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Prognostic Factors in Inflammatory Breast Cancer and Therapeutic Implications

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223 inflammatory breast cancer patients were diagnosed at the Institut Curie between 1977 and 1987. Patients received chemotherapy and radiation treatment according to three consecutive randomised trials. Five- and 10-year survival rates were 41 and 32%, respectively. Disease-free interval rates were 25.5% at 5 years and 19% at 10 years. Parameters significantly linked with a pejorative prognosis in a multivariate analysis were: diffuse erythema, lymph node involvement, chest wall adherence, and age above 50 years. When therapeutic response parameters were included in the multivariate analysis, the five most important prognostic factors in order of significance were complete tumour regression after completion of induction treatment (at 8 months), complete regression of inflammatory symptoms after 3 months of neoadjuvant chemotherapy, limited erythema at presentation and, less significantly, complete regression of inflammatory symptoms at 8 months and tumour regression at 3 months. In conclusion, patients who achieved a rapid and complete remission had a better prognosis than patients who had an incomplete response to chemotherapy. High-dose chemotherapy and reversal or prevention of drug resistance will be evaluated in future trials. Detailed information on the biology of this disease should allow the design of new strategies aiming to improve patient management.
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INTRODUCTION

THE PRESENCE of inflammatory signs in breast cancer, either localised around the tumour or diffuse, are associated with a poor prognosis. Following local treatment only, the median survival commonly reported is between 16 and 26 months [1–3]. Therefore, inflammatory breast cancer behaves from the outset like a systemic disease whose course is not influenced by local treatment alone. This well-known clinical fact accounts for the usual therapeutic strategies which combine chemotherapy, hormonal manipulations and surgery or radiotherapy [2]. A review of the literature demonstrates marked differences in results which can be attributed to differences in protocols, duration of chemotherapy, dose intensity and selection of treated patients. The reported objective response rates vary widely between 14 and 96% [3, 4], and the overall median survival ranges from 23 to more than 60 months [5, 6]. Although the indication for first-line chemotherapy is no longer questionable, the duration of treatment and the modalities of salvage treatment of total or partial primary failures remain controversial.

In this study, we analysed the clinical, biological and therapeutic prognostic parameters in patients with inflammatory breast cancer. Our data are derived from three prospective randomised consecutive trials conducted at the Institut Curie with a median follow-up of 95 months.

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PATIENTS AND METHODS

223 patients with inflammatory breast cancer were included in three consecutive randomised trials of a multimodal treatment combining chemotherapy and radiotherapy, active between 1977 and 1987. The diagnosis of inflammatory cancer was based on the presence of two or more clinical signs characteristic of inflammation: erythema, oedema, increased volume of the breast with increased tenderness. The extent of the inflammation was measured according to the PEV classification criteria [7]. Only tumours classified as PEV 2 (limited inflammation but involving more than one half of the breast) or PEV 3 (diffuse inflammation involving the entire breast) were included in the trials.

Histological or cytological evidence of carcinoma was required for inclusion in the study. The pathological diagnosis of intra-lymphatic tumour emboli in the skin was not required for a positive diagnosis of inflammatory breast cancer. The tumour was graded according to the Scarff, Bloom and Richardson scale. From 1980 onwards, the oestrogen receptor (ER) and/or progesterone receptor (PR) concentrations were determined by a radioligand technique.

Treatments

In the first randomised trial, SI77 (Sein Inflammatoire 1977), 60 patients were included between June 1977 and December 1979. All patients were treated by chemotherapy and radiotherapy, and randomised for additional (three times per week) Bacillus Calmette-Guerin (BCG) scarifications over 2 years. The

AVCF chemotherapy regime combined doxorubicin (A) 45 mg/m^2 on day 1, vincristine (V) 1.2 mg/m^2 on day 1, cyclophosphamide (C) 400 mg/m^2 on days 1, 2 and 3, 5-fluorouracil (F) 500 mg/m^2 on days 1, 2 and 3. Three cycles were repeated at 28-day intervals and followed by cobalt 60 irradiation, delivering a dose of 55 Gy to the whole breast, 60 Gy to the inferior axillary lymph node chain, 45 Gy to the internal mammary chain and supraclavicular fossa, followed by a boost of 17 Gy to the tumour bed. Radiation was followed by four cycles of the same induction chemotherapy. Maintenance treatment with a CLM regimen consisted of a 12 monthly cycles of cyclophosphamide (C) 100 mg/m^2/day for 7 consecutive days, melphalan (L) 4 mg/m^2/day over 7 days, and methotrexate (M) 25 mg/m^2 on days 1, 8 and 15.

In the second trial, SI80, 102 patients recruited between December 1980 and December 1983 were randomly assigned to either the same AVCF regime used in the first trial, or the M2AC regime which consisted of six-weekly cycles of doxorubicin (A) 45 mg/m^2 on day 1, cyclophosphamide (C) 600 mg/m^2 on days 1 and 22, methotrexate (M) 25 mg/m^2 on days 2, 9, 23 and 30, mitomycin C (Mi) 7.5 mg/m^2 on day 22. In addition, radiation therapy was administered either upfront, or following 3 months of induction chemotherapy. For the duration of radiation treatment, a VCF chemotherapy without doxorubicin was administered simultaneously. Induction chemotherapy was continued for 8 cycles and followed by an intravenous (i.v.) CMF regime combining C 500 mg/m^2, M 40 mg/m^2, F 600 mg/m^2 once a fortnight for a total of 12 cycles.

The third trial, SI84, was active between May 1984 and January 1987, and was designed to evaluate the role of maintenance chemotherapy. Following three cycles of AVCF induction chemotherapy and irradiation (during which doxorubicin was discontinued), another six cycles of AVCF were administered. Patients were then randomised to receive an i.v. CMF maintenance chemotherapy for 12 months or no further chemotherapy.

Additional hormonal therapy was allowed to be prescribed in all three studies. Mastectomy was performed for persistent residual tumour between the sixth and eighth month of treatment.

Monitoring

The patients were examined monthly throughout the duration of treatment. The response to chemotherapy was evaluated by the regression of inflammatory signs, by changes in the size of the tumour (as measured by the product of the two largest diameters) and the regression of regional lymph nodes. Regular follow-up visits were initially at 4-month then at 6-month intervals until the end of the fifth year, and yearly thereafter. A complete physical examination, chest X-ray and laboratory assessment, including carcinoembryonic antigen (CEA) and/or CA 15.3 marker assays, were performed at each visit. Mammography was repeated every 6 months during the first year, then annually. Abdominal ultrasonography and bone scan were performed routinely every 12 months. All other complementary investigations were performed according to the clinical context.

Statistical methods

The survival and disease-free interval (DFI) were calculated from the first day of treatment. Standard error (S.E.) is indicated in brackets. Non-parametric estimates of survival and disease-free interval were calculated according to Kaplan–Meier. For DFI, the chosen endpoint was the first relapse (local or regional failure, metastasis, controlateral tumour). Patients with persistant disease were considered as zero DFI; patients without evidence of relapse were censored at the time of death or last follow-up. Univariate analysis using the logrank test was performed to determine one by one the prognostic role of the initial clinical parameters of the disease, the histological and biological parameters, and the criteria evaluating the efficacy of the treatment at 3 and 8 months (tumour regression and changes in the inflammatory signs). The prognostic relevance of the following clinical parameters: age, hormonal status, presence of erythema, breast oedema, size of the tumour, chest wall adherence and lymph node involvement was evaluated. The thickness of the skin on mammography as an indicator of cutaneous oedema was the only radiological parameter selected. Among the biological parameters, the histological grade, the presence of ER and/or PR, and the serum lactate dehydrogenase (LDH) level prior to treatment were selected.

Multivariate analyses were performed using the Cox regression model [8]. The relative risks and their confidence intervals are presented. For modelling procedures, each parameter was coded as a binary (or a set of binary) variable(s) and if necessary, missing values were coded as a separate variable. A first model took into account all relevant clinical, histological and biological parameters. For patients treated by first-line chemotherapy, a second model allowed the analysis of therapeutic efficacy following adjustment to the principal prognostic factors.

RESULTS

Survival and disease-free interval

The median follow-up of all the patients from their inclusion into the trials was 95 months. For patients alive at the time of the present evaluation, the median follow-up was 77 months. The median survival for the total population was 41 months. At 5 years 40.8% (S.E. 3.6) of patients were alive and 31.8% (S.E. 4) at 10 years (Figure 1). No difference was observed in the distribution of the clinical, histological and biological parameters between the three trials. In trial I, 41 out of 60 patients have died and the median survival is 30 months. In trial II, 63 out of 102 patients have died and the median survival is 44 months. In trial III, 27 out of 61 patients have died and the median survival is 43 months. Comparison of the survival curves between these

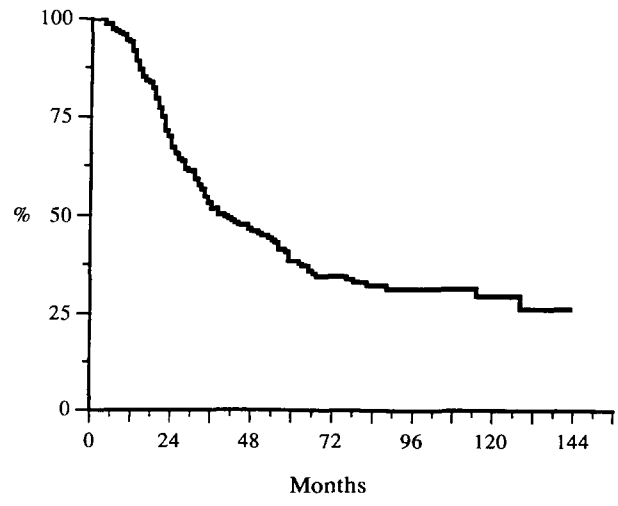

Figure 1. Inflammatory breast cancer: overall survival.

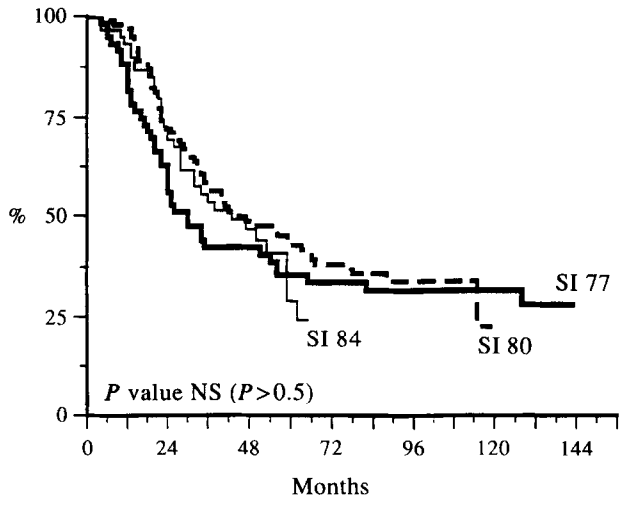

Figure 2. Inflammatory breast cancer: survival according to different protocols.

three studies did not reveal any significant difference ($P = 0.51$) (Figure 2).

The median DFI was 19 months. Five- and 10-year disease-free rates were 25.5% (S.E. 3.1) and 19.3 (S.E. 3.2), respectively (Figure 3). Recurrent disease was observed in 167 out of the 223 patients, 70 patients developed metastatic disease, 82 developed metastatic and local recurrences, 13 local recurrences and 2 contralateral breast tumours. In 21 patients, contralateral recurrences were associated with local and/or distant recurrences.

Factors influencing survival and recurrence

Clinical and biological variables. The clinical and biological parameters evaluated for their influence on survival and DFI are listed in Table 1. The presence of the following clinical parameters carried a pejorative prognostic significance for survival: age greater than 50 years ($P < 0.05$), the extent of erythema ($P < 0.0001$), the presence of oedema ($P < 0.002$), clinically-detectable lymph node involvement ($P < 0.008$), as well as the presence of a tumour in the opposite breast or axilla ($P < 0.004$). The same variables, as well as chest wall adherence, were significantly associated with shorter DFI. The mammographic evaluation of skin oedema was not of prognostic significance. Among the biological parameters, only raised serum LDH level prior to treatment had a pejorative significance on survival ($P < 0.004$), as well as disease-free interval ($P < 0.0001$). Progesterone (P: 0.01) and oestrogen (P: 0.03) receptors had a significant prognostic value only for DFI.

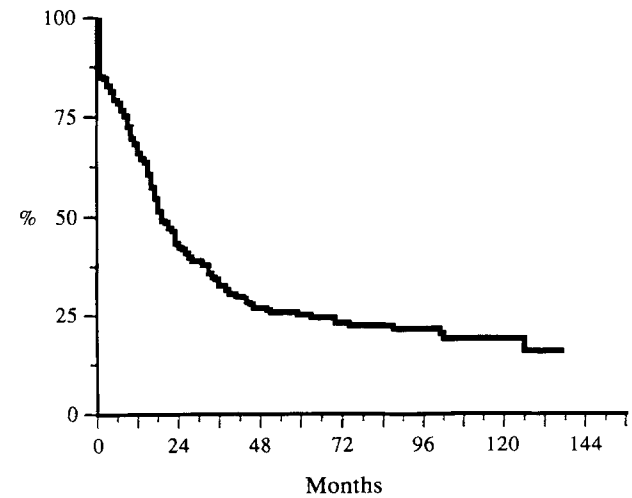

Figure 3. Inflammatory breast cancer: disease-free interval.

The influence of treatment response on survival. For the patients treated by first-line chemotherapy, the rate of complete disappearance of the inflammatory signs at 3 months was 57%, and 79% at 8 months. The complete tumour regression rate at 3 months was 11%, with a major objective response rate of 46%. Following radiotherapy, the complete tumour regression rate was 59% at 8 months, and all the patients had obtained an objective response (Table 2). The response to treatment, i.e. regression of the inflammatory signs and regression of the tumour volume initially measured at 3 months and at 8 months, markedly influenced survival (Figures 4 and 5) and DFI. However, the most important factor influencing survival was the kinetics of the response. The 5-year survival rate was 59% for patients with a rapid and early complete regression of inflammatory symptoms following 3 months of chemotherapy; for those who did not respond to first-line chemotherapy, but who responded at 8 months to combined radiotherapy and chemotherapy, the 5-year survival rate was only 21% (P: 0.0007). Regarding tumour regression, similar results were observed (Table 3).

Multivariate analysis

In a stepwise Cox regression analysis including all relevant clinical and biological parameters of the total population ($n = 223$), the following variables were most significantly associated with poor survival (Table 4): diffuse erythema ($P = 0.0001$), lymph node extension (N3) ($P < 0.015$), tumour adherence to chest wall ($P < 0.015$), age > 50 years ($P < 0.015$). For recurrence, the five most significant factors were lymph node involvement (P: 0.0003), diffuse erythema (P: 0.0004), age > 50 years ($P < 0.02$), raised lactate dehydrogenase ($P < 0.04$) and tumour adherence lactate ($P < 0.04$). When the Cox regression model included therapeutic parameters as well (in a subset of patients treated by first-line chemotherapy), the dominant prognostic parameters influencing prolonged survival were, in order of significance (Table 5), complete tumour regression at the completion of induction chemotherapy and radiation ($P < 0.0001$); complete regression of inflammatory symptoms following three cycles of chemotherapy ($P < 0.0001$); limited erythema at presentation ($P < 0.005$); and less significantly, regression of inflammatory symptoms at 8 months ($P < 0.03$) and tumour regression at 3 months ($P < 0.03$). Factors significantly associated with a prolonged DFI included the three most significant variables in the previous analysis as well as low serum LDH levels at presentation (P: 0.0008), absence of chest wall adherence ($P < 0.001$) and absence of supraclavicular lymph node involvement (N3) ($P < 0.03$).

DISCUSSION

Numerous retrospective studies published in the literature have documented the value of chemotherapy in the treatment of inflammatory breast cancer [2–4, 6, 9, 10], and shown a substantial improvement of the disease-free and the overall survival. Currently, it appears unethical in the management of inflammatory cancer to provide a local treatment alone without systemic chemotherapy [11, 12] and, therefore, the survival

Table 1. Univariate analysis of clinical and biological parameters with survival and disease-free interval

Initial factor	*n*	Survival			Disease-free interval		
		5-Year (%)	Median (months)	*P* value	5-Year (%)	Median (months)	*P* value
Consecutive trial				NS			NS
77	60	35.1	30		28.5	18	
80	102	44	44		24	19	
84	61	40	43		28.3	19	
Age (years)				<0.05			<0.05
≤50	99	49.4	56		31.7	24	
>50	124	33.3	35		20.3	17	
Menopausal status				NS			NS
Pre	116	46.1	51		26.9	24	
Post	107	34.7	35		24.3	17	
Erythema				<0.0001			0.0001
Limited	130	48.4	59		31.2	27	
Diffuse	89	25.9	26		16.8	15	
Missing	4						
Oedema				<0.002			NS (0.07)
Limited	78	54.5	65		30.1	25	
Diffuse	143	32	31		23.5	18	
Missing	2						
Clinical tumour size				NS (0.09)			NS
≤10	153	45.1	55		28	21	
>10	47	35.2	35		17.5	16	
Not measurable	23	24.2	34		26.8	17	
Deep adherence				NS (0.06)			<0.04
No	169	43	54		27.2	23	
Yes	21	31.7	22		14.1	9	
Missing	33						
Lymph node involvement*				<0.008			0.0002
N0–N1a	37	48.5	51		31.6	39	
N1b	111	41	38		28.4	21	
N2	35	55.4	63		30.6	27	
N3	34	24.2	25		8.8	4	
Missing	6						
Contralateral signs				0.004			0.0007
No	198	43.3	47		28	23	
Yes	18	17.3	21		11.1	9	
Missing	7						
Mammogram: thickness				NS			NS
No	22	49.6	56		41.3	43	
Yes	151	37.4	36		23.8	18	
Missing	50						
SBR				NS			NS
I–II	94	44.1	56		29.7	23	
III	73	33.5	31		20	17	
No gradable	17	48.8	40		11.8	15	
Missing	39						
Oestrogen receptor				NS (0.084)			0.03
Negative	84	31	28		18	16	
Positive	26	49.4	56		24.8	32	
Missing	113						
Progesterone receptor				NS (0.065)			
Negative	103	35.7	34		20	16	0.01
Positive	33	48.8	59		35.6	31	
Missing	87						
Serum level of LDH				<0.004			<0.0001
≤240	171	47.1	56		29.8	24	
>240	28	19.5	22		15.7	2	
Missing	24						

SBR, Scarff, Bloom and Richardson scale. LDH, lactate dehydrogenase; NS, non-significant. **P* value: test for trend. Sub-group comparison N0 to N2: NS.

Table 2. Kinetics of response

Number	CR (%)	PR > 50% (%)	CR + PR > 50%
Inflammatory signs prior to radiotherapy (after 3 months chemotherapy)			
171	97(57)	57(33)	90%
Inflammatory signs after radiotherapy			
163*	128(79)	17(10)	89%
Tumour regression prior to radiotherapy			
149†	17(11)	68(46)	57%
Tumour regression after radiotherapy (after 8 months)			
171	101(59)	70(41)	100%

*Eight missing values due to inflammatory skin reaction after radiotherapy. †Tumours initially measurable.

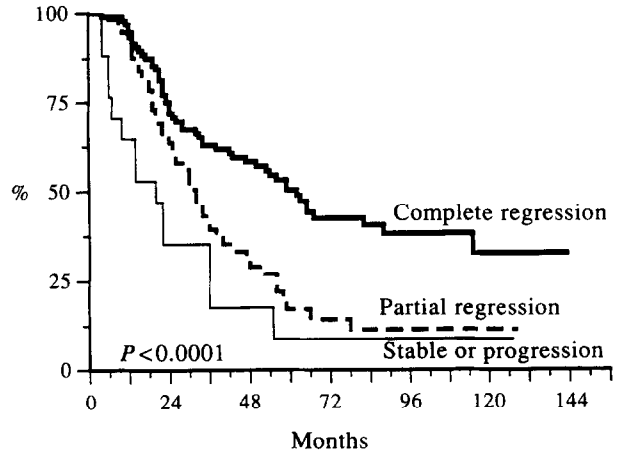

Figure 4. Inflammatory breast cancer: survival according to inflammatory regression following three cycles of chemotherapy.

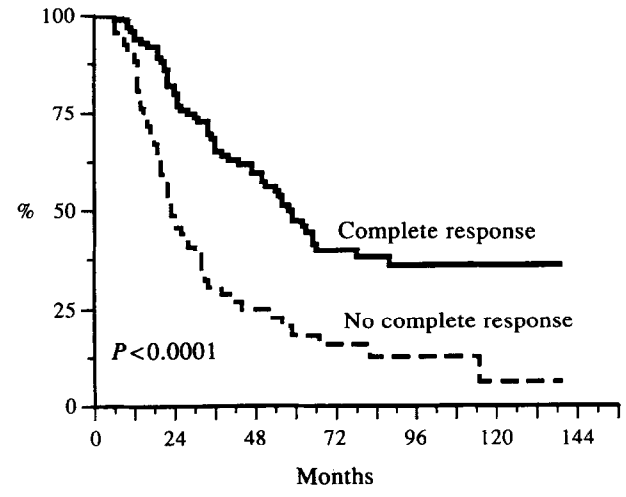

Figure 5. Inflammatory breast cancer: survival according to residual tumour after chemotherapy and radiotherapy.

advantages following systemic chemotherapy in inflammatory breast cancer can only be based on comparisons with historical control series [2].

In the present study, three homogeneous patient populations were treated according to three consecutive trials and randomised for either additional BCG therapy (I), for the type of chemotherapy combination (II), or for the prolonged treatment with a "maintenance" regime (III). These different treatment strategies did not show a difference in outcome at the present evaluation. Approximately one third of the patients are expected to be alive after 10 years, and not quite 20% of these will be clinically disease free. Survival curves decreased continuously up to the fifth year and then levelled off, but never flattened out to a plateau.

In many published series, the patients were treated by first-line irradiation and only occasionally by surgery after chemotherapy. The respective advantages of surgery and radiotherapy have been extensively discussed and, in the particular case of inflammatory breast cancer, the indications for irradiation cannot be dismissed. However, other studies have shown that radical mastectomy carried a favourable prognostic significance [13] with an impressive difference between local recurrence rates, according to whether mastectomy was performed (19% of local recurrences) or not (70% of local recurrences). The recurrence rates reported by Abbes [14] also appear to be lower in patients treated by mastectomy after induction chemotherapy. Wiseman [15] included surgery as a basic element of local treatment for inflammatory breast cancer, but the results by Schäfer and colleagues [16] showed that patients treated by chemotherapy and surgery all developed local recurrence within 8 to 17 months after surgery. In a small pilot study, Perloff [17] reported similar local recurrence rates (42%) in 8 patients treated by surgery compared with 12 patients treated by radiotherapy (55%). Although it is difficult to compare treatments in such small samples, the prognostic severity of local recurrence or lack of local control in inflammatory breast cancer appears to be clearly demonstrated. According to Brun [18], local recurrences are related to the persistence of intramammary residual disease at the end of radiotherapy and, therefore, are less frequent after mastectomy. In our group of 21 patients treated by mastectomy around the eighth month for residual tumour after radiotherapy, the prognosis was not significantly different from that of a comparable subpopulation of 39 patients treated without mastectomy. Median survival times were 42 and 30 months, but the delay in surgery may have biased these results.

Although it is clear that the improvement in the survival of the disease depends on an optimal local control by use of surgery and/or radiotherapy, the contribution of a systemic chemotherapy appears essential. Considerable progress has been made, but many questions remain unresolved. Some concern the modalities of application of chemotherapy, the prevention of drug resistance and the possibilities of evaluating small populations with an extremely evolutive variety of breast cancer. We did not see an advantage of either prolonging maintenance therapy, of administering chemotherapy and radiotherapy in sequence or concomittantly, or of two different but generally efficient chemotherapy regimes. The addition of BCG scarifications did not change outcome. Prolonging chemotherapy beyond the 8-month period for the initial treatment phase, did not seem to improve our 5-year local recurrence rates which were 46%. Comparable local recurrence rates were reported by Rouessé [3], and appeared to be influenced by the intensity of systemic chemotherapy. A number of signs at presentation are associated with a poor prognosis and do not appear to be modified by different therapeutic strategies [3, 19, 20]. The extension of the inflammatory signs still constitutes a discriminant prognostic factor as confirmed by our results. A correlation between the presence of inflammatory signs and the clinical evaluation of the

Table 3. Univariate analysis of therapeutic parameters with survival and disease-free interval (n = 171)

Response to treatment if initial chemotherapy	*n*	Survival			Disease free interval		
		5-Year (%)	Median (months)	*P* value	5-Year (%)	Median (months)	*P* value
Inflammatory response							
To induction chemotherapy				<0.0001			<0.0001
CR	97	51	62		36	25	
PR	57	18.9	32		10.7	17	
NR	17	8.8	20		5.9	4	
At 7–8 months				<0.0001			<0.0001
CR	128	42.3	53		27	23	
PR	17	15.7	36		19.6	16	
NR	18	—	18		—	4	
Missing values*	8						
To induction chemotherapy when CR at 7–8 months				0.0007			<0.002
CR	81	59.1	82		37	38	
No CR	47	21.1	34		9.6	10	
Tumoral response							
To induction chemotherapy				0.0005			<0.002
CR	17	67.6	—		51.5	—	
PR	68	53.2	66		29.5	23	
NR	64	21.2	31		11.5	16	
Missing values†	22						
At 7–8 months				<0.0001			<0.0001
CR	101	47.2	58		34	34	
No CR	70	18.1	23		7.7	8	
To induction chemotherapy when CR at 7–8 months				<0.02			<0.03
CR	14	75.7	—		56.2	—	
PR	43	62.9	88		41.4	44	
NR	30	27.3	48		17.8	19	
Missing values	14						
Inflammatory tumoral and nodal response							
To induction chemotherapy				<0.04			<0.04
CR	11	77.9	—		50.9	—	
No CR	160	36.8	36		23.3	18	
At 7–8 months				<0.0001			<0.0001
CR	74	51.2	63		36.7	39	
No CR	89	19	24		10.6	10	
Missing values*	8						

— not reached; CR, complete response; PR, partial response; NR, no response. *Missing values: response unevaluable for inflammatory signs after radiotherapy due to cutaneous reactions. †Missing values: tumours initially not measurable.

growth kinetic by measuring the doubling time was reported by Tabbane and Paradiso [19, 21]. The inflammatory signs resolved after the induction phase of chemotherapy in 57% of cases (97/171) and after the treatment sequence of chemotherapy and radiotherapy in 79% of cases (128/163). Complete tumour regression was obtained in only 11% of treated cases (17/149) after 3 months of chemotherapy and in 59% of cases after chemotherapy and radiotherapy at the eighth month (101/171). These response rates as well as the mean duration of the response are analogous to those reported by other authors [3, 11, 12, 14, 17, 18].

In the multivariate analysis, the early response to treatment in terms of tumour regression as well as regression of inflammatory signs at 3 months proved to be highly significantly related to outcome. In 171 patients treated with first-line chemotherapy, the symptoms at presentation, but more importantly the kinetics of response to chemotherapy, were highly significant for survival and DFI.

CONCLUSIONS

The prognostic significance of an early response suggests that the initial phase of treatment is essential and that failure of the primary treatment cannot be salvaged later on. These results also explain the relative inefficiency of secondary mastectomies reported in our study. These findings suggest that late chemotherapy dose intensification in the course of treatment may be of little use, and suggests that treatment should be intense and short with possibly an optimal duration of 6 months.

Future prospective multicentre studies should focus on:

(1) The choice of new combinations for induction treatment,

Table 4. Multivariate Cox regression model

Order†	Parameter	Significance	RR	95% CI
Initial parameters selected for overall survival (n = 223)				
1	Erythema	0.0001	2	1.4–2.9
2	LN	<0.015	2.1	1.4–3.3
3	Adh	<0.015	1.8	1.1–3.1
4	Age	<0.015	1.5	1.1–2.2
Initial parameters selected for disease-free interval (n = 223)				
1	LN*	0.0003	2.4	1.6–3.6
2	Erythema*	0.0004	1.8	1.3–2.5
3	Age	<0.02	1.5	1.1–2.1
4	LDH	<0.04	2.1	1.3–3.3
5	Adh*	<0.04	2.5	1.4–4.2

LN, lymph node extension; Adh, deep adherence; LDH, lactate dehydrogenase; RR, relative risk; CI, confidence interval. *Statistical sygnificance at the level of entry. †Order of entry into the model by an ascending stepwise procedure.

Table 5. Multivariate Cox regression model

Order†	Parameter	Significance	RR	95% CI
Initial and therapeutic parameters selected for overall survival (n = 171)				
1	Tum. R8*	<0.0001	2.2	1.5–3.3
2	Infl. R3*	<0.0001	1.7	1.1–2.7
3	Eryth.*	<0.005	1.7	1.2–2.6
4	Infl. R8	<0.03	1.7	1.0–2.7
5	Tum. R3*	<0.03	1.6	1.0–2.5
Initial and therapeutic parameters selected for disease-free interval				
1	Tum. R8*	<0.0001	3.3	2.2–4.9
2	Infl. R3*	0.0001	2.4	1.6–3.5
3	LDH*	0.0008	2.8	1.6–4.8
4	Adh*	<0.001	3.2	1.5–5.8
5	LN*	<0.03	1.7	1.1–2.7
6	Eryth.*	0.03	1.6	1.1–2.3

RR, adjusted relative risk; 95% CI, 95% confidence interval of the relative risk; Tum. R8, tumour response at 8 months [complete response (CR) versus no CR]; Infl. R3, response of inflammation to chemotherapy at 3 months (CR versus no CR); Eryth., initial erythema; Infl. R8, response of inflammation to chemotherapy at 8 months (CR versus no CR); Tum. R3, tumour response at 3 months (CR or partial response versus no response); LDH, lactate dehydrogenase; Adh, deep adherence; LN, clinical lymph node extension. *Statistical significance at the level of entry. †Order of entry into the model by an ascending stepwise procedure.

the timing of intensive chemotherapy and the ways of avoiding an early acquired drug resistance.

(2) The optimal timing and choice for local treatment; should surgery be preferable to radiotherapy?

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