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Original paper

Neoadjuvant Chemotherapy in Young Breast Cancer Patients: Correlation between Response and Relapse?

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The aim of this analysis was to assess how the clinical response to chemotherapy corresponded to long-term prognosis in patients of less than 35 years of age. A retrospective analysis was made of response and survival data of 609 premenopausal patients who had been treated by four cycles of neoadjuvant chemotherapy followed by surgery and/or radiotherapy. Patients were stratified into three age groups (group 1, $\leq$35 years; group 2, 35–40 years; group 3, $\geq$41 years). Objective and complete clinical response rates were significantly higher in the youngest patients (below 35 yrs: $P = 0.005$ and $P = 0.001$, respectively) in stark contrast to a particularly poor outcome of this subpopulation. Five-year local recurrence rates were 31% in the youngest patients, compared with 26% and 16% in groups 2 and 3, respectively ($P = 0.0007$). Group 1 patients also had significantly higher 5-year metastatic relapse rates (41% versus 35% and 28%; $P = 0.007$) and 5-year survival figures were 70%, 82% and 84% for groups 1, 2 and 3 respectively ($P = 0.002$). Finally, stratification by age and by response revealed that, whilst the outcome of the youngest patients was highly dependent on their response to primary chemotherapy, complete responders showed disease-free survival rates at 5 years that were lower than these of older patients, whatever their response. Despite a seemingly better control of the primary tumour by chemotherapy, the patients in the youngest age group remained at a high risk for local and metastatic relapse. This apparent paradox may be in part attributable to rapid disease progression of micrometastatic tumour subpopulations that are refractory to chemotherapy. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

PATIENTS OF a young age, and in particular those patients below the age of 35 years, have been considered to be at an increased risk of recurrence in previous studies [1–4]. These patients, representing less than 6% of the total breast cancer population, have been associated with tumours of poor grade [1–3], an important in situ component and high proliferative indices. Very young patients have also been associated with poorer survival and shorter disease-free interval, independent of tumour size, grade or progesterone receptor status [2–4] with a 2-fold higher risk of cancer-related mortality than patients aged over 40 years. Data from the San Antonio cancer registry also confirmed young age to be an adverse predictor of outcome, independent of type of treatment [4]. Despite the frequent administration of adjuvant chemotherapy treatments in the 1980s and early 1990s, young patients have been shown to have the poorest outcome [2].

In this context, the debate concerning the best treatment schedule for very young patients remains open, especially for tumours larger than 3 cm. Primary chemotherapy has been proposed in patients with operable tumours by many centres. Clinical response rates of 60–90% are commonly reported, allowing breast conservation in 63–90% of patients [5–8] and achieving a complete response (CR) in 30–40%. However, despite excellent response figures, the long-term benefit

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remains uncertain. Previous data from our centre (S6) have shown a trend towards better survival for premenopausal patients treated with neoadjuvant chemotherapy [7]. More detailed analysis has shown statistical links between a high proliferative index and chemosensitivity as well as between chemosensitivity and better outcome [8–11]. Highly proliferative tumours carry an adverse prognosis [11] and this apparent paradox warranted further evaluation in a larger population of young patients, whose tumours are more frequently poorly differentiated and highly proliferative. The results for patients treated between January 1983 and December 1992 were reviewed. During this period, a total of 609 premenopausal patients, aged less than 50 years and who had received four courses of neoadjuvant chemotherapy for breast tumours that were larger than 3 cm in size, were available for analysis. This retrospective analysis aimed to define the impact of neoadjuvant chemotherapy in this population.

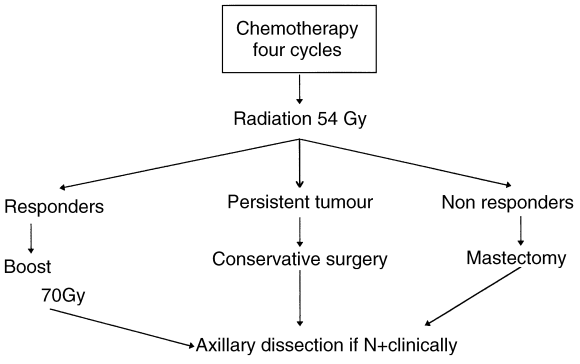

Figure 1. Treatment schedule.

PATIENTS AND METHODS

Patient characteristics

For the time interval between 1983 and 1992 the database registered 609 premenopausal patients below the age of 50 years who fulfilled the following criteria: primary, non-metastatic breast carcinoma, tumour size 3–7 cm and clinical lymph node status not involved or involved but non-adherent. Inflammatory, bilateral or locally advanced tumours were excluded from the analysis (Table 1). Three groups were defined according to the age of the patient at diagnosis: group 1 included 106 patients aged ≤ 35 years; group 2 included 127 patients between the ages of 36 and 40 years; and group 3 included 376 patients aged 41 years or over.

Pathological diagnosis and histological grading had been performed in all patients on a drill biopsy specimen [12]. Steroid receptor levels had been assessed by a quantitative radioimmunoassay. A cut off value of 250 fmol/g of DNA was used, over which the steroid hormone receptor status was considered to be positive [10]. For 193 tumours, the cellular S-phase fraction (SPF) was determined according to techniques described previously [11]. The cut-off value for the SPF was 5%, above which the proliferative index was considered to be high.

Treatment

Treatment in consenting patients consisted of neoadjuvant chemotherapy together with radiotherapy and limited surgery aimed at breast preservation (Figure 1). Chemotherapy included four monthly courses of an intravenous (i.v.) drug combination with or without anthracycline and was administered at 28 day intervals or longer depending on the recovery of bone marrow. Table 2 details the most commonly used drug combinations from 1983 to 1992. The clinical response was evaluated at 2 and 4 months and scored according to the Eastern Cooperative Oncology Group (ECOG) criteria [13].

Radiotherapy was delivered with a mean dosage to the breast of 54 Gy over 6 weeks and followed by a clinical evaluation of tumour response. 257 patients (42%) with a response > 95% underwent a radiation "boost" (16 Gy) to

Table 1. *Tumour characteristics according to age at diagnosis*

	Age (years)			
	≤ 35 ($n=106$) n (%)	36–40 ($n=127$) n (%)	≥ 41 ($n=376$) n (%)	P-value
Tumour size				
T2	65 (61)	91 (72)	225 (60)	
T3	41 (39)	36 (28)	151 (40)	0.06
N0	46 (43)	59 (46)	198 (53)	
N1	60 (57)	68 (54)	178 (47)	0.17
Grade				
I	3 (3)	18 (14)	72 (19)	
II	56 (53)	57 (45)	183 (49)	< 0.0001
III	25 (23)	27 (21)	57 (15)	
Unknown	22 (21)	25 (20)	64 (17)	
Receptor status				
PR+	31 (29)	69 (54)	214 (57)	
PR–	55 (52)	43 (34)	112 (30)	< 0.0001
Unknown	20 (19)	15 (12)	50 (13)	
ER+	35 (33)	67 (53)	196 (52)	0.02
ER–	38 (36)	35 (27)	105 (28)	
Unknown	33 (31)	25 (20)	75 (20)	
S-phase				
< 5%	8/24 (33)	18/34 (64)	90/135 (67)	0.006
$\geq 5\%$	16/24 (67)	13/34 (46)	45/135 (33)	

Patients aged ≤ 35 years had tumours of a higher grade ($P < 0.0001$), with lower receptor levels ($P < 0.0001$) and a higher proliferative index ($P = 0.006$) than patients older than 35 years. Size and nodal status were well balanced. PR, progesterone receptor; ER, oestrogen receptor.

Table 2. Primary chemotherapy regimens

FAC	Doxorubicin 25 mg/m^2/day D1 and D8 Cyclophosphamide 500 mg/m^2/day D1 and D8 5-Fluorouracil 500 mg/m^2/day D1, D3, D5, D8
M2AC	Doxorubicin 50 mg/m^2 D1 Cyclophosphamide 500 mg/m^2 D1 Methotrexate 25 mg/m^2 D2 and D9
CMF	Cyclophosphamide 100 mg/m^2/day D1 to D14 5-Fluorouracil 600 mg/m^2/day D1 and D8 Methotrexate 40 mg/m^2/day D1 and D8
FACV	Doxorubicin 25 mg/m^2/day D1 and D2 Vindesine 3 mg/m^2/day D1 and D5 5-Fluorouracil 600 mg/m^2/day D1 to D5 Cyclophosphamide 400 mg/m^2/day D1 to D4
FEC	Cyclophosphamide 600 mg/m^2/day D1 and D8 5-Fluorouracil 600 mg/m^2/day D1 and D8 Epirubicin 50 mg/m^2/day D1
CTF	Cyclophosphamide 700 mg/m^2/day D1 and D8 5-Fluorouracil 500 mg/m^2/day D1 D3, D5 and D8 Thiotepa 10 mg/m^2/day D1 and D8

D, day.

the tumour bed. 192 patients (32%) with a partial response underwent surgical excision of their residual mass. 158 patients (26%) with minimal response underwent a radical mastectomy. Breast conservation was possible in 452 patients (74%), with no significant difference among the three groups: 76% in group 1, 83% in group 2 and 70% in group 3 ($P = 0.21$). A surgical dissection of the axilla was performed in 336 patients (55%) at the end of radiotherapy.

Statistical methods

Clinical response to chemotherapy was assessed at 2 or 4 months and analysed according to age at diagnosis. The significance of associations between age and treatment response was tested by the chi-squared test. Survival curves were drawn using Kaplan–Meier estimates. The comparison between curves was performed by the log rank test [14]. The following six parameters were entered in a Cox regression model: age (≥ 35 years), tumour size (T2/T3), SPF, oestrogen receptor status, progesterone receptor status and response to chemotherapy. Relative risks are presented with their 95% confidence interval (CI).

RESULTS

Patient characteristics

Tumour size, node status and histological types were well balanced among the three groups according to age at diagnosis (Table 1). In group 1, there was a higher incidence of poor histological grade Scarff Bloom and Richardson (SBR III) ($P < 0.001$) and low progesterone receptor levels ($P < 0.001$) and, on average, higher proliferative indices ($P = 0.0057$) than in groups 2 and 3. There was no significant difference in chemotherapy regimes, which were distributed evenly in the three age groups (data not shown).

Tumour response to neoadjuvant chemotherapy

Response rates were evaluated in all patients after 2 and 4 months of chemotherapy and showed a linear relationship with young age, with the response rate in (group 1) those ≤ 35 years of age being significantly greater than that in the other two age groups (Table 3).

Table 3. Cinical response rates (%) according to age at diagnosis and type of locoregional treatment

	Age (years)			
	≤ 35	36–40	≥ 41	*P*-value
Clinical response				
At two cycles				
OR	54	45	45	0.028
At four cycles				
OR	71	64	66	0.005
CR	38	24	17	< 0.001
Conservative treatment	76	83	70	0.21
RT alone	51	48	38	
RT + S	25	35	32	

OR, objective response including partial and complete responses (CR); RT, radiotherapy; S, surgery.

Long-term outcome

The median follow-up time was 74 months (range 7–157). Currently, 137 patients (22%) have died. Analysis of the overall survival by age (Figure 2a) illustrates the poor survival in patients ≤ 35 years of age (group 1) ($P = 0.002$). The 5-year probability of survival was 70% in patients diagnosed ≤ 35 years of age, 82% for those between 36 and 40 years of age and 84% for those ≥ 41 years of age. These differences in survival were paralleled by higher local recurrence (Figure 2b) and metastatic progression (Figure 2c). At 5 years, local recurrence rates were 31% in group 1, 26% in group 2 and 16% in group 3 ($P = 0.0007$). Again, metastatic recurrence rates (Figure 2c) were significantly higher in patients $\leq$ 35 years at diagnosis, with 5-year rates of 41% in group 1, 35% in group 2 and 28% in group 3 ($P = 0.007$). Disease-free survival rates (Figure 2d) were highly significantly lower in the youngest age group ($P = 0.0003$).

Multivariate analysis

In a multivariate Cox regression analysis (Table 4) the relative risk (RR) of breast cancer-related death was evaluated using six parameters in a forward stepwise procedure. Parameters associated with poor prognosis by order of entry into the model were grade (SBR III, RR 2.2 95% CI 1.4–3.4), large clinical tumour size (T3, RR 2.2 95% CI 1.4–3.3), absence of PR expression (RR 1.8 95% CI 1.2–1.8) and young age (RR 1.6 95% CI 1–2.5). Absence of ER, high SPF and detection of tumour cells in an axillary node dissection after chemotherapy were not retained in this model.

Stratification by age and by response to primary chemotherapy

To clarify the apparent paradox of high response rates in a population with the highest failure rates, the outcome was evaluated in patient populations stratified by age groups and by response patterns. The RR for each subgroup are shown in Table 5. Recurrence and cancer-related mortality curves were strongly divergent as a function of response or resistance to chemotherapy in the patients ≤ 35 years of age, whilst only minimal differences were apparent in the older age groups. Five-year disease-free survival rates of the best responders in the youngest patients remained systematically below that of any group of older patients, irrespective of the response to chemotherapy.

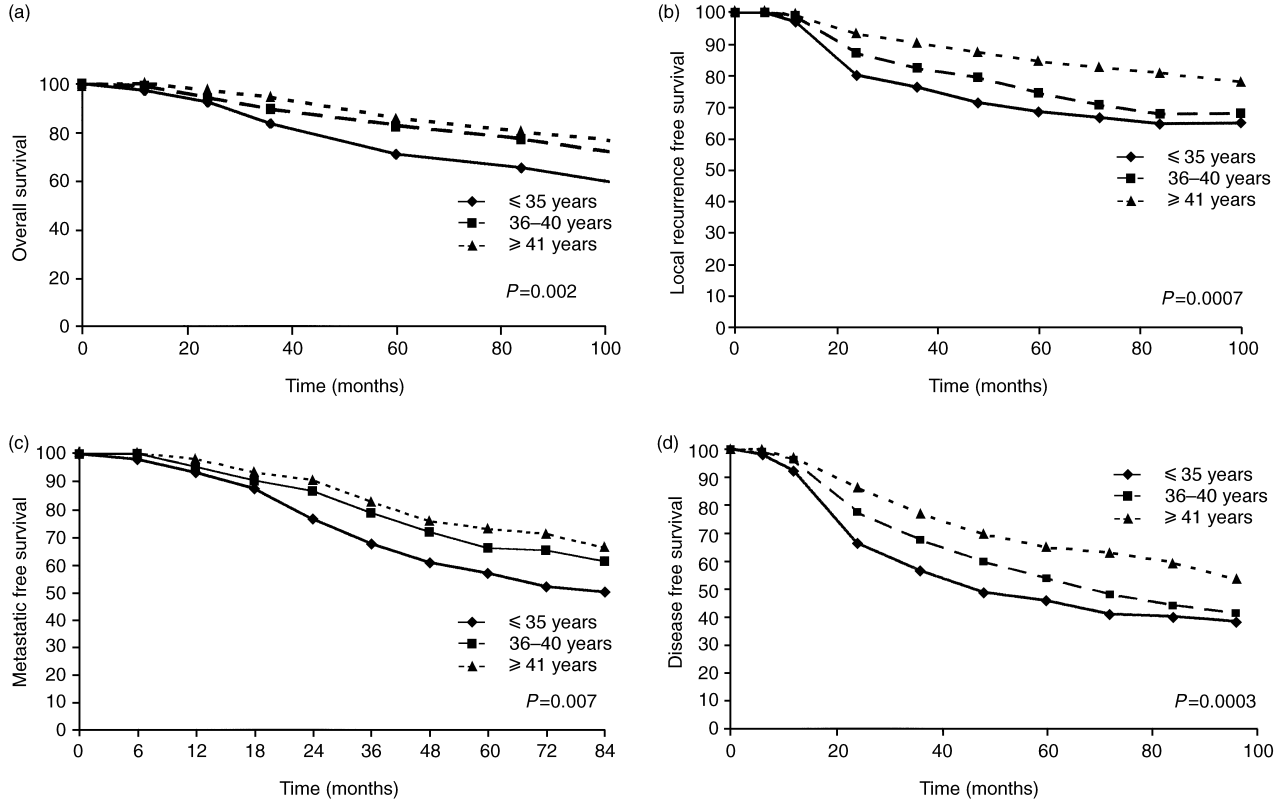

Figure 2. (a) Overall survival according to age at diagnosis. The 5-year rates were 70% (age ≤ 35 years), 82% (age 36–40 years), 84% (age ≥ 41 years). (b) Survival free from local recurrence (LRFS) according to age. The 5-year LRFS were 69% for group 1 (age ≤ 35 years), 74% for group 2 (age 36–40 years) and 84% for group 3 (age ≥ 41 years). (c) Survival free from metastatic progression (MRFS) according to age at diagnosis. The 5-year MRFS rates were 59% for group 1 (age ≤ 35 years), 65% for group 2 (age 36–40 years) and 72% for group 3 (age ≥ 41 years). (d) Disease-free survival (DFS) according to age at diagnosis. The 5-year DFS rates were 45% for group 1, 52% for group 2 and 64% for group 3.

DISCUSSION

Young breast cancer patients, in particular those ≤ 35 years of age, have been repeatedly associated with a less than optimal outcome [1, 2]. Several studies have documented their higher local and distant recurrence rates and, as a corollary, their lower overall survival rates [2–4, 15]. Chemotherapy has been administered as primary treatment in these patients, not only for its potential to reduce tumour size and allow breast conservation, but mostly with the aim to provide early treatment for occult systemic disease. This retrospective analysis was performed to evaluate the immediate and the long-term benefit of primary chemotherapy in young patients, ≤ 35 years of age. Several references support the inverse correlation between response and outcome in patients with high-SPF [9, 11], but the authors are not aware of any published data documenting that the response to chemotherapy was not linearly related to better survival. Young age, together with high SPF (> 5%) and small tumour size, was one of several

Table 4. Multivariate regression analysis of prognostic factors for overall survival

	Relative risk	(95% CI)	*P*-value
Grade SBR			
I + II	1		
III	2.2	(1.4–3.4)	< 0.001
Tumour stage			
II	1		
III	2.2	(1.4–3.3)	< 0.001
Progesterone receptor			
+	1		
–	1.8	(1.2–2.8)	0.001
Age (years)			
> 35	1		
≤ 35	1.6	(1.0–2.5)	0.05

Variables are presented by order of entry in a forward stepwise procedure. CI, confidence interval; SBR, Scarff Bloom and Richardson.

Table 5. Analysis of outcome according to age at diagnosis and clinical response

Age (years)	Clinical response	Survival		Disease-free survival	
		RR	5 years (%)	RR	5 years (%)
≤ 35	CR	1.00	88	1.00	52
	PR	1.94	65	0.88	48
	NR	3.77	44	2.66	17
36–40	CR	1.00	87	1.00	61
	PR	2.29	76	1.18	54
	NR	1.81	87	1.11	56
≥ 41	CR	1.00	91	1.00	70
	PR	1.37	87	1.05	65
	NR	2.25	80	1.22	63

5-year survival rates and relative risk (RR) were determined in complete responders (CR), partial responders (PR) and non-responders (NR).

parameters that favourably influenced chemosensitivity in a multivariate analysis of 200 patients from Institute Curie [9, 11]. The present data suggest that using clinical response to neoadjuvant chemotherapy as a surrogate endpoint for survival [9] may not be a generally valid proposition. Over the last decade, much progress has been made in improving clinical response rates with newer chemotherapy schedules and drug combinations. The present patient population had been treated between 1983 and 1992 and the drug combinations and dose intensities in the early years of neoadjuvant treatments may have been suboptimal. Still, the response rates of the youngest population (71%) were comparable to those of other trials (63–85%) [8, 16, 19] and were, on average, higher than those of older premenopausal patients, who had better long-term survival. Differences in drugs, schedules and dosage may have affected the outcome of patients at high risk of recurrence (young patients, with highly proliferative tumours) more profoundly than patients with more indolent tumours. The results indicated that whilst young patients who responded to chemotherapy fared the best, those with minimal response or no response had an extremely short disease-free survival time. The speed of recurrence and cancer progression rates were thus accelerated in the very young and, in particular, in those who had failed to respond to primary chemotherapy. However for each type of response, the 5-year median survival rate was significantly lower than that of patients in the higher age categories (Table 5).

Early systemic therapy may increase local control and, therefore, intuitively seems to hold some promise in improving long-term outcome [5–8]. Whether primary (as compared to adjuvant) chemotherapy may indeed improve outcome in some patients remains open for debate. In a phase III study from the authors' centre comparing neoadjuvant versus adjuvant chemotherapy in premenopausal patients with operable breast cancer, the 8-year median survival curves showed a trend towards improved outcome (Mantel 0.09; Breslow 0.05) but no difference in terms of metastatic or local recurrence rates [7, 17]. These results could be interpreted by a reduction in the number of circulating micrometastases in responding patients treated by primary chemotherapy, leading to an improved overall survival due to a lower number of metastatic sites, but no difference in the time interval to the clinical detection of first metastatic recurrence. The only other mature randomised trial designed to compare the effect of neoadjuvant and adjuvant chemotherapy on long-term outcome was the National Surgical Adjuvant Breast and Bowel Project B-18 (NSABP-B18) [18]. This trial included 1,523 premenopausal and postmenopausal patients. The failure to detect a survival advantage in favour of the neoadjuvant population could be due to a variety of factors. Anti-oestrogen treatment as a confounding variable may have obscured the issue. Lack of power due to dilution by a large population with a relatively better prognosis, a high proportion of small tumours and, lastly, a smaller impact of chemotherapy on outcome in older patients could have obliterated a possible advantage of early chemotherapy in the subpopulation of high risk, which is underrepresented in most trials. This question will need to be addressed in future randomised trials focusing specifically on young patients. The pathological response at the tumour site and in axillary lymph nodes has been suggested as a surrogate endpoint following primary chemotherapy. NSABP-B18 thus reported a positive correlation between a complete pathological response in 9% of patients treated with neoadjuvant chemotherapy and survival [18] and it would be of interest to analyse the fraction of premenopausal and, in particular, of very young patients who achieved a pathologically complete response. The lack of a pathological analysis in more than two-thirds of patients in the present study, subsequent to exclusive radiotherapy and breast conservation, prevented the evaluation of its influence on survival in this particular subgroup.

Local and metastatic relapse occurred earlier and more frequently in the youngest women, despite very high clinical response rates, and nearly two-thirds of the patient population ≤ 35 years of age had recurred by 5 years. The assumption, therefore, that higher chemosensitivity can lead to anything but improved outcome may have to be reviewed. The 5-year median disease-free survival rates of responding patients in the youngest group, although dramatically better than non-responders, were still at or below the level of non-responders in the older age categories. Whilst the discrepancy in outcome between responders and non-responders was far more noteable in the youngest age group than in older premenopausal patients, the relationship between response and survival was not directly correlated. This higher metastatic risk of tumours that readily respond to chemotherapy remains puzzling. One could argue that distant spread may have occurred prior to treatment and that it may be dormant or less chemosensitive than the primary tumour. In metastatic disease, clinical response to chemotherapy is more frequently incomplete, with shorter benefit, and does not lead to cure. Better evaluation by more elegant parameters of invasion, such as circulating or bone marrow micrometastases, might be helpful to gain more insight into treatment efficacy. Contradictory results have been reported regarding correlations between p53, bcl-2 and Her2/neu overexpression and chemosensitivity, or lack thereof [20–24], raising more questions than answers for future adjuvant strategies. Trying to kill all tumour cells with cytotoxic modalities may be a naive and counterproductive approach. Associations of chemotherapy with biological therapies, as these become available, appear mandatory for high-risk patients as defined here, irrespective of their response to chemotherapy.

In conclusion, whilst young patients appear to have a better outcome if they respond to primary chemotherapy, the overall long-term prognosis of young patients is at odds with early clinical expectations. It is also difficult to conceive how parameters such as rapid proliferation [25] can be positively associated both with response to treatment and with recurrence. By analogy, clinical response might be pictured as a modification of the visible part of an iceberg, with the dynamics of its growth or regression being more dramatic in younger individuals. It is likely, therefore, that the greatest impact of treatment can yet be achieved in the very young high-risk population, provided we learn to quantify residual microscopic tumour mass and improve on existing treatments.

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