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Original Paper

Breast Tumour Response to Primary Chemotherapy Predicts Local and Distant Control as Well as Survival

S.M. Scholl,[1] J.Y. Pierga,[1] B. Asselain,[2] P. Beuzeboc,[1] T. Dorval,[1] E. Garcia-Giralt,[1] M. Jouve,[1] T. Palangié,[1] Y. Remvikos,[3] J.C. Durand,[4] A. Fourquet[5] and P. Pouillart[1]

[1]Département de Médecine Oncologique; [2]Unité de Biostatistiques; [3]CNRS URA 620; [4]Département de Chirurgie; and [5]Département de Radiothérapie, Institut Curie, 26 rue d'Ulm, 75231 Paris, Cedex 05, France

The purpose of the present paper was to evaluate correlations between clinical response to chemotherapy and outcome in a subgroup analysis of premenopausal patients with tumours considered too large for breast conserving surgery, treated with primary chemotherapy (n = 200) from a previously published trial (Scholl S.M., Fourquet A., Asselain B, *et al. Eur J Cancer* 1994, 30A, 645–652). Objective response rates amounted to 65% following four courses. In a multivariate Cox regression analysis, comparing seven parameters, the following variables were associated with poor survival: clinically involved nodes [N1b: RR: 2.7 (95% CI 1.3–5.3)], the failure to respond to chemotherapy [D: RR: 2.62 (95% CI 1.3–5)] and a raised S phase fraction [SPF > 5%: RR: 2.4 (95% CI 1.2–5)]. Parameters associated with increased metastatic recurrence rates, by order of entry in the model, were: young age [<35: RR: 2.46 (95% CI 1.2–5)], large clinical tumour size [T3: RR: 2.02 (95% CI 1.2–3.4)], poor histological grade (SBR III: RR: 1.93 (95% CI 1.1–3.3)] and the failure to respond to chemotherapy [D: RR: 1.91 (95% CI 1–3.4)]. The assessment of both tumour cell proliferation rates as well as possibly drug resistance markers (although not available in the present study) should be helpful in selecting patients likely to benefit from intensified chemotherapy regimens. The most accurate predictor of response in the present study appeared to be the response to chemotherapy treatment itself.

Key words: breast cancer, neoadjuvant chemotherapy, chemosensitivity, drug resistance, prognosis, breast preservation, S phase
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INTRODUCTION

WHILE STEROID hormone receptor levels have been shown for over a decade to be predictive for the magnitude of tumour response to hormonal manipulations, the accurate prediction of a response to cytotoxic chemotherapy has so far eluded us. Resistance to natural (non-synthetic or semisynthetic) drugs has been associated with an overexpression of the multidrug resistance gene (*MDR1*) [1], but induction of *MDR1* may be secondary to chemotherapy treatment [2] and does not preclude an initial response to these same drugs. Tumours with *C-ERBB2/NEU* overexpression have also been repeatedly shown not to benefit from standard adjuvant chemotherapy [3, 4]. These tumours may benefit from chemotherapy dose intensification, as suggested by a recent paper by Muss and associates [5]. Overexpression of GSTp, frequently co-amplified with members of the fibroblast growth factor family, has equally been linked with a poor outcome despite adequate treatment [6]. As a result, chemosensitivity can not be tested by a simple biological test and the most accurate test might be treatment itself.

In the present paper, the clinical response to neoadjuvant chemotherapy was evaluated for its predictive role on survival, recurrence and breast conservation in both univariate and multivariate analysis. We screened for associations between clinical response and various clinical and biological parameters in an attempt to identify subsets of patients who might be more likely to benefit from chemotherapy.

PATIENTS AND METHODS

Patient presentation

Premenopausal patients with tumours 3–7 cm in size, with or without clinical node involvement and with a pathological

Correspondence to S.M. Scholl.
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diagnosis of invasive breast cancer following drill biopsy were considered eligible for entering a randomised trial comparing neoadjuvant and adjuvant chemotherapy. Results of this trial have been previously reported [7]. Inflammatory, bilateral, locally advanced or metastatic breast cancer as well as adherent axillary nodes were exclusion criteria. Two hundred evaluable patients were included in the neoadjuvant treatment arm and 195 were evaluable for response to two cycles of primary chemotherapy for the purpose of the present analysis. Here we report our results on the association of a response to chemotherapy with outcome. We also screened for parameters potentially associated and therefore predictive for a response to chemotherapy. Steroid receptor measurements were available in 161/195 (83%), and 47% (92/195) had additional fine needle aspirates of their primary tumour for the measurement of S phase fractions according to a technique previously described [8].

Treatment

Chemotherapy was started after completion of the initial assessment. It consisted of two to four monthly cycles of intravenous cyclophosphamide, doxorubicin and 5-fluorouracil [CAF] at respective dosages of 800, 50, 2000 mg/m^2/cycle, to best response in two to four courses. 155 patients were evaluable following four cycles of neoadjuvant chemotherapy. The averaged percentage of the planned dose for the three drugs that was actually received in each cycle was 81.3% [+/−10.3%]. Cycles of chemotherapy were repeated at 28-day intervals or longer, depending on recovery of bone marrow. Treatment delays occurred in 20% of all patients. Less than four cycles of chemotherapy were given in 6.5% of patients due to poor tolerance and details on drug schedules and tolerance have been previously reported [7].

A complete response (CR) resulted in the disappearance of clinically palpable disease; partial responses were evaluated as the product of the two largest tumour diameters.

Following chemotherapy, radiotherapy was delivered with a cobalt-60 unit with a mean dosage to the breast of 54 Gy over 6 weeks. The response to radiotherapy was evaluated by clinical examination and mammography. Patients with a response >95% received a radiation "boost" to the tumour bed to achieve a total dose of 75–80 Gy and no surgery was performed. All patients received 54 Gy to the axillary nodes followed by 10–15 Gy 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 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 persisting tumour was performed. Those patients with minimal or no response to prior treatments had a mastectomy. These patients had surgical dissection of the axilla and received minimal or no radiation to the axillary area.

Statistical methods

In the initial trial, patients had been randomised into primary chemotherapy or primary radiotherapy arms. Survival and disease-free interval as well as breast preservation rates were the principal endpoints and 5 year results have been reported [7]. In the present analysis, survival as well as local or distant recurrences were analysed according to response to treatment, following completion of two or four courses of chemotherapy. Inoperable recurrence in the breast and/or extensive inoperable chest wall recurrences were considered metastatic disease. The log-rank test [9], together with estimates of the distribution of the recurrence-free and overall survival duration, based on the product-limit (Kaplan–Meier) estimator [10] were used to establish associations of treatment response with recurrence. Median time of follow-up at the present analysis was 66 months (extremes: 14–92 months). The following seven parameters were compared for their predictive value for survival and metastatic recurrence in Cox regression models: age (+/−35), tumour size (T2/T3), clinical node status (N0, N1a/N1b), tumour grade (SBR I/II+III), oestrogen receptor (ER) and progesterone receptor (PR) status (+/−), S phase fraction (+/−5%), and response to chemotherapy (CR, PR ≥ 50%, PR < 50%, NR). Significance of associations was tested by the chi-square test.

RESULTS

Outcome as a function of response to neoadjuvant chemotherapy

(1) *Recurrence and survival.* (a) *Evaluation according to response following two cycles of anthracycline-containing combination chemotherapy (evaluable*: 195/200). A small but statistically non-significant survival advantage was apparent for those patients whose tumours had decreased by ≥50% after two cycles of primary chemotherapy (P = 0.16) (Figure 1a). Five-year survival rates were 87% [95% confidence intervals (CI) 80–94] for responding patients and 79% [95% CI 70–88] for non-responding patients. Disease-free intervals (62% and 54%) were

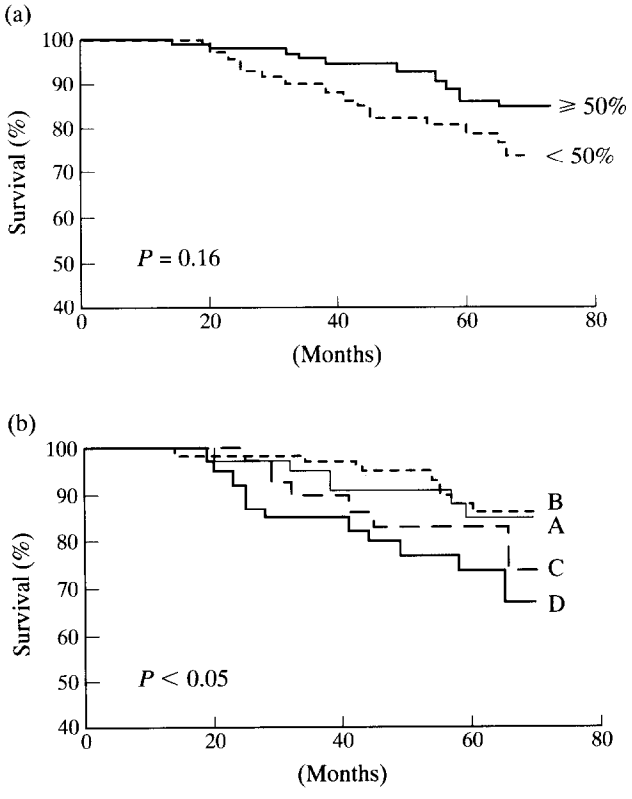

Figure 1. (a) Survival according to response following two cycles of chemotherapy at a median follow-up of 66 months. Patients remaining at risk at 5 years: Responders ≥50%: 71; <50%: 43. (b) Survival according to response following four cycles of chemotherapy. A: complete clinical response (n = 45); B: partial response (>50% tumour regression, n = 79); C: <50% tumour regression (n = 31); D: treated with two courses of chemotherapy only due to poor response +/− poor tolerance (n = 40). Number of patients remaining at risk at 5 years in the respective groups: A: 28, B: 49, C: 13, D: 22.

not significantly different ($P = 0.3$), but the difference in local recurrence rates (Figure 2a) approached significance ($P = 0.06$) with 78% [95% CI 70–86] and 67% [95% CI 56–78] in the respective arms, in favour of responding patients. Distant relapse rates (72% and 71%) were similar for both groups ($P = 0.9$) (Figure 3a).

(b) *According to response as assessed at the end of four treatment courses.* The study design allowed for patients who showed no response or progressive disease after two cycles of chemotherapy to go on to local treatment, consisting of radiotherapy and/or surgery. 40 patients were thus removed from the primary chemotherapy treatment arm (group D; Figures 1b–4b). The patients who received four cycles of chemotherapy therefore represent a selected subgroup. Five-year survival rates (Figure 1b) were 85% [95% CI 74–96] in the patient group with a complete response (group A) versus 87% [95% CI 79–95]) for patients with a major, but incomplete response (group B). The patient group with a minor or doubtful response (group C) had slightly better survival figures (83% [95% CI 69–97]) than the patients who stopped chemotherapy at two cycles (group D) (75% [95% CI 61–89]). This difference in survival was statistically significant ($P < 0.05$). Local recurrence rates (Figure 2b) were significantly higher ($P = 0.03$) in the small group (C: $n = 31$) of patients who, following four cycles of chemotherapy, had achieved only a minor response, with 35% [95% CI 3–67] free of local recurrences at 5 years as compared to 84% [95% CI 76–92] in B and 70% [95% CI 56–84] in A. The patients who failed to respond at two cycles (D) had fewer local recurrences,

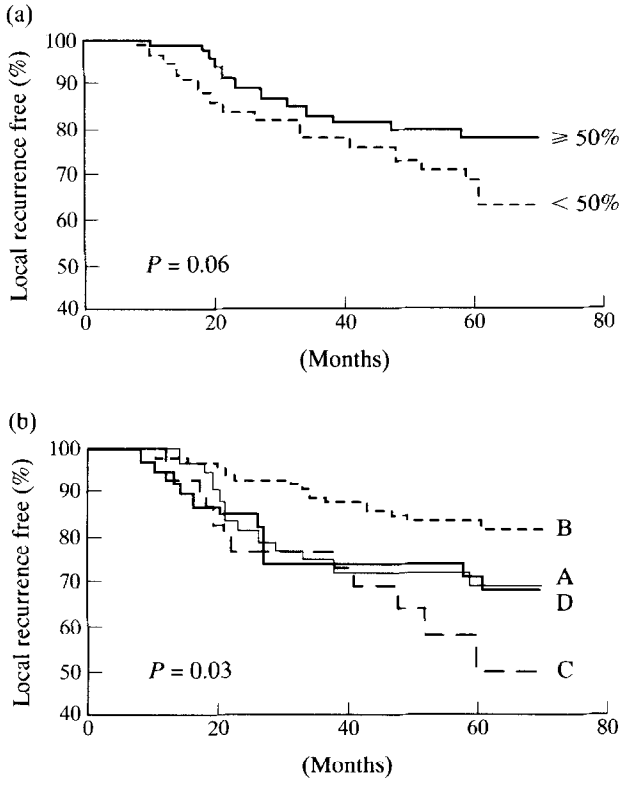

Figure 2. (a) Local recurrence-free rates according to response following two cycles of chemotherapy. Number of patients remaining at risk at 5 years: Responders ≥50%: 59; <50%: 33. (b) Local recurrence-free rates according to response at 4 months of chemotherapy. Number of patients remaining at risk at 5 years in the respective groups: A: 21, B: 44, C: 6, D: 20.

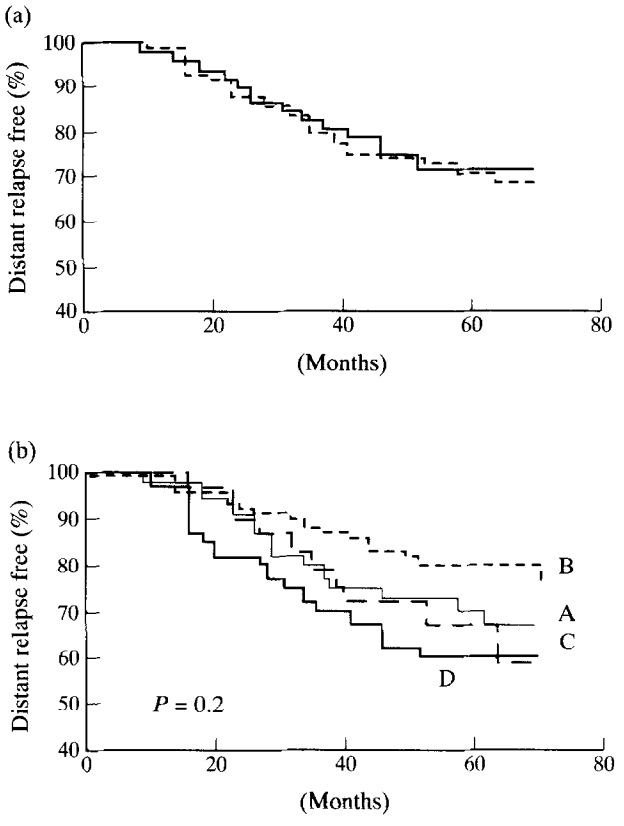

Figure 3. (a) Distant relapse-free rates according to response at 2 months of chemotherapy. Number of patients remaining at risk at 5 years: Responders: 61; minor or non-responders: 35. (b) Distant relapse-free rates according to response at 4 months. The number of patients remaining at risk at 5 years in the respective groups: A: 24, B: 44, C: 9, D: 17.

50% [95% CI 28–72] due to significantly higher mastectomy rates (Figure 4b). Distant disease-free rates (Figure 3b) were higher in patients with chemosensitive tumours (A: 70% [95% CI 56–84], B: 80% [95% CI 70–90]) as compared to 67% [95% CI 49–85] in minor responders (C), and 60% [95% CI 44–76] in non-responders (D), but not significantly so ($P = 0.2$). However, group B had a significantly better outcome than the remaining patient groups ($P = 0.05$). Five-year disease-free rates between all four groups were not significantly different ($P = 0.09$), with 57% [95% CI 42–72] for A, 68% [95% CI 58–78] for B, 34% [95% CI 12–56] for C and 54% [95% CI 38–70] for group D, respectively. Again, when B alone was compared to the remaining groups, the disease-free survival was significantly better ($P = 0.03$).

(2) *Survival following recurrence.* Initially, chemosensitive patients who developed metastatic and/or local recurrences had a prolonged survival following recurrence as compared to that of patients who had not shown a clinical response to chemotherapy in the primary tumour site ($P = 0.05$). Median survival post recurrence for responding patients was 39 months ($n = 10$), whereas it was 25 months ($n = 17$) for patients with chemoresistant tumours.

(3) *Breast preservation.* We did observe a highly significant difference in the need for surgical treatment, with more frequent breast preservation in those patients whose tumours had responded following two courses of chemotherapy (73% [95% CI 65–81]), whereas rates for non-responders were 54% [95% CI

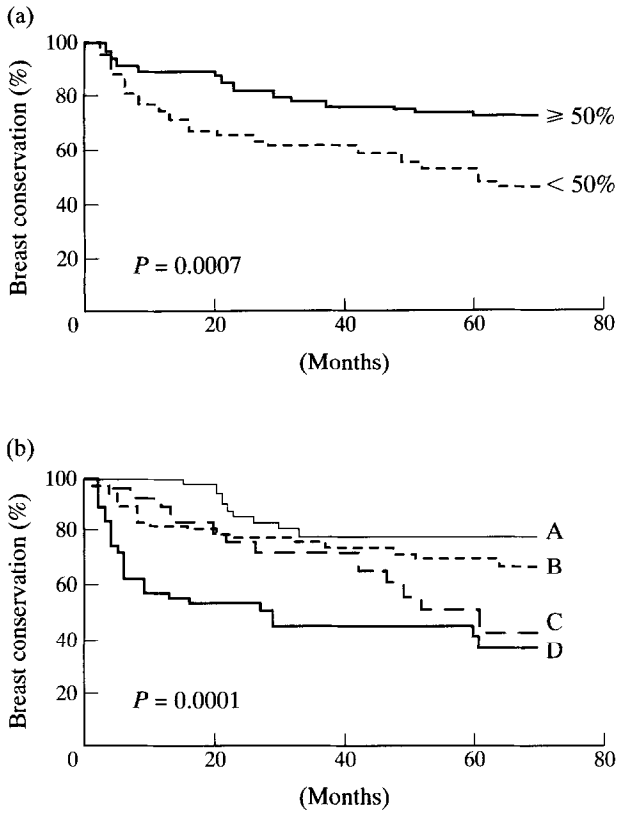

Figure 4. (a) Breast preservation rates evaluated according to response at 2 months of chemotherapy. The number of patients remaining at risk at 5 years were: responders: 54; non-responders: 22. (b) Breast preservation rates evaluated according to response at 4 months. Number of patients remaining at risk at 5 years: A: 23, B: 35, C: 6, D: 10.

44%–64%] ($P = 0.007$) (Figure 4a). In the selected subgroup treated with four courses, similar trends have become more significant over time. Breast conservation rates at 5 years for the respective groups were: A: 80% [95% CI 68–92], B: 71% [95% CI 61–81], C: 52% [95% CI 32–72], D: 41% [95% CI 25–57] ($P < 0.0001$).

Multivariate analysis

In a multivariate Cox regression analysis (Table 1), we evaluated the relative risk for metastatic recurrence and cancer related death associated with the failure to respond to chemotherapy, together with six classical parameters in a forward stepwise procedure. Parameters associated with increased metastatic recurrence rates, by order of entry in the model were: young age [<35: RR: 2.46 (95% CI 1.2–5)], large clinical tumour size [T3: RR: 2.02 (95% CI 1.2–3.4)], poor histological grade [SBR III: RR: 1.93 (95% CI 1.1–3.3)] and the failure to respond to chemotherapy [group D: RR: 1.91 (95% CI 1–3.4)]. Associated with a poor survival were: clinically involved nodes [N1b: RR: 2.7 (95% CI 1.3–5.3)], the failure to respond to chemotherapy [D: RR: 2.62 (95% CI 1.3–5)] and a raised S phase fraction [SPF > 5%: RR: 2.4 (95% CI 1.2–5)].

Factors associated with response to chemotherapy

Factors tested for a potential association with clinical response are listed in Table 2. Interestingly, steroid receptor negative tumours [ER – ($P = 0.01$); PR – ($P = 0.04$)] as well as tumours in patients under 35 years of age ($P = 0.06$) were over-represented at both extremes of the response spectrum (complete response or progressive disease) as compared to higher incidences of partial responses in ER+ and PR+ patients or in the older age group. All patients below 35 ($n = 19$) had continued chemotherapy to four courses, whereas a large fraction of patients above 35 (40/176) had discontinued. The observed differences in response as a function of age ($P = 0.001$) must, however, be viewed with caution due to potential differences in tolerance. The decrease in the number of patients who were evaluable for response at 4 months was evenly distributed in the ER/PR positive or negative subgroups, but the difference in response to chemotherapy seen at 2 months, was not seen at 4 months.

Smaller tumours were also more frequently associated with a complete early response (at 2 months) and less likely to have stable or progressive disease as compared to tumours >5 cm ($P = 0.03$). Response rates did not differ from that of T3 tumours after four treatment courses.

S phase fractions had been determined in 92/195 (47%) of patients in the neoadjuvant group. Major responses (≥50%) were more likely to be achieved in tumours with high (≥5%) S phase fractions and this trend was highly significant after four cycles of chemotherapy ($P = 0.0042$), when two thirds of all patients had achieved a response. This difference remained significant when the patients who had stopped chemotherapy at the end of two courses (D), were entered in their respective SD/PD subgroups.

DISCUSSION

Breast preservation

The dilemna of how conservative surgery should be remains open. In the present trial, we can identify a subgroup of chemosensitive tumours (group B) who could be treated with no or minimal surgery and yet have good local control and better survival figures as compared to the chemoresistant patients. Can we improve these results by reducing surgical intervention further? In the absence of surgery, no precise documentation of residual disease at either the primary tumour site or in the axilla can be achieved and it will be difficult to intensify therapy without a pathological evaluation of its efficacy. Furthermore, patients who achieved a complete clinical response following chemotherapy (A) and were treated with exclusive irradiation, experienced higher local recurrence rates, necessitating a secondary mastectomy. It is reassuring to note that the local control overall was better in patients with a major clinical response to chemotherapy, but a few mastectomies for early recurrences might have been prevented if limited surgery had been carried out immediately after chemotherapy. The early higher "local relapse" rates in CRs, together with the uncertainty of leaving active disease after conservative treatment indicates a need for considering routine surgical excision and pathological examination of the tumour bed prior to irradiation. Arguments against a systematic surgical approach in all patients are the increased difficulty of locating the initial tumour site following a complete response as well as the proven efficacy of radiotherapy in a high percentage of patients. Adequate local control could be achieved in patients who did not respond to chemotherapy at the expense of higher primary mastectomy rates.

Factors associated with a response to chemotherapy

Clinically chemosensitive tumours appear to be frequently associated with a high proliferation rate, favouring an efficient drug action, and with little fibrotic reaction, minimising clinical detection of a persistant palpable mass. Flow cytometric analysis

Table 1. Multivariate Cox regression analysis (n = 195)

		RR	95% CI
Parameters selected for survival			
Clinical node status	N0, N1a	1	
	N1b	2.7	1.3–5.3
Response to chemotherapy	A, B, C	1	
	D*	2.62	1.3–5
S phase fraction	<5%	1	
	>5%	2.4	1.2–5
Parameters selected for metastatic recurrence			
Age	>35	1	
	≤35	2.46	1.2–5
Clinical tumour size	T2	1	
	T3	2.02	1.2–3.4
Histological grade	SBR I + II	1	
	SBR III	1.93	1.1–3.3
Response to chemotherapy	A, B, C	1	
	D*	1.91	1–3.4

* A = complete response; B = major response; C = minor response at 4 months; D = no response at 2 months; no further chemotherapy. Variables are presented by order of entry in a forward stepwise procedure.

Table 2. Parameters associated with response to chemotherapy

Parameters		At two cycles					At four cycles		
Tumour size		T2	T3	*P**	Tumour size		T2	T3	*P**
n = 195	CR	6 (4%)	1 (2%)	0.03	*n* = 155	CR	34 (30%)	11 (26%)	ns
	MAJ	69 (50%)	31 (53%)			MAJ	54 (48%)	25 (58%)	
	MIN	50 (36)	15 (26%)			MIN	23 (21%)	5 (12%)	
	SD/PD	12 (9%)	11 (19%)			SD/PD	1 (1%)	2 (5%)	
Age		<35	≥35		Age		<35	≥35	
n = 195	CR	2 (10.5%)	5 (3%)	0.06	*n* = 155	CR	8 (42%)	37 (27%)	0.001
	MAJ	11 (58%)	89 (51%)			MAJ	6 (32%)	73 (54%)	
	MIN	2 (10.5%)	63 (36%)			MIN	2 (11%)	26 (19%)	
	SD/PD	4 (21%)	19 (11%)			SD/PD	3 (16%)	0	
S phase fraction		<5%	≥5%		S phase		<5%	>5%	
n = 92	CR	2 (4%)	4 (9%)	0.1	*n* = 76	CR	6 (15%)	17 (49%)	0.0042
	MAJ	18 (37.5%)	21 (48%)			MAJ	20 (49%)	15 (43%)	
	MIN	23 (48%)	12 (27%)			MIN	14 (34%)	3 (9%)	
	SD/PD	5 (10%)	7 (16%)			SD/PD	1 (2%)	0	
ER		ER−	ER+		ER		ER−	ER+	
n = 161	CR	4 (6%)	1 (1%)	0.01	*n* = 131	CR	17 (30%)	19 (25%)	ns
	MAJ	37 (53%)	49 (54%)			MAJ	29 (52%)	40 (53%)	
	MIN	16 (23%)	35 (38%)			MIN	8 (14%)	15 (20%)	
	SD/PD	13 (19%)	6 (6.5%)			SD/PD	2 (4%)	1 (1%)	
PR		PR−	PR+		PR		PR−	PR+	
n = 160	CR	5 (6%)	1 (1%)	0.04	*n* = 129	CR	19 (30%)	18 (27%)	ns
	MAJ	40 (52%)	44 (53%)			MAJ	31 (49%)	35 (53%)	
	MIN	19 (24.5%)	32 (39%)			MIN	11 (18%)	12 (18%)	
	SD/PD	13 (17%)	6 (7%)			SD/PD	2 (3%)	1 (2%)	

* By chi square test. Clinical node status, menopausal status and pathological grade were not associated with the response to chemotherapy. CR, complete response; MAJ, major response (≥50%); MIN, minor response (<50%); SD/PD, stable and progressive disease; ns, not significant.

was available on half of all patients in the present study. A clear correlation between a high proliferation rate (S phase fraction >5%) with response to primary chemotherapy was seen in the present population ($P = 0.0042$) [11], as well as in a separate, larger study ($P = 0.0017$) [12]. Furthermore, when disease-free interval rates were evaluated in patients with the most actively proliferating tumours (S phase 5–10%) from two different trials, it was dramatically superior in the patients with a clinical response to chemotherapy who also fared significantly better than those, resistant to treatment [12]. High S phase fractions have been repeatedly associated with a poor prognosis (for review see ref [13]), but this finding was not confirmed in more recent studies in which all patients had been treated by chemotherapy [14, 15]. These authors suggest [15, 16] that the correlation between high S phase and poor prognosis might have been modified by the preferential efficacy of chemotherapy in tumours with a high proliferation rate. Results from Institut Curie [11, 12 and Y Remvikos, V Mosseri, unpublished] suggest that high SPF may be marginally associated with poorer overall survival ($P = 0.05$), whereas it was highly significant ($P < 0.0001$) for the prediction of a poor outcome in patients with a minor or no response to chemotherapy. Thus, a high proliferation rate appears to be useful for predicting response, but not sufficient for predicting outcome. In the present series, the patient group who experienced the best response, also had the highest average S phase fractions. By definition, these patients were not resistant to chemotherapy initially, but surprisingly this particular group (A) had higher local and distant relapse rates than patients with lesser clinical response (B). Patient group A were treated more conservatively than any other group and the local persistence of microscopical disease following high dose irradiation cannot be excluded.

It was of interest to note that other factors that had been linked with poor outcome in the past, e.g. absence of ER and PR expression [16] and very young age (<33 years) [17] proved not only more frequently associated with complete clinical remissions than controls, but the opposite trend (progressive disease) was equally more frequent than in controls. The present population had not been screened systematically for over-expression of drug resistance phenotypes, such as mdr1 and GSTp. A combination of high proliferative rates with or without expression of drug resistance phenotypes might explain these seemingly contradictory results.

Thus, the concurrent measurement of several biological parameters including S phase, steroid receptor expression and over-expression of drug resistance genes together with the clinical assessment of tumour response to chemotherapy at an early stage, may permit adaptation of our management of breast cancer patients towards a greater efficacy as well as to avoid treatment related toxicity in patients with a low likelihood of response.

Relapse and survival according to chemosensitivity

In the subgroup of patients whose tumours showed a complete regression or a major (≥50%) reduction in size in response to two courses of chemotherapy, we did not observe significant differences in survival statistics, but less local recurrences as well as significantly lower mastectomy rates. Metastatic recurrence rates were identical.

It was puzzling to note that highly chemosensitive tumours (≥50% shrinkage in two courses) showed no significant reduction in metastatic rates when compared with lesser responders. Micrometastatic spread has occurred, by definition, prior to or during the treatment of the primary tumour [18]; its clinical diagnosis depending on the metastatic site, the delay in appearance of first symptoms, the presence of biological marker proteins, as well as the availability of sophisticated diagnostic procedures. When we compared the least chemosensitive patients (C + D) with the remaining patients, a striking difference in metastatic recurrence and survival was apparent, both in univariate and multivariate analysis. Groups C and D were comparable with the highly chemosensitive population as regards age, clinical tumour size, node status, histological type and grade, ER and PR expression, the only difference being a lower mean SFP (A/B = 6.7%, C = 3.1%; D = 5.7%; $P = 0.0006$). A small population at increased risk for the development of metastases while also being resistant to the commonly accepted adjuvant or curative treatment can thus be defined. It seems unlikely that more intensive chemotherapy regimens will benefit patients who fail to respond to conventional chemotherapy at adequate dosage. The early initiation of different non-crossresistant drug combinations or the addition of drug-resistance reversing-agents might be attempted in the adjuvant treatment of these high risk patients. Endocrine ablation by oophorectomy or luteinising hormone-releasing hormone (LH-RH) antagonists might be considered in the presence of steroid receptor expression associated frequently with well differentiated tumours. In the advent of metastatic recurrences despite optimal adjuvant treatment in "chemoresistant" patients, newer therapeutic approaches, including tumour suppressor gene therapy, antisense oligonucleotides to selected growth factors and receptors, or adoptive immunotherapy might be considered as first-line treatment of recurrent disease as they become available.

The question of whether intensified chemotherapy regimens will be able to promote a cure in chemosensitive solid tumours with initial micrometastatic spread remains to be addressed. To answer that question, a precise documentation of micrometastatic disease will be needed, together with life long surveillance of patients in order to determine whether we only delay clinical detection of metastatic disease or whether patients eventually die of cancer-unrelated causes. Two to four courses of adjuvant chemotherapy might be insufficient treatment for curing micrometastatic disease in some of our patients, and new marker molecules for the detection of micrometastatic disease activity in early metastasis would be useful. Detailed screening for early spread, longer treatment courses or drug intensification regimens should therefore be evaluated in carefully controlled future trials in selected patients with chemosensitive tumours.

We were able to define both a good prognostic subgroup as well as a small subset of patients at high risk of distant metastases following two to four courses of primary chemotherapy in premenopausal breast cancer patients with tumours >3 cm. Two thirds or more of all primary breast cancer patients are likely to respond to combination chemotherapy and thereby decrease their risk of recurrence as well as the need of mutilating surgery, while improving their survival time. First-line chemotherapy appears to be useful in defining a chemosensitive population, thereby allowing drug intensification in selected high risk patients with a potential for cure. This trial was started when first-line chemotherapy was not well established and early chemoresistant patients were not continued on a non-cross reacting protocol. Chemoresistant patients had less systemic treatment making the interpretation of our data difficult, but reflecting the complexity of clinical trials. This patient group warrants detailed investigations aimed at understanding their

failure to respond, as well as to design alternate treatment protocols.

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