	45	NS
Mean tumour size (mm)	47.35	45.26	NS
N0	80	80	
N1a	42	39	
N1b	76	70	
NX	2	1	NS
SBR I	40	28	
SBR II	89	102	
SBR III	35	37	
Unknown	25	18	NS
ER−	73	77	
ER+	93	96	NS
PR−	80	74	
PR+	85	98	NS

T, UICC classification of clinical tumour size; N, clinical node status; SBR, pathological grade, according to Scarff, Bloom and Richardson; ER, oestrogen receptor status (cut-off 250 fmol/mg DNA); PR, progesterone receptor status (cut-off 250 fmol/mg DNA).

Treatment (*Figure* 1)

Chemotherapy. Chemotherapy was started either after the initial assessment was completed (neoadjuvant therapy) or within 2 weeks of ending the locoregional therapy (adjuvant therapy). Chemotherapy for both groups consisted of four cycles of intravenous doxorubicin (A), cyclophosphamide (C) and 5-fluorouracil (F). In the neo-adjuvant setting, the tumour response to chemotherapy was evaluated after each cycle of chemotherapy and the clinically non-responding patients started local-regional therapy after two cycles. Response was evaluated by measurement of the two largest tumour dimensions. 153

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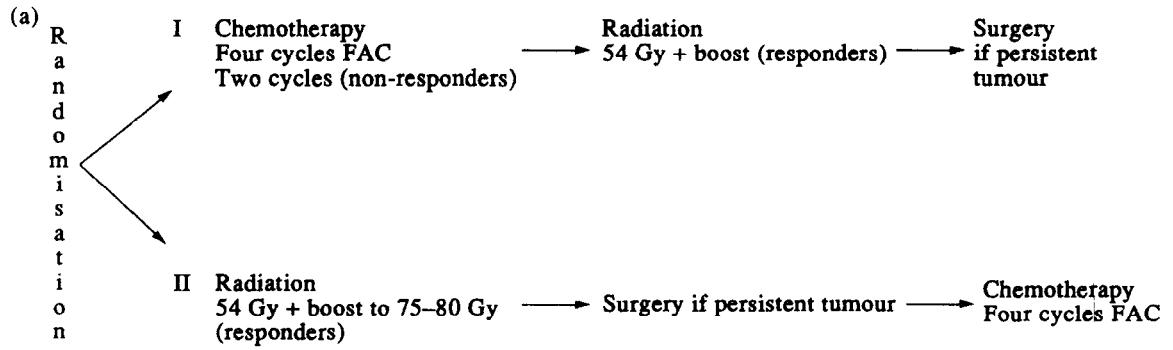
Members of the Breast Cancer Group were also involved in this study.
Revised and accepted 6 December 1993.



(b)

Randomised		414	
Not treated at Curie	Neoadjuvant 8	Adjuvant 16	
Evaluable		390	
	Neoadjuvant 200	Adjuvant 190	
One cycle of chemotherapy or less	2	24	No chemotherapy
Errors randomisation protocol violation	7	12	Error randomisation protocol violation
Evaluable for response at 2 cycles	191	154	Treated with two cycles
Evaluable for response at four cycles	153	143	Treated with four cycles
	153/200 (76.5%)	143/190 (75%)	

Figure 1. Sequence of treatments according to the patients randomisation into arm I (neoadjuvant chemotherapy) or arm II (first line local-regional treatment). (a) Study design; (b) execution.

patients went on to receive four cycles of neoadjuvant chemotherapy. The drug dosage was as follows: A: 25 mg/m^2 days 1 + 8, C: 500 mg/m^2 days 1 + 8, F: 500 mg/m^2 days 1 + 3 + 5 + 8. Cycles of chemotherapy were repeated at 28-day intervals or longer, depending on recovery of bone marrow. The patients in the adjuvant setting received four cycles of the same chemotherapy regime following their local-regional treatment. 24 patients (13%) in the adjuvant setting did not receive chemotherapy as planned. These patients had surgery for an incomplete tumour regression following radiotherapy, and were found to be node negative on pathological diagnosis. All survival and recurrence figures were calculated with and without these 24 patients.

Dose calculations included all patients treated as randomised and excluded patients who did not receive chemotherapy (2 in group I and 24 in group II) or who differed from the planned protocol (7 in group I and 12 in group II). The total dose delivered (averaged fractions of three drugs × number of cycles) was identical in both groups ($P = 0.15$). The averaged percentage of the planned dose for the three drugs combined in each cycle was 81.3% (±10.3%) in the neoadjuvant treatment group and 78.8% (±9.7%) in the adjuvant group ($P = 0.06$). The dose of doxorubicin alone was higher in the neoadjuvant group (40.2 ± 5.5 mg/m^2) than in the adjuvant group (38.8 ± 4.8 mg/m^2). The relative percentages of the planned dosages were 80.6 versus 77.6% and this difference was significant ($P = 0.02$). Due to the study design, group I had fewer treatment courses than group II ($P = 0.008$).

Radiation treatment. Irradiation was either as primary treatment or following two to four courses of chemotherapy. The locoregional treatment was meant to begin with radiotherapy and was aimed to cure the tumour as well as to preserve the breast through primary irradiation. Radiation therapy was delivered with a Cobalt 60 unit according to a technique which has been described previously [29]. The aim of this technique was to reduce the radiation dose received to the cardiac area, in particular for tumours of the left breast. The mean ('basic') dosage to the breast was 54 Gy over 6 weeks. The response to treatment was evaluated by clinical examination and mammography. Patients with either a complete or near to complete response (>95%) received a radiation 'boost' to the tumour bed to achieve a total dose of 75–80 Gy and no surgery was performed. This boost was delivered either with a Cobalt 60 unit or with Iridium 192 Curie therapy, and was withheld in those patients who did not show a significant tumour regression at 54 Gy. All patients

had radiation treatment (54 Gy) to the axillary nodes followed by a 10–15 Gy boost to the inferior axilla in patients with N1 disease (if no surgery was performed) and 45 Gy to the supraclavicular nodes and the internal mammary chain.

Surgery. Surgery was limited to those patients who presented with a persisting mass after 54 Gy. When technically and cosmetically feasible, a wide surgical resection of the residual tumour was performed. Those patients with minimal or no response to prior treatments had a mastectomy. These patients had a surgical dissection of the axilla and received minimal or no radiation boost to the axillary area.

In the neoadjuvant treatment arm, the locoregional treatment strategy was determined by the residual amount of tumour following first-line chemotherapy. Patients with a complete response had exclusive radiotherapy to the breast and axillary, supraclavicular and internal mammary nodes, with a boost to the primary tumour site. Patients with an incomplete regression had either exclusive radiotherapy, or radiotherapy with wide excision or mastectomy according to the response to radiotherapy. Details of the local regional treatment are shown in Table 2. 20 patients (10%) in the neoadjuvant arm and 4 patients (2%) in the adjuvant arm underwent mastectomy without radiotherapy.

Statistical methods

According to Freedman's method [30], for an α risk of 5%, a β risk of 10%, and an expected 15% increase in survival rates (60–75%), 414 patients had to be included. Survival, calculated from date of randomisation to death or date of last follow-up, was the principal endpoint. Other endpoints were disease-free interval, local recurrence, metastasis-free interval and breast conservation. Survival curves were drawn using Kaplan–Meier estimates. Comparison of survival distributions were made by log-rank test [31]. Five-year rates were expressed with their 95% confidence intervals.

RESULTS

Table 1 shows the clinical, pathological and biological characteristics of both treatment groups. There was no statistically significant difference between these two groups. The average tumour size was 4.7 cm in group I and 4.6 cm in group II.

Patient survival and recurrence

The primary goal of this study was to determine whether the timing of chemotherapy offered survival advantages. At a median follow-up of 54 months, we observed a survival advantage for the group of patients treated with primary chemotherapy

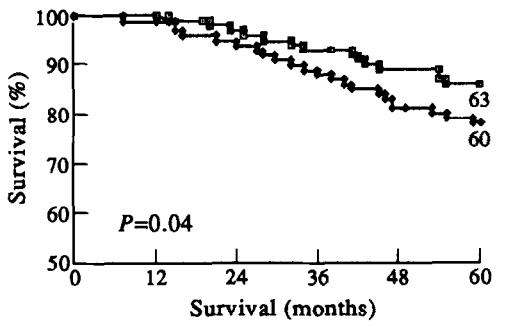


Figure 2. Overall survival according to timing of chemotherapy at a median follow-up of 54 months. The 5-year rates were 86% for the neoadjuvant group (open squares) and 78% for the adjuvant group (closed diamonds) with 63 and 60 patients remaining at risk in the respective groups. This difference was statistically significant at $P = 0.04$.

($P = 0.039$) (Figure 2). The 5-year probability of survival was 86% (83–89%) for the neoadjuvant group and 78% (71–85%) for the adjuvant group. This difference did not reflect in an improved disease-free interval (DFI). The 5-year DFI rates were 59% (51–67%) and 55% (47–63%) in groups I and II, respectively ($P = 0.4$). Distant metastases occurred in 48/200 patients in group I and in 60/190 patients in group II. The 5-year metastases-free rates were 73% (70–76%) in group I and 64% (60–68%) in group II, but these differences did not reach statistical significance ($P = 0.09$; Figure 3). The survival after metastatic recurrence was similar for both groups ($P = 0.1$). The outcome of

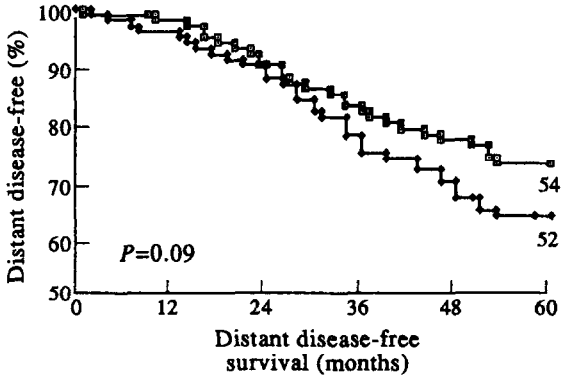


Figure 3. Time to metastatic recurrence: the 5-year distant disease-free rates were 73% for group I (open squares) and 68% for group II (closed diamonds), 54 and 52 patients remain at risk. This difference failed to reach statistical significance: $P = 0.09$.

Table 2. Distribution of patients according to locoregional treatment

	Primary chemotherapy $n = 200$	Primary radiotherapy $n = 190$
Breast-preserving treatment	164 (82%)	147 (77%)
Radiotherapy alone	102 (51%)	87 (46%)
Radiotherapy + tumorectomy	26 (13%)	60 (32%)
Tumourectomy + radiotherapy	36 (18%)	
Mastectomy	36 (18%)	43 (23%)
Radiotherapy + mastectomy	16 (8%)	39 (21%)
Mastectomy ± radiotherapy	20 (10%)	4 (2%)

the 24 node-negative patients in group II who did not receive their adjuvant treatment as planned was identical to that of their original group.

Tumour response and breast-conserving treatments

A second goal in this trial was to evaluate a potential gain in breast conservation following first-line chemotherapy. The distribution of the primary local-regional treatments in both arms, as shown in Table 2, documents very similar results by either one of these treatment regimens ($P = 0.37$). Surgery was withheld in approximately half of all patients in both treatment arms in favour of exclusive chemotherapy and radiation treatment. Approximately a further 30% of patients in both treatment arms had limited surgery, bringing total breast preservation rates at the end of therapy to 82%, following neoadjuvant chemotherapy, and to 77% in the other treatment arm. These differences were not statistically significant. Mastectomies as part of the primary treatment were performed in 18 and 23% of patients in those two treatment categories.

(1) *Response to neo-adjuvant chemotherapy.* Due to a good compliance, with dosages >75% of the planned treatment dose in the present trial, no such dose/response effect as reported in an earlier trial [21] was perceived. The tumour response to primary chemotherapy was evaluable in 191 patients at 2 months; 153 patients went on to receive four cycles of chemotherapy. Figure 4a, showing the degree of tumour regression following two and four cycles of chemotherapy, illustrates a progression of the objective response rates (tumour reduction >50% of its original size) from 56% at 2 months to 82% at 4 months. At 2 months, only 4% had a complete response, a further 52% had a major response, 33% had a minor response (25–50% size reduction) and 13% had stable or progressive disease. 38 patients (20%) with minor clinical changes in tumour volume or poor tolerance, following two cycles of chemotherapy, started local-regional treatment at this stage. At 4 months, 153 patients were evaluable, and the response rates were 30, 52 and 16%, respectively. 3 patients had stable disease. The patients presenting an objective response at 4 months (82%) represented 65% of the original group of 191 patients.

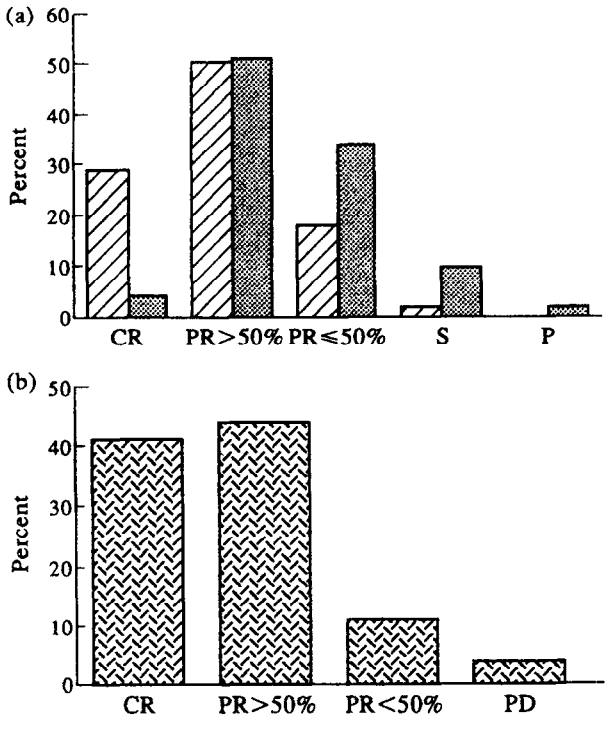


Figure 4. (a) Tumour response to primary chemotherapy. Percentage of patients responding at 2 months (dotted histograms) and at 4 months of chemotherapy (striped histograms). CR, complete clinical response; PR, >50% (major) or ≤50% (minor) tumour regression as measured by product of two dimensions; S, stable disease; P, progression. 191 patients were evaluable at 2 months, 153 were evaluable at 4 months. (b) Tumour response to primary irradiation (54 Gy). Percentage of patients responding with a CR, more than 50% tumour regression (PR > 50), minor response (PR < 50), and progressive disease (PD).

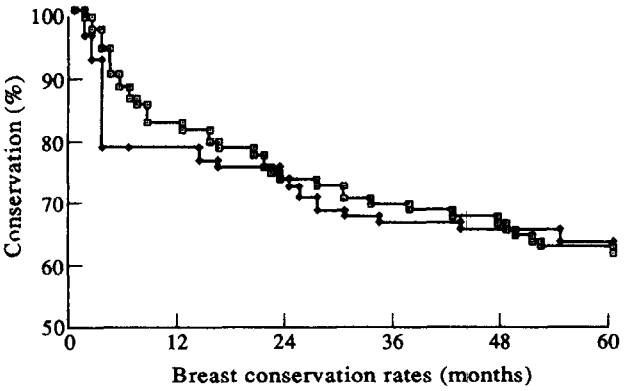


Figure 5. Breast conservation rates were similar for the neoadjuvant (open squares) and the adjuvant (closed diamonds) arm.

(2) *Response to primary radiation treatment (Figure 4b).* Following a basic treatment dose of 54 Gy to the breast, 41% of patients had a complete response, 44% had a major response and 11% had a minor response. Four per cent had progressive disease. A total of 85% of all patients treated by first-line radiation had a major response (>50% tumour regression) at 54 Gy. Of 69 patients with residual disease following four cycles of chemotherapy, 42 (61%) achieved a complete response by irradiation to 54 Gy.

Breast conservation and local recurrence

Breast or chest wall recurrences, either isolated or concomittant to clinical axillary node recurrences, occurred in 48/200 patients of group I and 35/190 patients of group II. Isolated axillary node recurrences occurred in 1 and 2 patients of these respective groups. The 5-year actuarial local control rates were 73% (69–77%) in group I and 81% (78–84%) in group II ($P = 0.21$). Most patients whose tumour recurred in the breast were treated by mastectomy, bringing absolute numbers of radical surgery to 73/200 patients (36 for the initial treatment and 37 for a recurrence) in group I and to 66/190 patients (44 and 22) in group II. The 5-year breast preservation rates (Figure 5) were 61% (57–65%) in group I and 63% (59–67%) in group II ($P = 0.95$). Among the patients who recurred locally, metastatic spread of the disease was apparent concomittantly in 36% of patients treated by first-line radiotherapy, and in 39% of patients in the neoadjuvant chemotherapy group.

Treatment-related toxicity

Leucocyte counts were significantly lower when chemotherapy succeeded primary irradiation (Table 3; $P = 0.0018$) and contributed to a lower dose intensity in the adjuvant

Table 3. Treatment-induced toxicity (WHO grades 3 and 4)

	Neoadjuvant	Adjuvant	*P* value*
Haematological			
Platelets		1	
Leucocytes	21	33	
Grade 3	4	12	0.0018
Grade 4			
Fever		3	6
Infectious disease		2	1
Other			
Sudden death			1
Complete alopecia	44	36	ns
Mucus membrane ulceration		6	4
Nausea and vomiting	22	21	ns
Diarrhoea		6	2
Pericarditis		1	1
Lymphoedema (>5 cm)		6	5
Rib fractures			4
Plexitis			1

* by χ^2 test. ns, non-significant. A significant difference in grade 3 + 4 leucocyte toxicity ($P = 0.0018$) was seen with lower counts for those patients who had received radiotherapy prior to chemotherapy.

treatment group (Table 3). Treatment was prematurely stopped for poor tolerance in 6.5% and delayed in 20% of all patients. One sudden death due to pulmonary embolism occurred on day 21 of a third cycle of chemotherapy, and 3 patients needed admission to an intensive care unit for sepsis.

Pericarditis was observed in 2 patients, and irradiation was prematurely stopped in 1 patient. Radiation-induced brachial plexopathy occurred in 1 patient, and rib fractures in 4 patients. Lymphoedema occurred in 11 patients.

DISCUSSION

Attempts to use systemic therapy earlier in the course of neoplastic disease have been prompted by still disappointingly high distant recurrence rates in tumours larger than 3 cm, and the inability to cure most solid tumours after relapse. Besides a theoretical potential to reduce distant relapse and improve cure rates, neo-adjuvant chemotherapy also has the potential to reduce the primary tumour size, thus allowing an increase in breast conserving treatment.

The present trial attempted to define a potential survival advantage by comparing first-line systemic treatment in so-called operable breast cancer, with a first-line radiation treatment. Emphasis was on breast conservation, avoiding mastectomy whenever possible.

Survival

In the present study, we did reach a statistically significant improvement in survival in favour of the neo-adjuvant setting ($P = 0.039$), and this advantage might prove a consequence of smaller or delayed metastatic recurrences. Fewer and delayed distant recurrences would be in keeping with the theoretical basis for this treatment proposal, but larger patient populations, as well as longer follow-up periods, will be needed to substantiate such a difference. The only other published study [20], randomising patients into neoadjuvant or adjuvant treatment arms, did show only a transient advantage in overall survival at an early time point, in favour of the neoadjuvant arm. This advantage disappeared at a median follow-up period of 47 months. Our study is comparable to that by Mauriac and colleagues [20] for tumour size of the patients recruited into the trial (which ranges from 3 to 7 cm) as well as for the randomisation between primary or secondary chemotherapy. Different, however, are the local-regional treatment regimen, which at Institut Curie consisted, as a rule, of radiation treatment in a first instance [28], as well as a different combination of chemotherapeutic agents.

The Scandinavian Multicenter Trial [14], using immediate postoperative chemotherapy, reported a 10% reduction in death rates for the chemotherapy group at 10 years. It showed only a marginal difference at 4 years of follow-up, and these early results from our study as well as that from the Bordeaux group do not preclude a more substantial difference in outcome at a later stage.

Both groups received the same total amount of chemotherapy, but fewer and, therefore, slightly more aggressive courses, in particular doxorubicin administered in the neoadjuvant group. The presence of an evaluable tumour mass and its response to treatment may have motivated dose increments in this group. Equally, the decreased haematological tolerance following first-line irradiation will have contributed to slightly decreased dosages in the adjuvant setting.

Breast conservation and tumour response

A recent survey on neoadjuvant chemotherapy in breast cancer by Bonnadonna [22] documented the subsequent feasibility of conservative surgery in 73 and 97% of tumours, according to whether the initial tumour size was above 5 cm or below 4 cm. The degree of tumour response proved inversely proportional to the initial tumour size. In the Bordeaux study concerning operable breast cancer greater than 3 cm [20] and treated with first-line chemotherapy, a tumour reduction allowing breast preserving treatment (exclusive radiation or a combination of radiotherapy and minimal surgery) was achieved in 63% of patients. In the present trial, which associated induction chemotherapy and radiation, 80% of patients with an average tumour size of 4.7 cm had minimal or no surgery as part of their primary treatment.

The tumour cell sensitivity to chemotherapeutic drugs was reflected in the clinical evaluation of tumour regression at two and at four cycles of chemotherapy. Primary chemotherapy in resectable breast cancer has been tested in several centres [22], and major response rates in 70–87% of patients were commonly achieved following four to six treatment cycles. In the present trial, the planned treatment was aborted at 2 months in 38 patients, rendering them inevaluable at 4 months. The true response rate at four cycles for all 191 evaluable patients is, therefore, estimated to be lower than 82%. The speed of a clinical assessable tumour response varies between patients, and a minor response at 2 months may not preclude a major response at 4 months. If no response would have been achieved in all of these 38 patients after four cycles of chemotherapy, the total response rate at four months would have been 65%. This rate is slightly below that of published results by other centres [22], but it is in keeping with that of another randomised study [20], and higher response rates might in fact reflect patient selection in non-randomised studies. In addition, a total of four cyles of chemotherapy might not have achieved the most optimal effect and more chemotherapy, a different drug combination, shorter delay between courses or a different administration (continuous perfusion, or intra-arterial administration) might enhance treatment efficacy in chemosensitive tumours.

A high percentage of patients (85%) achieved a major response following a basic irradiation dose of 54 Gy to the whole breast, which allowed breast preservation in 77% of the patients who received radiotherapy as the primary treatment. These results are higher than those published by other centres [32]. The breast preservation rate was also higher in this trial as compared to previously published results on 1133 patients from our institute [33] according to which 60% of patients treated with primary radiotherapy had breast conserving treatment, and in which 22% of the patients who received surgery had no residual microscopic disease.

Forty one per cent of the patients who received first-line irradiation (54 Gy) achieved a complete response as compared to only 24% of the patients after four cycles of chemotherapy. A fraction of patients (69/106) with residual disease following four cycles of chemotherapy went on to a complete tumour regression at 54 Gy showing that patients with an incomplete response to chemotherapy can respond to radiation. The percentage of complete responses achieved by the sequential treatment of chemotherapy and radiation in this subgroup of patients (65%) is adequate to justify this treatment regimen in our opinion. The design of this study (with surgery as an additional variable), did not allow us to evaluate percentages of patients with cross-resistant or cross-sensitive tumours. Primary chemotherapy might, at least in theory, have a radiosensitising effect, but the different subgroups in local regional treatments did not allow assessment of this.

Breast conservation and local relapse

Decreased local recurrence rates have been documented following adjuvant chemotherapy [34, 35]. No difference in breast or chest wall recurrence rates between the two treatment arms could be detected in the present study, indicating that the use of neoadjuvant chemotherapy did not improve local control over that achieved by primary radiotherapy and adjuvant chemotherapy. Approximately 62% of all patients alive at 5 years are expected to preserve their breast, which is better than that of a comparable historical series from our institute [28, 33]. Higher local failure rates were shown to occur following breast preservation according to several randomised trials comparing mastectomy and breast-conserving treatments in early breast cancer [35, 36] as well as in retrospective studies of patients with larger tumours treated with exclusive radiotherapy [25–28, 37]. However, a recurrence in the preserved breast does not appear to impair survival, hence favouring the use of breast-conserving treatment over mastectomy, at least in early stages (NCI consensus conference, 1990) [38]. Long-term breast recurrence rates in patients with larger tumours treated by exclusive irradiation vary between 20 and 35% [26–28, 37]. Breast recurrence rates in these patients are significantly increased by young age, poor histological grade and large tumour size [25, 37], by the total radiation dose to the tumour as well as by adjuvant chemotherapy. Whether these high risk groups might benefit from neoadjuvant chemotherapy remains to be established in the future. Although delay in initiating radiation treatment has been associated with increased breast failure rates [39], no trial exists to our knowledge that evaluated the impact of the relative timing of chemotherapy and radiotherapy on local control. In the present trial, similar local control rates were achieved in both treatment arms ($P = 0.21$), suggesting that the relative delay in initiating local treatment (i.e. radiotherapy) in group I may have been counterbalanced by beneficial effects of chemotherapy on local control.

According to our results, the combination of chemotherapy and radiotherapy provides the opportunity to achieve high breast preservation rates and good local control in T2 and T3 breast cancer patients who would classically undergo a radical mastectomy. The role and timing of limited surgery in association with both these treatments remains to be determined [40].

CONCLUSION

At a median follow-up time of 54 months, a statistically significant improved survival in favour of the neoadjuvant chemotherapy arm was observed. This difference did not reflect in an improved disease free interval or local recurrence rates, but a trend towards delayed or fewer distant recurrences if chemotherapy is readily administered at optimal regimes might become valid over time.

Primary chemotherapy does permit the reliable identification of chemosensitive patients, and may allow selective enhancement of treatment efficacy in a defined population. Our results show no detrimental effects and better tolerance by using chemotherapy as first-line treatment in these premenopausal patients and, in paticular, no increased local relapse rates due to the delay in starting radiation treatment. Similarly, primary radiation treatment allows the selection of highly radiosensitive patients who can benefit from dose intensification, thus allowing a conservative treatment regimen with optimal local control. Future studies will focus on the detection of clinical and biological markers, and, in particular, the percentage of cells in S phase in an attempt to define predictors of the response to primary chemotherapy or to primary radiation therapy. Such an approach may permit the selection of the most promising initial treatment for each patient's particular tumour, while still allowing dose intensification in selected responding tumours.

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