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Original Paper

Locally Advanced Non-metastatic Breast Cancer: Analysis of Prognostic Factors in 125 Patients Homogeneously Treated with a Combined Modality Approach

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125 stage III breast cancer patients, including 51 cases of inflammatory carcinoma, were treated with the following combined modality approach: three courses of primary 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) chemotherapy followed by locoregional treatment and subsequent adjuvant chemotherapy consisting of three courses of FAC alternating with three courses of cyclophosphamide, methotrexate, 5-fluorouracil (CMF). Clinical response to primary FAC was 65% (complete 10%). Residual tumour mass in the mastectomy specimen was >1 and ≤1 cm in 82 and 18% of cases, respectively. Complete pathological response following primary chemotherapy was achieved in only 3.5% of cases. After primary FAC and local treatment, 97% of patients were disease-free. Overall survival (S) and progression-free survival (PFS) at 5 years were 56 and 34%, respectively. Univariate analysis showed that age, receptor status and clinical and pathological response to primary chemotherapy did not appear to influence treatment outcome significantly, whereas stage, presence of inflammatory disease and number of involved nodes had a significant impact on both S and PFS.

Key words: breast cancer, locally advanced, multimodality treatment, prognostic factors, univariate analysis
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INTRODUCTION

THE TERM locally advanced breast cancer (LABC), defined as stage III by the American Joint Committee, describes a heterogeneous disease that is associated with high mortality following locoregional treatment alone. LABC is not a rare finding since it represents approximately 20% of breast cancer patients [1]. In a retrospective analysis of 109 LABC patients treated with radical mastectomy, Haagensen and Stout reported a 5-year local recurrence rate of 48% and no patient cured at 8 years of follow-up [2]. Radiation therapy subsequently became the conventional treatment for this disease. Even though radiation therapy results in local control of disease in over 70% of patients [3, 4], 5-year overall survival rates are only 13–24% [5–7]. In selected series of patients, combined mastectomy and radiation programmes have yielded improved local control and 5-year survival rates that vary from 38 to 45% [7, 8]. However, the majority of women die of metastatic disease, indicating that occult micrometastases are present at the time of diagnosis. Various reports have suggested that survival can be improved by using chemotherapy in association with surgery and/or radiotherapy [9–11]. In the present study, the impact on disease outcome of various patient and tumour characteristics is analysed in a large series of stage III breast cancer patients homogeneously treated with a combined modality approach consisting of three courses of primary chemotherapy followed by surgery and/or radiotherapy and subsequent adjuvant chemotherapy.

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PATIENTS AND METHODS

From September 1983 to December 1989, 135 consecutive patients with LABC presented at the oncology ward. Review showed that of the 135 patients, 5 had metastatic disease at diagnosis, 4 refused chemotherapy and 1 patient was lost to follow-up after her first cycle of chemotherapy. Therefore, 125 patients with stage III non-metastatic LABC are the object of

this retrospective analysis. Patients received three cycles of primary 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) chemotherapy followed by locoregional treatment and adjuvant chemotherapy comprising one course of FAC alternated with one course of cyclophosphamide, methotrexate, 5-fluorouracil (CMF) for a total of six cycles. Therefore, patients received a total of nine courses of cytotoxic therapy.

Pretreatment evaluation

Pretreatment evaluation included history, physical examination, complete blood count, complete blood chemistries, ECG, chest X-ray, bone scan and liver ultrasonogram if indicated. Breast lesions were evaluated by physical and mammographic examination. All patients had a biopsy-proven diagnosis of breast cancer and no evidence of distant metastases. Only patients with normal renal function (serum creatinine ≤ 1.5 mg/dl), serum bilirubin ≤ 2 mg/dl and adequate bone marrow function white blood cell count ((WBC) $\geq 4000/mm^3$, Hb ≥ 11 mg/dl, platelet count $\geq 150000/mm^3$) entered the programme. Informed consent was required.

Primary chemotherapy

Primary FAC chemotherapy consisted of 5-fluorouracil 600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 600 mg/m^2, on day 1, every 3 weeks. After three courses the patients were evaluated for response and operability.

Locoregional treatment

Patients with responding or stable disease and technically operable lesions underwent surgery within 3 weeks after completion of primary FAC chemotherapy. The preferred surgical procedures were modified radical or radical mastectomy. In addition, patients with inflammatory breast cancer (IBC) and patients with ipsilateral supraclavicular involvement received radiation treatment within 4 weeks of termination of adjuvant therapy.

Inoperable cases and those patients who refused surgery, in whom there was no evidence of distant metastases, underwent radiation treatment. Radiation treatment in patients not undergoing surgery consisted of 50 Gy in 25 fractions over 5 weeks to the breast and draining lymph node areas with a boost (10 Gy/five fractions) limited to the tumour.

Adjuvant treatment

Locoregional treatment was followed within 4 weeks by adjuvant chemotherapy comprising one cycle of FAC alternated with 1 cycle of CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2) every 3 weeks for a total of six courses (three FAC and three CMF). No dose modifications for haematologic toxicity on day 21 were allowed and treatment was delayed until marrow recovery (WBC $\geq$ 3500/mm^3 and platelet count $\geq 100000/mm^3$) was evident. None of the patients received adjuvant endocrine therapy.

Prognostic variables

The following prognostic variables were studied: age at diagnosis; stage of disease (IIIA or IIIB); presence of IBC characterised clinically by diffuse brawny induration of the skin of the breast with an erysipeloid edge (with or without an underlying palpable mass), rapidly appearing in a previously healthy breast. The pathologic documentation of dermal lymphatic invasion was not considered mandatory for the diagnosis of IBC [12, 13].

Tumour oestrogen receptor status was also studied, determined by the dextran-coated charcol method; values ≥ 10 fmol/mg cytosol protein was considered positive. Response to primary FAC was another prognostic variable, assessed by physical examination at each cycle and, after three cycles, by both physical and mammographic examination. Clinical response was evaluated by both the medical and surgical oncologist. Responses were assessed according to the International Union Against Cancer guidelines. Complete response (CR) was defined as complete disappearance of all objective evidence of disease. Partial response (PR) required a decrease of 50% or more in the sum of the products of perpendicular diameters of measurable disease. Stable disease (SD) was defined as a decrease $<50\%$ or an increase $<25\%$ in the sum of the products of perpendicular diameters of measurable disease providing no new lesions appeared during the study. Progressive disease (PD) required an increase at $\geq 25\%$ in the sum of the products of perpendicular diameters of measurable lesions, or new lesions appearing during study. The criteria for CR and PR had to be satisfied on at least two consecutive evaluations at least 1 month apart.

Finally, residual tumour size after primary chemotherapy, determined by measuring the largest tumour diameter in the mastectomy specimen, and number of positive axillary nodes (as determined pathologically at the time of surgery) categorised as none (N$-$), one to two positive nodes (N 1–3), four or more positive nodes (N 4+) were studied.

Statistical methods

Survival time was calculated in months from the date of the first cycle of primary chemotherapy to death or to the date of the last observation for those patients still alive. Progression-free survival was the number of months from the date of the first cycle chemotherapy to progression or to the date of the last observation for those patients still progression-free. Survival and progression-free survival were calculated by the Kaplan–Meier method [14]. The statistical significance of the difference between curves was calculated by the log-rank test [15].

RESULTS

Characteristics of the 125 patients with locally advanced breast cancer are shown in Table 1 and a detailed description of the extent of local disease is reported in Table 2. Of the 125 patients, median age 54 years (range 23–76), 27 had stage IIIA disease and 98 stage IIIB, including 51 cases of IBC. 5 patients with IBC

Table 1. Patients' characteristics at diagnosis

	No.	%
Total no. of patients	125	100
Age (median 54 years; range 23–76)		
≤ 50 years	50	40
>50 years	75	60
Stage		
IIIA	27	22
IIIB	98	78
Inflammatory carcinoma		
Yes	51	41
No	74	59
Receptor status		
ER positive	47	48
ER negative	51	52
ER unkown	27	—

ER, oestrogen receptor.

Table 2. Clinical stage at diagnosis

Stage	No. of patients
IIIA (27 patients)	
T2 N2	4
T3 N0	1
T3 N1	13
T3 N2	9
IIIB non-inflammatory (47 patients)	
T4a–c N0	10
T4a–c N1	20
T4a–c N2	13
T4a–c N3*	3
T1 N3*	1
IIIB inflammatory (51 patients)	
T4d N1–2	46
T4d N3*	5

*Metastasis to ipsilateral supraclavicular lymph nodes (stage IV according to the 1987 AJC TNM classification).

and 4 patients with non-IBC stage IIIB disease showed clinical evidence of metastatic disease to the ipsilateral supraclavicular lymph nodes.

Clinical response and locoregional treatment

The overall response rate to primary FAC chemotherapy was 64.8% [95% confidence interval (CI): 54.8–72.6%]. CR was observed in 12 (9.6%) patients and PR in 69 (55.2%) cases. Disease was stable in 40 (32.0%) patients and 4 (3.2%) patients progressed during primary treatment. The 4 patients with PD after primary FAC (3 stage IIIB non-IBC and 1 IBC) were given alternative cytotoxic treatment with CMF and radiation therapy. The 121 patients with responding or SD (27 stage IIIA disease, 44 stage IIIB non-IBC and 50 IBC) underwent locoregional treatment which consisted of surgery alone in 27 (100%) patients with stage IIIA and 39 (89%) patients with stage IIIB non-IBC; surgery plus radiotherapy in 46 (92%) patients with IBC and 3 patients with stage IIIB non-IBC who had involved supraclavicular lymph nodes; and radiotherapy alone in 6 patients who refused surgery (4 IBC and 2 stage IIIB non-IBC, including 1 patient with supraclavicular involvement). Clinical response to primary FAC in these 6 patients was as follows: 1 CR, 4 PR and 1 SD.

Pathological response

Pathologic examination at mastectomy showed that the primary tumour was >1 cm in its greatest dimension in 94/115 (82%) patients and ≤1 cm in 21/115 (18%) patients, including 4 (3.5%) cases with no pathologic evidence of disease in the breast and axillary nodes (pathological CR). Axillary node status was not available in 12 of 115 patients undergoing surgery. Therefore, in 103 patients a median number of 14 axillary nodes were examined (range four to 33) and no nodal involvement was shown in 11 (10.7%) patients, one to three involved nodes in 29 (28.2%), four to nine positive nodes in 33 (32%) and ≥10 involved nodes in 30 (29.1%) cases.

Patient survival and recurrence

After primary therapy and locoregional treatment, 121 of 125 patients (97%) were disease-free. The subsequent six cycles of adjuvant chemotherapy were completed at the prescribed doses in 104/121 (86%) patients. Reasons for earlier discontinuation included disease progression (3 patients), toxicity (3 patients), treatment refusal (11 patients).

All patients were considered for survival analysis. At a median follow-up of 48 months (range 12–80), 60 of 125 patients relapsed and 35 patients died. Median survival has not been reached. Median progression-free survival (PFS) was 39 months. First site of relapse was locoregional alone in 33 cases, at distant sites alone in 20 patients and both locoregional and distant metastases were observed in 7 patients. Locoregional relapse, whether or not associated with concomitant distant metastases, occurred in 6/27 (22%) patients with stage IIIA, 7/47 (15%) patients with stage IIIB non-IBC and 27/51 (53%) patients with IBC. Of the latter 27 IBC patients, distant metastses were detected concomitantly with locoregional relapse in 5 patients; in 11 cases, distant metastases occurred within a few months of the first evidence of locoregional failure.

The impact on both survival and PFS of patients' and disease characteristics is shown in Table 3 and 4, respectively. Data demonstrate that age, response to primary chemotherapy and amount of residual disease found at surgery did not influence either survival or PFS. Stage IIIA patients had a significantly improved survival and PFS compared with patients with stage IIIB disease. Inflammatory disease was associated with significantly decreased survival and PFS. Survival and PFS of patients according to stage and presence of IBC is shown in Figure 1. In patients undergoing surgery, cases with one to three involved axillary nodes had significantly improved survival and PFS compared to patients with four or more positive nodes. As

Table 3. Actuarial survival according to prognostic variables

		Survival (%)		
	Deaths/total	3 years	5 years	*P*
All patients	35/125	68.4	56.1	
Age at entry				
≤50 years	14/50	68.7	60.0	
>50 years	21/75	68.0	53.4	0.73
ER status (fmol)				
≥10	9/47	81.5	70.7	
<10	18/51	63.4	44.8	0.07
Stage				
IIIA	4/27	95.7	79.0	
IIIB	31/98	60.6	49.1	0.05
Inflammatory				
No	14/74	77.8	66.5	
Yes	21/51	57.4	44.0	0.024
No. of involved nodes				
0	2/11	NR	NR	
1–3	2/29	89.8	89.8	
>3	22/63	66.0	43.8	0.003
Clinical response				
CR+PR	22/81	66.9	62.1	
SD+PD	13/44	72.3	36.1	0.60
Size of residual mass				
≤1 cm	7/21	72.0	64.0	
>1 cm	22/94	72.9	57.9	0.66

NR, not reliable due to limited number of events; ER, oestrogen receptor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Actuarial and median progression-free survival (PFS) according to prognostic variables

	Relapsed/ total	PFS (%) 3 years	5 years	Median PFS (months)	P
All patients	60/125	50.2	34.2	39	
Age at entry					
≤50 years	26/50	47.2	36.7	36	
>50 years	34/75	52.6	31.8	39	0.85
ER status (fmol)					
≥10	23/47	55.7	35.7	54	
<10	25/51	47.8	34.0	36	0.51
Stage					
IIIA	7/27	84.8	53.9	72	
IIIB	53/98	40.5	28.6	22	0.004
Inflammatory					
No	26/74	67.9	42.9	58	
Yes	34/51	29.1	23.3	18	0.001
No. of nodes					
0	2/11	NR	NR	NR	
1–3	10/29	76.6	47.1	59	
>3	35/63	40.3	29.5	25	0.01
Clinical response					
CR+PR	39/81	51.9	38.4	40	
SD+PD	21/44	47.7	21.8	36	0.60
Size of residual mass					
≤1 cm	9/21	63.2	47.4	47	
>1 cm	42/94	52.2	33.0	46	0.50

See Table 3 for abbreviations.

Figure 2 shows, survival at 5 years was 90 and 44% in patients with one to three and four or more positive nodes, respectively ($P = 0.003$). Due to the small number of patients involved, the impact of receptor status on survival and PFS was not statistically significant. However, an 18% difference in survival at 3 years and a 25% difference at 5 years in favour of oestrogen-receptor positive tumours was observed.

DISCUSSION

Our results show that 5-year survival was significantly decreased in patients with stage IIIB disease compared with stage IIIA, with inflammatory disease compared with patients with no inflammatory component and with more than three involved axillary nodes versus one to three involved nodes. Although not statistically significant, a trend showing improved PFS and survival for oestrogen-receptor-positive tumours was observed. Age, response to primary chemotherapy and amount of residual disease at surgery were not found to have an impact on disease outcome (Tables 3 and 4).

Objective response to the initial three courses of FAC was observed in 65% of patients, with a clinical CR occurring in 10% of cases. Using a fixed number of courses of FAC before local treatment, Hortobagyi and coworkers reported overall response and CR rates of 83 and 15%, respectively [16]. In a more recent large series by Perloff and associates, clinical response to the initial three courses of chemotherapy was 77% and CR occurred in 22% of cases [10]. Overall response observed in the present series to primary FAC is comparable, although CR was less frequently observed than in the above reports. Higher rates of response have been obtained using a flexible number of primary

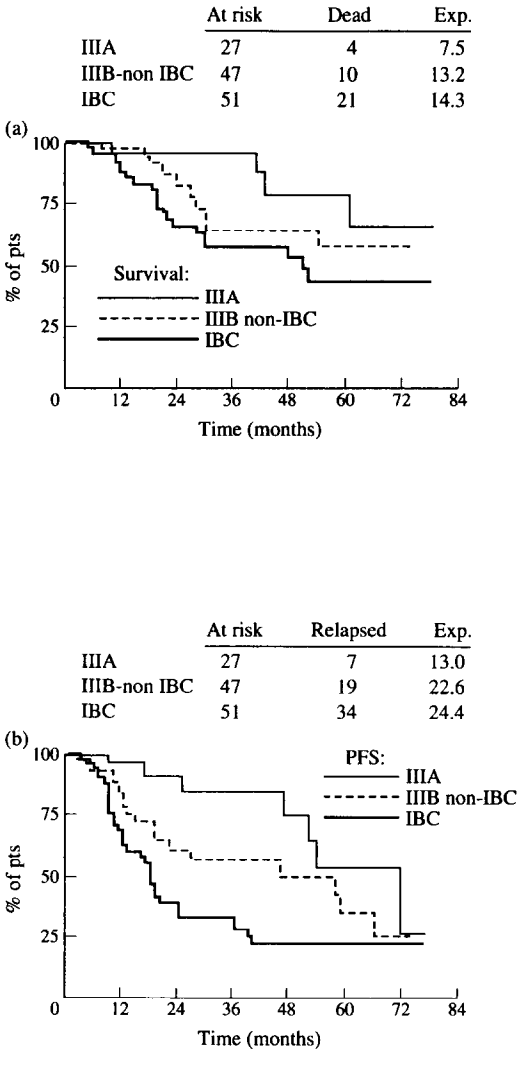

Figure 1. Survival curves according to stage and presence of inflammatory breast cancer (IBC). (a) Overall survival (stage IIIA versus IBC: $P = 0.01$; stage IIIB non-IBC versus IBC: $P = 0.1$). (b) Progression-free survival (stage IIIA versus IBC: $P < 0.001$; stage IIIB non-IBC versus IBC: $P = 0.04$).

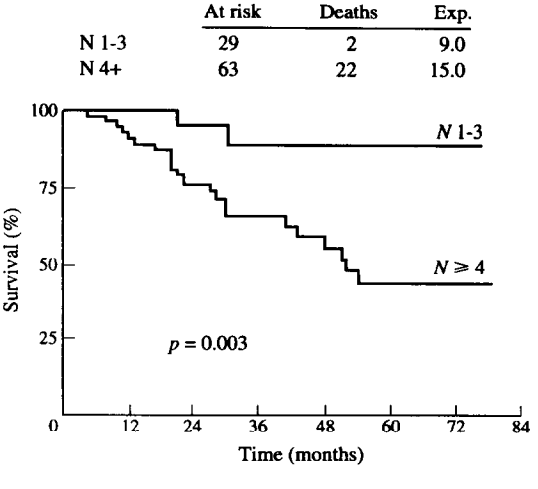

Figure 2. Survival according to number of involved nodes.

chemotherapy courses. In fact, Swain and colleagues observed that objective response could be obtained in 93% and CR in 49% of 76 LABC patients after three to five cycles of cytotoxic treatment [17]. Since overall median disease-free survival was 34 months in the above study and 39 months in the present series, improved response of the primary tumour to chemotherapy does not appear to affect final disease outcome greatly.

Kantarjian and colleagues showed that there was only a trend toward prolongation of the disease-free interval in complete responders compared with partial responders and patients with SD [18]. Results from the present series showed that patients with clinically SD after the initial three courses of FAC did not have a greater risk of relapse and death than responding patients. In addition, patients in whom residual disease at mastectomy was more than 1 cm had comparable survival and PFS to patients in whom residual disease was less than 1 cm (Tables 3 and 4). Although pathological response criteria are not completely comparable to those adopted in the present study, Feldman and colleagues reported that the amount of residual disease in the mastectomy specimen significantly influenced prognosis [19]. In conclusion, although some indication exists that clinical and pathologic response to primary chemotherapy is correlated with PFS and survival, no relationship was observed in the present series. Skipper and coworkers when outlining the basic principles for the use of adjuvant chemotherapy, suggested that the response of a primary tumour may not be indicative of the response at metastatic sites [20]. Tumour growth in micrometastases is considered to be exponential and rapidly proliferating cells have been shown to be more responsive to cytotoxic drugs. Conversely, large tumour masses, where a greater percentage of the cell population is comprised of non-dividing cells may be less responsive to chemotherapy [21]. In the present series, patients whose primary tumours did not respond to chemotherapy had survival comparable to responding patients. These findings suggest that a poor response of the primary tumour does not necessarily imply a poor response at occult micrometastatic foci.

In the present series, locoregional failure was a significant problem in patients with inflammatory disease. The proportion of patients experiencing a locoregional recurrence as first site of relapse was 18% (13/74) in patients with stage IIIA/IIIB non-IBC and 53% (27/51) in patients with IBC. As locoregional treatment, most patients (89%; 66/74) with stage IIIA/IIIB non-IBC received surgery alone, while most patients (90%; 46/51) with IBC underwent surgery followed by radiation therapy. Results, therefore, suggest that locoregional control in patients with IBC is determined primarily by tumour biology rather than by locoregional treatment. With locoregional therapy alone, 5-year survival of non-inflammatory LABC varies from 13 to 45% [5–8] and less than 10% of patients with IBC are alive [22, 23]. Systemic treatment has been added in an attempt to improve the survival rate by decreasing distant relapse rates. However, its role in standard therapy is still undefined, principally because randomised trials have been unable to demonstrate a survival benefit following its use.

The European Organization for the Research and Treatment of Cancer (EORTC) conducted a four-arm study comparing radiation therapy alone with the same treatment followed by chemotherapy, hormonotherapy or chemoendocrine treatment in 363 evaluable patients, 15% of whom had an inflammatory component. The estimated incidence of locoregional recurrence was significantly lower for the groups treated with systemic therapy, but the overall survival did not differ among the four groups [24]. A second randomised trial, by Schaake-Koning and associates, compared radiotherapy alone (arm I) with the same treatment followed by adjuvant chemotherapy (arm II) or primary chemotherapy, then radiotherapy, followed by adjuvant chemotherapy (arm III) in 118 patients with LABC [25]. Tamoxifen was added in arms II and III during the entire treatment period. Patients with IBC could be included in the study, but the authors did not indicate how many patients with IBC were acutally enrolled. Relapse-free survival was not significantly different among the groups and the overall survival at 5 years was 37% for all three treatment arms [25]. Many of the patients enrolled in this study were not receiving what could be considered "adjuvant therapy" since following radiotherapy they had gross residual disease. Furthermore, the number of patients enrolled would not permit the detection of a small benefit for either chemotherapy and hormone therapy. If systemic treatment can be effective in an early disease setting (stage I and II), it can be hypothesised that chemotherapy and/or hormone therapy would be of some value to patients with locally advanced disease after complete resection of their lesions. In the present series, 96% of cases were rendered free of disease by primary chemotherapy and locoregional treatment. Survival at 5 years of LABC patients treated with the combined modality approach described was 66% in patients with no inflammatory component and 44% in patients with IBC. Although not validated in a randomised study, these findings suggest that improved survival can be obtained with multimodality treatment in LABC patients. Results are particularly encouraging in patients with IBC.

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