



Predictive factors of response to first-line chemotherapy in 1426 women with metastatic breast cancer

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Abstract

Since response to chemotherapy is a major determinant of survival in metastatic breast cancer, the purpose of our study was to analyse the predictive factors of response. 1426 patients enrolled into eight consecutive randomised trials of anthracycline-based first-line chemotherapy in metastatic breast cancer, between 1977 and 1992, were analysed. A forward stepwise logistic regression analysis was used. The objective response rate (ORR) to chemotherapy in the total population was 63.6% (95% confidence interval (CI): 61.5–67.7). The complete response rate was 17.5%. Multivariate analysis defined adjuvant chemotherapy, lactate dehydrogenase (LDH), Karnofsky index (KI), and pleural and lung metastases to be the five main variables correlated with ORR. A predictive score was calculated using the coefficient of these five variables. The score was established as follows: $-1.32 + 0.54$ (if prior adjuvant chemotherapy) $+ 0.80$ (low KI) $+ 0.75$ (raised LDH) $+ 0.49$ (lung metastases) $+ 0.51$ (pleural metastases). A low score (less than -0.78) was associated with an ORR greater than 70.0%, representing 41.2% of our population. An intermediate score (between -0.78 and 0) was associated with an ORR of 50 to 70%, representing 37.5% of our population and a positive score was associated with an ORR of less than 50%, representing 21.3% of our population. This score can be used to predict objective response rates to first-line anthracycline-based chemotherapy. This method now needs to be evaluated prospectively in phase II trials. Identification of various risk groups may also be useful for interpretation and design of clinical trials. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The treatment of patients with metastatic breast cancer remains essentially palliative. However, breast cancer is a chemosensitive tumour, and among the many agents that can induce a tumour response in a substantial number of patients, anthracyclines remain the reference for their antitumour activity [1]. In several randomised trials, anthracycline-containing regimens have achieved longer times to progression and occasionally survival differences when compared with reference cyclophosphamide, methotrexate and 5-fluorouracil (CMF)-based combinations [2–5]. Treatment of metastatic disease has

had an impact on response rates, but survival gains are rarely reported. First-line anthracycline-based chemotherapy achieves a response rate of 50–70% [6]. Although palliative, an objective response has a beneficial therapeutic effect. Women achieving complete remission have a better overall survival than non-responders [7,8]. Several studies have analysed the characteristics and outcome of complete responders, but few studies have attempted to characterise prognostic factors associated with response to treatment.

1430 women with metastatic breast cancer were entered, at the Institut Curie, into one of eight protocols of first-line chemotherapy, all containing anthracyclines, between 1977 and 1992. In this series of patients, we observed that overall survival was strongly correlated with response rate to chemotherapy [9]. The aim of this study was to screen for predictive factors of response and outcome.

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2. Patients and methods

From 1977 to 1992, a total of 1430 women with metastatic breast cancer were entered into eight controlled trials conducted at Institut Curie. All data had been collected prospectively and had been entered into a centralised patient data management system. The various trials studied different modalities of first-line chemotherapy and included anthracyclines with or without endocrine therapy. Eligibility criteria were similar in the eight studies. Prior endocrine therapy, either for adjuvant therapy or for metastatic disease, was allowed, but patients were not allowed to have received chemotherapy for metastatic disease. The main characteristics of the trials are summarised below.

2.1. Trials of first-line chemotherapy

SPM77 included 144 patients from 1977 to 1978 and compared AVEF + Bacillus Calmethe-Guérin (BCG) vaccine versus AVEF alone (AVEF = doxorubicin 45 mg/m² day 1, cyclophosphamide 400 mg/m² days 2–4, vincristine 1.2 mg/m² day 2, 5-fluorouracil (5-FU) 500 mg/m² days 2–4).

SPM78 included 223 patients from 1978 to 1980 and compared AVEF versus AVEF alternating with VMM, followed by endocrine therapy versus no endocrine therapy (VMM = VM26 (teniposide) 120 mg/m² day 1, mitomycin C 10 mg/m² day 2, methotrexate 20 mg/m² days 2–3).

SPM80 included 79 patients from 1980 to 1981 and compared AVEF + medroxyprogesterone acetate (MPA) versus AVEF + MPA + tamoxifen (TAM).

SPM81 included 247 patients from 1981 to 1982 and compared TAM followed by TAM + ACF versus ACF + TAM versus ACF followed by TAM (ACF = doxorubicin 45 mg/m² day 1, cyclophosphamide 400 mg/m² days 2–4, 5-FU 500 mg/m² days 2–4, methylprednisolone 80 mg/m² days 2–4).

SPM83 included 82 patients from 1983 to 1985: patients were treated with ACF for various durations according to the unfavourable survival index.

SPM85, (1965, 1980) included 94 patients and compared AVCF versus FUCONTIN (AVCF = doxorubicin 45 mg/m² day 1, cyclophosphamide 400 mg/m² days 1–3, vindesine 4 mg/m² day 1, 5-FU 500 mg/m² days 1–3; FUCONTIN = doxorubicin 11.5 mg/m² days 1–3, day 16, day 19, vindesine 4 mg/m² day 1, 5-FU 500 mg/m² administered from day 1 to day 5 and from day 15 to day 19).

SPM86 included 218 patients from 1987 to 1990 and compared cyclophosphamide, 5-FU and doxorubicin (CFA) + MPA versus CFA in premenopausal patients

and CFA + TAM versus CFA + TAM + diethylbesterol in postmenopausal patients.

SPM90 included 258 patients from 1990 to 1992 and compared 5-FU, doxorubicin and cyclophosphamide (FAC) versus FULON (FAC = doxorubicin 50 mg/m² day 1, cyclophosphamide 400 mg/m² days 1–3, 5-FU 500 mg/m²; FULON = doxorubicin 15 mg/m² day 1, day 8, day 15, day 22, cyclophosphamide 300 mg/m² day 1, day 8, day 15, day 22, 5-FU 250 mg/m² infused continuously from day 1 to day 22).

Taking account of all the trials, 506 patients received chemo-endocrine therapy. 67 patients treated in 1977 before the beginning of SPM77 and 18 patients treated after the end of SPM90 were also included in the analysis. 4 patients were excluded from the analysis because of the absence of a response assessment.

2.2. Data collection

Registered characteristics of primary disease were clinical tumour and nodal status (TNM), Scarff–Blood–Richardson (SBR) grade, oestrogen and progesterone receptor status, initial surgery, adjuvant radiotherapy, adjuvant chemotherapy and adjuvant endocrine therapy.

Clinical and laboratory characteristics collected on inclusion of the patients into the trials for metastatic disease were age, performance status (Karnofsky index), weight loss before treatment, menopausal status, disease-free interval from primary tumour diagnosis to metastases, year of inclusion in a metastatic trial, number of sites and location of metastases, serum lactic dehydrogenase (LDH), serum alkaline phosphatase, γ glutamyl transferase γ GT), aspartate aminotransferase (AST), serum albumin levels and absolute lymphocyte count.

2.3. Evaluation of response

Response to chemotherapy was assessed at 4, 8 and 12 months after the start of treatment. For each patient, the maximal response observed within 12 months was retained. Complete response (CR) was defined as the disappearance of all known sites of disease. Partial response (PR) was defined as at least a 50% decrease of all measurable lesions. Minor response (MR) was defined as less than a 50% decrease of at least one of all measurable lesions. No response (NR) was defined by stability or progression of at least one of all measurable lesions. Complete response of bone lesions required the disappearance of pain in known tumour sites, plus evidence of recalcification of osteolytic metastases on X-ray and partial response required partial recalcification of osteolytic metastases on X-ray. These definitions are in agreement with the International Union against Cancer (UICC) guidelines [10]. Objective response was defined by the achievement of a complete or partial

response. Response assessed by the treating physician was reviewed by an independent physician from the Institute. Patients who died before 4 months of treatment ($n=166$) were evaluated as non-responders regardless of the cause of death (toxic or tumour progression).

All trials were therapeutically equivalent, i.e. similar response rates and survival. The data from individual trials were pooled to obtain a more reliable reference database. Response rates and median survival for the individual trials are given in Table 1.

2.4. Study design

The aim of this study was to evaluate predictive factors able to discriminate objective responders. Firstly, we performed univariate analysis of the parameters associated with objective response, including the clinical and laboratory characteristics of primary and metastatic tumours. Secondly, multivariate analysis was performed on the factors identified as significant in the univariate analysis in order to determine risk factors independently correlated with objective response. Finally, a predictive score was calculated from the main prognostic factors available for the majority of the patients. Use of this score can, therefore, predict the individual's response to chemotherapy for patients with metastatic breast cancer according to prognostic factors determined before

starting chemotherapy. We subsequently verified that overall survival was correlated with response rate.

2.5. Statistical methods

For categorical variables, initial statistical comparisons were performed with the Pearson χ^2 test. The odds ratio (OR) was used as the basic measure of the relative risk and is expressed with a 95% confidence interval (95% CI). A logistic regression model was used to estimate and test for the association of variables with response while simultaneously adjusting for variables included in the model. Variables associated with objective response on univariate analysis ($P < 0.20$) and with the year of breast cancer diagnosis were included in the multivariate analysis [11]. A forward stepwise logistic regression model was used, and the selection process at each step was based on a comparison of the maximised log-likelihoods.

A predictive score was calculated from the beta (β) coefficients estimated by the model for each variable. A simplified score was then derived from the five most important predictive variables in order to present a useful predictive score for clinical applications. Finally, this score was divided into three classes, according to high response rate ($> 80\%$ objective response), low response rate ($< 50\%$ objective response) and intermediate response rates. The score was also evaluated separately for patients with and without endocrine

Table 1
Response rates and survival in the individual trials

Trials	Patients (n)	Arms	Response	Overall median survival
SPM 77	144	AVEF + BCG AVEF alone	Overall RR 63% (NS) (Total: 25% CR + 38% PR)	21 m (NS)
SPM 78	233	AVEF \pm hormonotherapy AVEF alternating with VMM, \pm hormonotherapy	Overall RR 66% (NS) (Total: 22% CR + 44.5% PR)	24 m (NS)
SPM 80	79	AVEF + MPA AVEF + MPA + TAM	RR 48% RR 60% (NS) (Total: 11% CR + 42% PR)	24 m (NS)
SPM 81	247	TAM followed by TAM + ACF ACF + TAM ACF followed by TAM	RR 59% RR 74% (overall NS) RR 62% (Total: 20% CR + 45% PR)	26 m (NS)
SPM 83	82	ACF (various durations)	Not published	
SPM 85	94	AVCF FUCONTIN	RR 76% RR 60% (NS) (Total: 11% CR + 57% PR)	27 m (NS)
SPM 86	218	CFA + MPA (premenopausal) CFA (premenopausal) CFA + TAM (postmenopausal) CFA + TAM + diethylbesterol (postmenopausal)	Not published	
SPM 90	258	FAC FULON	RR 54% RR 53% (NS) (Total 14% CR + 40% PR)	22 m (NS)

See text for details of regimens. m, months; RR, response rate; NS, non significant; CR, complete response; PR, partial response.

therapy. The Hosmer–Lemeshow goodness-of-fit test was used to test the hypothesis that the model adequately fits the data. Observed objective response rates (ORR) were given for each class of the score. Survival time was measured from the date of entry into the study to the date of death or last follow-up. Survival curves were estimated using the Kaplan–Meier method and compared using the logrank test [12,13]. Statistical analysis was performed by BMDP software (BMDP statistical software, Inc., Los Angeles, CA, USA).

3. Results

3.1. Patient characteristics

The median age of the 1426 patients analysed was 54 years (range: 23–79 years) and 44.5% were premenopausal. The main patient characteristics at metastatic recurrence are summarised in Table 2.

Of the 1426 patients analysed, CR was achieved in 249 (17.5%) and PR was achieved in 658 (46.1%), corresponding to an ORR of 63.6% (95% CI 61.5–67.7). Minor responses were achieved in 257 (18.0%) patients, while 262 (18.4%) patients did not respond.

3.2. Objective response according to premetastatic characteristics (Table 3)

ORR was lower in women with T3–T4 or N1b–N2–N3 tumours at initial diagnosis compared with T0–T1–T2 or N0–N1a tumours (ORR for tumour size: 65.3% versus 71.7%; $P=0.05$ and ORR for nodal status: 58.9% versus 67.5%; $P=0.005$). Adjuvant chemotherapy, adjuvant endocrine therapy and negative oestrogen receptors were also associated with lower ORR ($P<0.001$, $P=0.02$ and $P=0.006$, respectively). However, progesterone receptors and SBR grade were not significantly correlated with ORR.

3.3. Objective response according to clinical and laboratory characteristics at the time of metastatic recurrence (Table 4)

Performance status (KI) <60 , weight loss $>7\%$, elevated LDH, SGOT $>3\times N$ (normal levels), low serum albumin and absolute lymphocyte count <800 (cells/ μ l) were all associated with an ORR less than 50% and alkaline phosphatase $>1\times N$ was associated with an ORR less than 60%; the associations with ORR were significant for each parameter with $P<0.001$. Premenopausal status was also correlated with a higher ORR ($P=0.005$). γ GT $>1\times N$ had an ORR of 60.9% and was also significant ($P=0.006$).

Table 2

(a) Patient characteristics at primary diagnosis and (b) at metastatic recurrence ($n=1426$)

	Patients <i>n</i> (%)
(a) Primary diagnosis	
Clinical tumour status (TNM)	
T0,T1,T2	510 (35.8)
T3,T4	331 (23.2)
NA	585 (41.0)
Clinical nodal status (TNM)	
N0,N1a	716 (50.2)
N1b,N2,N3	577 (39.1)
NA	133 (9.3)
SBR grade	
I	131 (9.2)
II	552 (38.7)
III	232 (16.3)
NA	511 (35.8)
Oestrogen receptor	
Positive	316 (22.2)
Negative	237 (16.6)
NA	873 (61.2)
Progesterone receptor	
Positive	290 (20.3)
Negative	380 (26.6)
NA	756 (53.0)
Adjuvant radiotherapy	1111 (77.9)
Prior surgery	900 (63.1)
Adjuvant chemotherapy	445 (31.2)
Adjuvant endocrine therapy	161 (11.3)
(b) Metastatic recurrence	
Year of randomisation	
1990–1992	266 (18.7)
1985–1989	332 (23.3)
1980–1984	471 (33.0)
1977–1979	357 (25.0)
Disease-free interval (months):	
0–6	203 (14.2)
6–12	79 (5.5)
12–24	238 (16.7)
≥ 24	906 (63.5)
Karnofsky index	
≥ 60	1130 (79.2)
< 60	248 (17.4)
NA	48 (3.4)
Recent weight loss	
$\leq 7\%$	981 (68.8)
$> 7\%$	219 (15.4)
NA	226 (15.8)
Postmenopause	
Site of metastases	
Bone	780 (54.7)
Lung	340 (23.8)
Pleura	325 (22.8)
Liver	462 (32.4)
Intra-abdominal	81 (5.7)
Skin	345 (24.2)
Lymph node	390 (27.3)
Contralateral breast	72 (5.0)
Local recurrence	293 (20.5)
Other	67 (4.7)
Number of sites	
1	514 (36.0)
≥ 2	912 (64.0)

NA, not available; SBR, Scarff–Blood–Richardson.

3.4. Objective response according to metastatic characteristics (Table 4)

Women with several metastatic sites achieved a lower ORR (59.0%) than women with only one metastatic site (72.0%) ($P < 0.001$). Lymph node metastases were associated with a higher ORR (69.3%) compared with patients without lymph node metastases (61.5%). Skin, intra-abdominal, ipsilateral and contralateral breast sites were not significantly associated with a lower ORR. All other sites of metastases were associated with a lower ORR. Moreover, patients treated before January 1980 achieved a lower ORR (56.6%) than those treated after 1980 (66.0%) ($P = 0.004$).

3.5. Multivariate analysis of factors predictive of non-response to first-line chemotherapy for metastatic disease (Table 5)

For all variables tested, the reference class was the class associated with the best objective response.

Absence of response was therefore the event studied in logistic regression in order to present the odds ratio like a risk factor (odds ratio greater than one). All variables found to be significant on univariate analysis were included in the multivariate analysis. For liver function tests, only the LDH level was included because of its very strong correlation with alkaline phosphatase, SGOT and γ GT. Fifteen variables were, therefore, selected for multivariate analysis. All variables, except disease-free interval from primary diagnosis and liver metastases, contributed significantly to the model. Following adjustment, the odds ratio associated with disease-free interval between 6 and 12 months decreased from 2.34 to 1.56. Similarly, following adjustment for elevated LDH and poor performance status, liver as the site of recurrence was no longer associated with resistance to first-line chemotherapy. By order of entry in the model, elevated LDH, poor performance status, prior adjuvant chemotherapy, the presence of lung or pleural metastases, low absolute lymphocyte count, the presence of bone metastases, prior adjuvant endocrine

Table 3

Univariate analysis of the influence of primary tumour characteristics on resistance to first-line chemotherapy for metastatic disease ($n = 1426$)

	Patients n (%)	Objective response ^a (%)	Odds ratio ^b	(95% CI)	P value
Clinical tumour status (TNM)					
T0,T1,T2	510 (35.8)	71.7	1.00		
T3,T4	331 (23.2)	65.3	1.34	(1.00–1.81)	0.05
NA	585 (41.0)				
Clinical nodal status (TNM)					
N0,N1a	716 (50.2)	67.5	1.00		
N1b,N2,N3	577 (39.1)	58.9	1.44	(1.15–1.83)	0.005
NA	133 (9.3)				
SBR grade					
I	131 (9.2)	68.5	1.00		
II	552 (38.7)	66.5	0.93	(0.62–1.39)	0.76
III	232 (16.3)	59.9	1.24	(0.79–1.93)	0.35
NA	511 (35.8)				
Oestrogen receptor					
Positive	316 (22.2)	70.6	1.00		
Negative	237 (16.6)	59.3	1.67	(1.17–2.37)	0.006
NA	873 (61.2)				
Progesterone receptor					
Positive	290 (20.3)	67.7	1.00		
Negative	380 (26.6)	63.1	1.23	(0.88–1.68)	0.21
NA	756 (53.0)				
Prior X-ray therapy					
No	315 (22.1)	68.2	1.00		
Yes	1111 (77.9)	61.6	1.30	(1.00–1.70)	0.05
Prior surgery					
No	526 (36.9)	60.6	1.00		
Yes	900 (63.1)	65.3	0.82	(0.65–1.02)	0.07
Adjuvant chemotherapy					
No	981 (68.8)	66.9	1.00		
Yes	445 (31.2)	56.4	1.56	(1.24–1.96)	< 0.001
Adjuvant endocrine therapy					
No	1265 (88.7)	64.8	1.00		
Yes	161 (11.3)	54.7	1.52	(1.09–2.12)	0.02

CI, confidence interval; NA, not available.

^a Complete or partial remission greater than 50%.

^b Absence of response was the event studied.

Table 4
Univariate analysis of the influence of clinical and laboratory characteristics at metastatic recurrence on resistance to first-line chemotherapy (n = 1426)

	Patients n (%)	Objective response ^a (%)	Odds ratio ^b (95% CI)	P value
Karnofsky index				
≥ 60	1130 (79.2)	67.5	1.00	
< 60	248 (17.4)	44.8	2.57 (1.94–3.39)	< 0.001
NA	48 (3.4)			
Recent weight loss				
≤ 7%	981 (68.8)	68.0	1.00	
> 7%	219 (15.4)	49.3	2.18 (1.62–2.94)	< 0.001
NA	226 (15.8)			
Menopause				
No	634 (44.5)	67.8	1.00	
Yes	792 (55.5)	61.2	1.39 (1.12–1.73)	0.005
LDH (units)				
≤ 1×N	1039 (72.9)	68.4	1.00	
> 1×N	295 (20.7)	48.4	2.30 (1.77–2.99)	< 0.001
NA	92 (6.5)			
Alkaline phosphatase (units)				
≤ 1×N	959 (67.3)	77.0	1.00	
> 1×N	363 (25.5)	55.1	1.66 (1.30–2.12)	< 0.001
NA	104 (7.3)			
γGT (units)				
≤ 1×N	433 (30.4)	69.3	1.00	
> 1×N	658 (46.1)	60.9	1.45 (1.12–1.88)	0.006
NA	335 (23.5)			
AST (units)				
≤ 3×N	1129 (79.2)	66.2	1.00	
> 3×N	172 (12.1)	48.3	2.11 (1.52–2.91)	< 0.001
NA	125 (8.8)			
Albumin (g/l)				
≥ 1×N	1090 (76.4)	64.9	1.00	
< 1×N	61 (4.3)	32.7	3.79 (2.19–6.57)	< 0.001
NA	275 (19.3)			
Lymphocyte count (cells/μl)				
≥ 800	956 (67.0)	67.6	1.00	
< 800	263 (18.4)	48.7	2.20 (1.67–2.90)	< 0.001
NA	207 (14.5)			
Year of randomisation				
1990–1992	266 (18.7)	65.9	1.00	
1985–1989	332 (23.3)	69.3	0.84 (0.60–1.18)	0.86
1980–1984	471 (33.0)	63.9	1.07 (0.78–1.46)	0.68
1977–1979	357 (25.0)	56.6	1.45 (1.05–2.02)	0.03
Disease-free interval (months):				
0–6	203 (14.2)	68.5	1.00	
> 6–12	79 (5.5)	48.1	2.34 (1.38–3.99)	0.003
> 12–24	238 (16.7)	58.0	1.57 (1.06–2.33)	0.03
≥ 24	906 (63.5)	65.3	1.15 (0.83–1.60)	0.40
Site of metastases				
Bone				
No	646 (45.3)	67.3	1.00	
Yes	780 (54.7)	61.3	1.35 (1.08–1.67)	0.01
Lung				
No	1086 (76.2)	66.8	1.00	
Yes	340 (23.8)	53.5	1.74 (1.36–2.23)	< 0.001
Pleura				
No	1101 (77.2)	67.1	1.00	
Yes	325 (22.8)	52.0	1.88 (1.46–2.41)	< 0.001
Liver				
No	964 (67.6)	66.5	1.00	
Yes	462 (32.4)	61.6	1.46 (1.16–1.64)	0.002
Peritoneum				
No	1345 (94.3)	62.0	1.00	
Yes	81 (5.7)	58.1	1.28 (0.81–2.02)	0.28

(continued on next page)

Table 4 (continued)

	Patients <i>n</i> (%)	Objective response ^a (%)	Odds ratio ^b (95% CI)	<i>P</i> value
Skin				
No	1081 (75.8)	62.7	1.00	
Yes	345 (24.2)	63.5	1.01 (0.78–1.30)	0.96
Lymph node				
No	1036 (72.7)	61.5	1.00	
Yes	390 (27.3)	69.3	0.71 (0.55–0.91)	0.005
Contralateral				
No	1354 (95.0)	65.4	1.00	
Yes	72 (5.0)	63.9	0.99 (0.60–1.62)	0.96
Local relapse				
No	1133 (79.5)	63.8	1.00	
Yes	293 (20.5)	63.1	1.03 (0.79–1.34)	0.85
Other				
No	1359 (95.3)	63.5	1.00	
Yes	67 (4.7)	63.7	0.91 (0.54–1.52)	0.72
Number of sites				
1	514 (36.0)	72.0	1.00	
≥2	912 (64.0)	59.0	1.78 (1.41–2.25)	<0.001

CI, confidence interval, NA, not available; LDH, lactate dehydrogenase; AST, aspartate aminotransferase.

^a Complete or partial response.

^b Absence of response was the event studied.

therapy, recent weight loss, postmenopausal status, low oestrogen receptor levels, lymph node metastases, and more than one metastatic site were successively included in a forward stepwise regression model.

Compared with women with normal LDH, those with LDH > 1×N (330 IU/l) always presented an increased risk of resistance to chemotherapy (adjusted odds ratio (aOR) = 1.88, 95% CI: 1.40–2.53; *P* < 0.001). Following adjustment, in particular for performance status, the odds ratio of women with recent weight loss decreased from 2.18 to 1.59, while remaining significantly correlated with poor response (*P* = 0.01). The odds ratio of women with absolute lymphocyte counts < 800 cells/μl decreased from 2.20 to 1.70, again remaining significant. Postmenopausal women, those with lower oestrogen receptor levels and those who had received adjuvant chemotherapy or endocrine therapy also had lower response rates, independently of all other variables. Moreover, the impact of the site of metastatic recurrence on response was not modified after adjustment, although the influence of several metastatic sites decreased slightly from 1.78 to 1.48 (*P* = 0.01).

3.6. Response rate according to prognostic score

A modified model was then constructed using the five dominant variables identified by the previous model. A predictive score was derived from the coefficients calculated by this model:

Score = $-1.32 + 0.54$ (if prior adjuvant chemotherapy) + 0.80 (if performance status less than 60) + 0.75 (elevated LDH) + 0.49 (if presence of lung metastases) + 0.51 (pleural metastases).

The median score for the entire patient population was -0.78 (range: -1.32 – 1.77). A low score (less than -0.78) was associated with an ORR greater than 80.0%, representing 41.2% of our population. An intermediate score (between -0.78 and 0) was associated with an ORR of 50.0–80.0%, representing 37.5% of patients. A score greater than 0 was associated with an ORR of less than 50.0%, representing 21.3% of the patient population.

The chance of achieving an objective response therefore decreased as the score increased. For example, the 78 patients of our study without prior adjuvant chemotherapy, with a performance status greater than or equal to 60, LDH less than or equal to 1×N, but with lung metastases and no pleural metastases had a score of -0.81 . The observed ORR was 72.2%, and a model predicted an objective response rate of 69.2%. The 29 patients of the study without prior adjuvant chemotherapy, with a performance status less than 60, normal LDH, but without lung and pleural metastases had a score of 0.23. The observed ORR was 44.8%, and the model predicted an ORR of 44.3%. Prospective testing of this index will be performed on a different patient population.

3.7. Correlation between response, score and survival

The median survival for the population with an objective response (complete and partial response) was 32 months which compared favourably with a median survival of 10 months for the patients who did not respond (logrank test; *P* < 0.001). Death occurred before 24 months for more than 70% of subjects who failed to respond to chemotherapy. Median survival was 35

months in the low score group, 24 months in the intermediate score group and only 13 months in the high score group (logrank test; $P < 0.001$) (Fig. 1).

4. Discussion

The aim of the present study was to determine a predictive score of response in metastatic breast cancer based on a multitude of clinical and laboratory parameters. ORRs for metastatic breast cancer reported in the literature vary between 33% and 77% depending on the presentation of the disease [10]. In the present series of 1426 patients, we observed an overall objective response rate of 63.6%, which is comparable with the ORR of 65% reported by Rahman and colleagues [14]

in a series of 1581 patients with metastatic breast carcinoma treated with doxorubicin-containing combination chemotherapy at a single institution.

Many pretreatment characteristics are correlated with response to therapy and 15 out of more than 30 parameters remained significantly associated with absence of response to chemotherapy on multivariate analysis. The large number of parameters selected may be due to the large number of patients allowing inclusion of parameters with low, but significant odds ratios. Most of the factors predictive for response were closely correlated with survival.

Adjuvant chemotherapy improved patient outcome mainly by reducing the incidence of relapse [15]. In agreement with previous studies, our data indicate that prior adjuvant chemotherapy is one of the main adverse

Table 5
Multivariate analysis of 13 factors most strongly predictive of resistance to first-line chemotherapy ($n = 1426$)

	Crude odds ratio	Adjusted odds ratio	(95% CI)	P value
Menopause				
No	1.00	1.00		
Yes	1.39	1.37	(1.08–1.75)	0.01
Oestrogen receptor				
Positive	1.00	1.00		
Negative	1.67	1.57	(1.06–2.34)	0.02
Adjuvant chemotherapy				
No	1.00	1.00		
Yes	1.56	1.62	(1.24–2.11)	<0.001
Adjuvant endocrine therapy				
No	1.00	1.00		
Yes	1.52	1.68	(1.16–2.44)	0.008
Karnofsky index				
≥ 60	1.00	1.00		
< 60	2.57	1.50	(1.08–2.08)	0.01
Recent weight loss				
$\leq 7\%$	1.00	1.00		
$> 7\%$	2.18	1.59	(1.13–2.22)	0.009
Lymphocyte count (cells/ μ l)				
≥ 800	1.00	1.00		
< 800	2.20	1.70	(1.26–2.30)	<0.001
LDH				
$\leq 1 \times N$	1.00	1.00		
$> 1 \times N$	2.30	1.88	(1.40–2.53)	<0.001
Site of metastases				
Lung				
No	1.00	1.00		
Yes	1.74	1.73	(1.31–2.29)	<0.001
Pleura				
No	1.00	1.00		
Yes	1.88	1.51	(1.12–2.02)	0.008
Lymph node				
No	1.00	1.00		
Yes	0.71	0.67	(0.49–0.91)	0.01
Bone				
No	1.00	1.00		
Yes	1.35	1.36	(1.05–1.79)	0.02
Number of sites				
1	1.00	1.00		
> 2	1.78	1.46	(1.10–1.95)	0.01

LDH, lactate dehydrogenase; CI, confidence interval.

factors correlated with low ORR [16–18]. This could be related to the prescription of adjuvant chemotherapy in patients with more aggressive tumours (node-positive, ER-negative). Nevertheless, in our series as in others [17], adjuvant chemotherapy was an independent prognostic factor at multivariate analysis, taking into account primary tumour characteristics. One explanation could also be the ability of adjuvant chemotherapy to induce persistent drug resistance [19,20].

Anthracycline-containing regimens, in several randomised trials, achieved longer times to progression and occasionally longer survival than other reference CMF-based chemotherapy combinations [2]. In the series reported by Gregory and associates [21], the only factor predictive of response, among the factors recorded at presentation and at initiation of chemotherapy, was the use of anthracycline-based regimens. In our series, all patients received anthracycline-based chemotherapy, so a major difference in the type of chemotherapy could not influence our analysis. Some of the trials included hormone therapy which may have modified response, either directly or indirectly through interaction with chemotherapy. Therefore, the validity of the score was evaluated separately for patients treated with chemotherapy with and without endocrine therapy and the results were the same if the hormone therapy trials were excluded.

The number of sites was also a major prognostic factor. More than one site was a adverse factor, even after adjustment for the site of metastasis, in agreement with the literature. Patients with disease confined to the skeleton had a better prognosis than patients who developed metastatic disease in non-bone sites [22]. Bone, as

well as lung and pleural sites were also independently correlated with low ORR, in contrast with lymph node involvement, thereby confirming previous studies [23]. Bone metastases were associated with better survival, but were not correlated with a high response rate to chemotherapy. Liver metastasis has been reported to be a factor of poor survival [24]. In our study, the association between liver metastases and low ORR was no longer observed after adjustment for laboratory markers of liver involvement (LDH and alkaline phosphatase). Serum LDH was selected by multivariate analysis and proved to be indicative of an unfavourable outcome for metastatic breast cancer patients in our study. Although Hortobagyi and colleagues [23] were the first to report the clinical importance of serum LDH for survival of metastatic breast cancer patients, most survival analyses do not refer to the significance of serum LDH. It is one of the most important indicators for survival in other malignant solid tumours such as lung cancer, aggressive non-Hodgkin's lymphoma or sarcoma and reflects tumour burden [25]. Similarly, in metastatic breast cancer, serum LDH reflects the aggressiveness of the disease.

Hormonal receptor-positive tumours (ER-positive) are more likely to recur in the bone with a better outcome and ER-negative tumours are more likely to recur in the viscera and brain with a poorer outcome [3,26–28]. Other factors could have a more important prognostic impact on metastatic breast cancer than receptor status. No data were available for either receptor status in many patients.

Breast cancer is much less frequent among women under the age of 35 years than in women over the age of

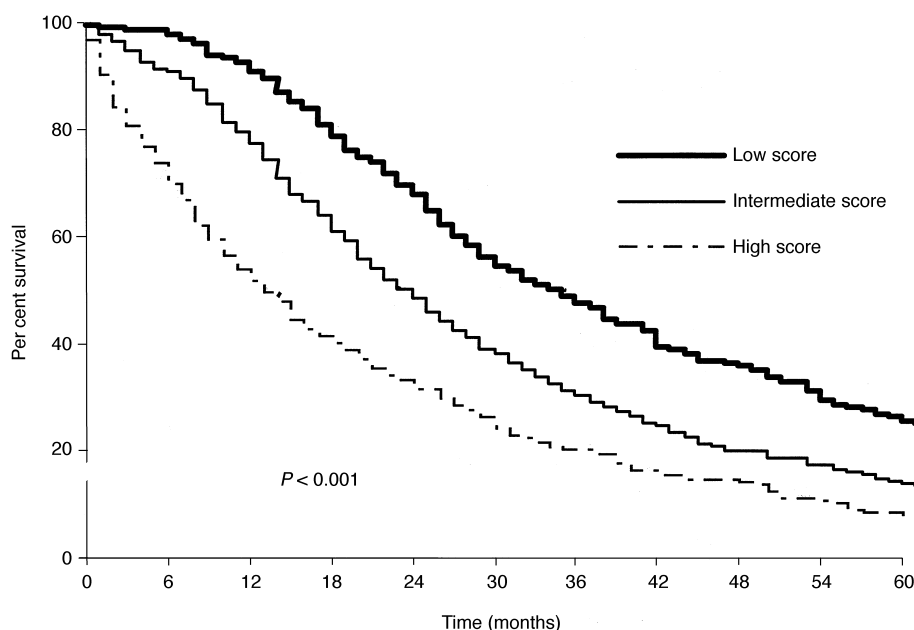


Fig. 1. Overall survival of 1296 patients with metastatic breast cancer according to predictive score of response.

35 years. Nevertheless, progression towards metastatic breast cancer and overall survival of these women is unfavourable (OR = 0.68; 0.39–1.18). We did not find a significantly different ORR compared with women aged between 35 and 50 years, probably because of the small sample size of women aged less than 35 years ($P=0.16$). Nevertheless, after adjustment, postmenopausal patients were found to have a lower response rate to chemotherapy. They are possibly more hormone-sensitive than younger patients. Adjuvant chemotherapy has a greater impact in premenopausal patients [15] and the action of chemotherapy could be due partially to the suppression of ovarian function.

Disease-free interval is an important factor reflecting the growth rate of the disease and has been shown to be one of the most reliable factors to assess the behaviour of the disease [25,29,30–32]. On univariate analysis, only disease-free interval between 12 and 24 months was correlated with a low response rate, and no relationship was observed between disease-free interval and ORR after adjustment. Most of the patients with a disease-free interval shorter than 6 months were not in early relapse, but were primary diagnosed metastatic breast cancer.

As each predictive factor may be individually helpful in predicting survival, more comprehensive information concerning prognosis might have been obtained by using some or all of these factors in combination. Several authors have published prognostic indexes of survival for patients with metastatic breast cancer, but a prognostic index for response to chemotherapy has never been previously described [33]. Many studies concerning predictive factors for metastatic breast cancer have considered overall survival. The prognostic factors identified by Dunphy included liver metastases and disease-free interval from breast diagnosis to metastatic disease of less than 1 year [34]. Nash identified these two factors to be prognostic factors correlated with ORR [35]. In our study, these characteristics, traditionally considered to be predictive, were not correlated with ORR on multivariate analysis. Multivariate analysis can identify the independent influence of several premetastatic, laboratory and metastatic characteristics, and especially can be used to calculate a simple prognostic score based on the main prognostic factors. Hortobagyi and associates reported a prognostic score obtained on 546 patients [23]. Variables were selected by stepwise regression analysis into three subgroups of factors. The first group contained history factors, the second group consisted of laboratory factors and the last group consisted of metastatic characteristics. The five main variables selected were weight loss; raised alkaline phosphatase; low haemoglobin; and prior radiotherapy. Robertson and colleagues confirmed an index for predicting survival in patients treated by primary endocrine therapy, including histological grade, oestrogen receptor

status, site of initial metastasis and disease-free interval [30]. This index was constructed retrospectively on 191 patients using a Cox multivariate analysis [36]. A similar retrospective study in 613 patients identified much the same factors (histological grade, site of first recurrence, and disease-free interval), but the authors did not combine them to produce an index [32].

As many phase II studies are based on the response rate in order to evaluate the efficacy of a new drug or a new combination of drugs, we focused our study on the prediction of response. Our score was derived from stepwise regression analysis including all historical, laboratory and metastatic characteristics in the same model. This method allowed us to assess the independent effect of each historical, laboratory and metastatic prognostic factor. Our simplified prognostic score then respected the five main factors available for more than 95% of our subjects. Adjuvant chemotherapy, performance status, LDH, lung and pleural metastases were included in our score and comparison of the observed and predicted ORRs then showed an excellent correlation. A low score was correlated with an ORR of greater than 70% with a median survival of 35 months and a high score was correlated with an ORR of less than 50% with a median survival of 13 months. This derived score was therefore well correlated with overall survival, as ORR is correlated with overall survival.

Prognostic factors correlated with ORR have to be studied individually in order to isolate independent predictive factors. The main advantage of a prognostic score is the ability to adapt new treatment strategies according to the value of the score. Patients with a low probability of response should receive alternative treatments. For patients with a poor general status (high LDH, low Karnofsky index, multiple metastatic sites), continuous 5-FU is usually used in our department [37]. As this score is based on the response to first-line anthracycline-based chemotherapy, the use of taxanes should be specifically evaluated [38,39]. Different chemotherapy regimens of greater or sometimes even similar efficacy may be associated with predictive or prognostic factors that are very different from those described here.

However, the influence of pretreatment factors independently of the treatment protocol could explain some of the long-term complete responses. A small percentage of patients can achieve complete remission and remain disease-free for a long time. New strategies, such as intensification or consolidation, are therefore required to increase the long-term survival rate in this group [7].

In conclusion, survival in our study was strongly correlated with response and most prognostic factors for response are also predictive factors for survival. By combining the clinical and laboratory factors selected by the Cox model, response to first-line anthracycline-based chemotherapy can be predicted more accurately

than by using any of these factors individually. The prognostic index provides a better separation of survival curves between groups. This index now needs to be evaluated prospectively in a new group of patients with metastatic breast cancer. Identification of different risk groups could also help in the design and interpretation of clinical trials. This type of score should be evaluated in trials of new drugs such as taxanes now used in first-line treatment. Alternative treatment should be used in the poor prognostic group.

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