A Phase II Trial of Neoadjuvant Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in the Treatment of Patients with Locally Advanced Breast Carcinoma

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BACKGROUND. Traditionally, primary surgical therapy is considered unsuitable for the treatment of patients with locally advanced breast carcinoma (LABC). Multiple reports have documented the efficacy of primary chemotherapy in this group of patients. The purpose of this study was to investigate the efficacy of a multimodality treatment program in reducing distant and local disease relapses in patients with LABC.

METHODS. Fifty-five patients with large operable or inoperable Stage III breast carcinoma, median tumor greatest dimension 7 × 8 cm, were treated with neoadjuvant MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) to achieve maximum clinical response, followed by modified radical mastectomy, adjuvant MVAC for six courses, and chest wall radiation. Of these patients, 37 had Stage IIIA disease and 18 had Stage IIIB or inflammatory breast carcinoma.

RESULTS. Forty-nine patients achieved overall responses to the neoadjuvant chemotherapy, including 16 complete clinical remissions. Histopathologic evaluation was performed for all patients; nine were pathologically free of disease and six had residual intraductal carcinoma only. After a median follow-up of 47 months (range, 8–76 months), 24 patients had relapsed: 6 locoregional and distant, and 18 distant only. The median disease free and overall survival have not been reached; the 5-year disease free and overall survival rates are 51% and 63%, respectively. The number of lymph nodes with metastases was found to be an independent predictor of relapse in univariate and multivariate analyses.

CONCLUSIONS. This multidisciplinary approach produced an excellent local control rate and a respectable 5-year distant relapse free rate. Axillary lymphadenectomy after primary chemotherapy provides crucial prognostic information, which can be important in planning multimodality treatment of patients with LABC. ***Cancer* 1998;82:503–11.** © *1998 American Cancer Society.*

KEYWORDS: breast carcinoma; locally advanced breast carcinoma; primary chemotherapy; neoadjuvant chemotherapy; methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC).

Primary locally advanced breast carcinoma (LABC) accounts for 10–20% of tumors of large size at presentation with involvement of skin or deeper structures and/or large regional metastases.[1] It corresponds approximately to Stage III in the TNM staging system,[2] which includes T3 or T4, N (any) M0, or T (any) N2, 3M0 tumors. Primary surgical therapy has traditionally been considered unsuitable for LABC, either because of categorically inoperable tumor or because technically resectable disease was almost invariably followed by poor

local control and dismal survival.[3] Improved radiation therapy techniques have allowed the delivery of high doses of radiation to these tumors with acceptable rates of local complication.[4] Despite the improvement in local control, however, most patients still die of distant metastases, and the disease free survival is brief for the majority of patients, with 5-year overall survival of 25–45%.[5]

The use of neoadjuvant chemotherapy in LABC dates back to 1973, when a regimen containing doxorubicin caused prompt tumor shrinkage and thereby facilitated subsequent radiation therapy or mastectomy.[6] Since then, multiple reports have appeared in the literature documenting the efficacy of primary chemotherapy in this group of patients. Most patients achieved a >50% decrease in their primary tumor mass and regional lymphadenopathy, and between 10% and 20% achieved a clinical complete remission.[1,7–9] No randomized studies have been published to document a significant survival advantage for neoadjuvant chemotherapy in operable Stage III breast carcinoma. The optimal treatment for these patients remains to be determined.

Although in a systematically screened population LABC should represent <5% of newly diagnosed breast carcinomas, Stage III and LABC may represent up to 20–30% of such patients in inner city hospitals and underserved areas of the country.[10] The University of Miami/Jackson Memorial Medical Center is an urban tertiary care center recognized as the second largest hospital in the U.S. It serves a multiethnic population, the majority of whom are indigent. Here, of approximately 150 new cases of breast carcinoma diagnosed each year, >20% are at a locally advanced stage.

The current study was a Phase II trial designed to examine the feasibility of a prolonged (approximately 1 year in duration) multimodality treatment program in reducing the distant and local disease relapses in patients with Stage IIIA or IIIB breast carcinoma. A preoperative chemotherapy regimen that included platinum was chosen, in view of the high response rates to cisplatin in previously untreated breast carcinoma patients reported previously.[11–13] Furthermore, the MVAC regimen includes three other drugs (doxorubicin, methotrexate, and vinblastine) that are known to be active agents in the treatment of breast carcinoma and could maximize clinical and pathologic response rates. Both mastectomy and radiation therapy were used to minimize the local relapse rate.

PATIENTS AND METHODS

Eligibility Criteria

All patients older than 18 years with clinically palpable LABC, T3–T4, any N, M0, any T, N3, M0, or ipsilateral supraclavicular lymph node involvement were eligible for this study. Patients were enrolled from October 1990 to September 1993 at Jackson Memorial Hospital/University of Miami-Sylvester Comprehensive Cancer Center. The diagnosis of breast carcinoma was confirmed by fine-needle aspiration cytology or trucut biopsy, and all participants underwent pretreatment evaluation that included complete blood counts; platelet count; routine chemistries and liver function tests; chest X-ray; bone scan; and electrocardiogram, multigated angiogram (MUGA), or echocardiogram. Patients were excluded from the study if they had abnormal liver or renal function tests, defined as creatinine >1.5mg/dL (or creatinine clearance <60mL/min), bilirubin ≥1.5mg/dL, or serum glutamic-oxaloacetic transaminase greater than or equal to twice the upper limit of normal. Patients with a prior history of myocardial infarction or congestive heart failure or patients with left ventricular ejection fraction of <50% were excluded.

Treatment Plan

After obtaining fully informed written consent, neoadjuvant chemotherapy with MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) was given intravenously. Actual body weight was used to calculate body surface area. Chemotherapy was given in a 28-day cycle according to the following schedule: on Day 1, methotrexate 30 mg/m^2 administered intravenously (i.v.); on Day 2, vinblastine 3mg/m^2 i.v. push, doxorubicin 30mg/m^2 i.v. push, and cisplatin 70mg/m^2 i.v. infusion over 2–4 hours; and methotrexate 30mg/m^2 i.v. push and vinblastine 3mg/m^2 i.v. administered on Days 15 and 22. Calcium leucovorin (10 mg) was given orally 24 hours after each dose of methotrexate, for a total of 6 doses. Dose modification according to the weekly blood cell count and symptomatic toxicity was allowed. If the white blood cell count was $<3.0 \times 10^9$/L and/or platelet count $<100 \times 10^9$/L, Day 1 and 2 chemotherapy was withdrawn for 1 week. If the blood counts recovered, treatment was then administered at full dose. For therapy to be given on Days 15 and 22, a white blood cell count of $\geq 2.0 \times 10^9$/L and a platelet count of $\geq 100 \times 10^9$/L were required; otherwise, the treatment was delayed 1 week. If this delay was >1 week, treatment was resumed using the Day 1 schedule. Dose reduction by 33% for the entire cycle was allowed for severe myelosuppression, defined as white blood cell count $<0.75 \times 10^9$/L or platelet count $< 20 \times 10^9$/L, thrombocytopenia with bleeding, or neutropenic fever.

If congestive heart failure occurred and was unrelated to hydration for cisplatin, doxorubicin was discontinued. A follow-up MUGA scan was not required

during the study unless the patient developed signs or symptoms suggestive of cardiomyopathy. If the left ventricular ejection fraction decreased by 10% or more, or if it was <40% at any time during the protocol, doxorubicin was discontinued. If the patient developed Grade 2 neurotoxicity, such as severe paresthesia or motor weakness, she was removed from the protocol. Cisplatin was discontinued if creatinine rose to >2.0mg/dL or twice the baseline; it was administered at full dose for creatinine 1.3–2.0 mg/dL. Methotrexate was held if creatinine was >2.0mg/dL and reduced by 50% for creatinine of 1.3–2.0 mg/dL. The patient was taken off study if creatinine remained >2.0mg/dL after 1 week of hydration.

The clinical size of the primary tumor was recorded at 4-week intervals during neoadjuvant therapy. No palpable abnormality at the tumor site indicated a clinical complete response (CR), and a reduction in size of >50% (the product of 2 perpendicular dimensions) indicated partial response (PR). A residual palpable abnormality after a good response, which sometimes was not measurable, was also classified within the PR category. Chemotherapy cycles were administered until maximal response had been achieved (all within a total of ≤5 cycles), as determined by no change in tumor size for 2 consecutive treatment cycles.

All patients then underwent modified radical mastectomy, followed by 6 courses of adjuvant chemotherapy with the same MVAC regimen. Postoperative radiation therapy to the chest wall was required 4–6 weeks after systemic therapy was completed. Radiation to the axilla and supraclavicular area was at the discretion of the radiation oncologist, depending on the pathology findings. Postmenopausal patients with tumors that were estrogen receptor (ER) or progesterone receptor (PR) positive (>10 fmol/mg protein) were given tamoxifen 10 mg orally twice daily when treatment was completed.

Pathologic Review

All pertinent cytology and surgical pathology reports and histologic sections were reviewed by one pathologist (C.M.) without knowledge of the clinical outcome. Each posttreatment mastectomy specimen was evaluated for residual carcinoma, which was further characterized as infiltrating ductal carcinoma with or without associated intraductal carcinoma versus intraductal carcinoma alone. The mastectomy specimens were not assessed prospectively according to a fixed protocol; an average of seven sections of tumor were taken in the macroscopically abnormal cases versus six slides from the macroscopically negative breasts. The histologic and nuclear grade of the invasive carcinoma were assigned separately according to a modification of the Bloom-Richardson system.[14–16] All slides from the axillary lymph node dissection specimens were also reviewed and the number of positive lymph nodes recorded.

TABLE 1
Patient Demographics

Characteristics	No. (%) of patients
Total no. of patients	55
Age (yrs)	
Median (range)	48 (29–68)
<50 yrs	32
≥50 yrs	23
Initial stage	
IIIA (T3, NX–N2)	37 (67%)
IIIB (T4, any N)	11 (20%)
Inflammatory	7 (13%)
Race	
White	13 (24%)
Black	23 (42%)
Hispanic	19 (35%)

Statistical Methods

The product limit of the Kaplan-Meier method was used to calculate the disease free survival (DFS) and overall survival.[17] Differences in these outcomes among different patient subsets were tested for significance by the log rank test and Wilcoxon's test.[18] Survival was calculated in months from the date of the study registration to death, or to the date of last follow-up for those patients still alive. The univariate descriptive statistical relationships between prognostic indicators and DFS were assessed. The variables evaluated for prognostic significance were age, primary clinical staging, clinical response, pathologic response, residual tumor size, and number of lymph nodes involved. A multivariate analysis using the Cox proportional hazards model for DFS was utilized.[19]

RESULTS

Patient Demographics

The study population was very heterogeneous in ethnicity, reflecting well the demographic composition of South Florida (Table 1). Response evaluation and duration were based on evaluation as of July 1, 1996. Of 60 eligible patients who gave informed consent to participate in the study, 5 were not evaluable because they refused to have mastectomy after neoadjuvant chemotherapy,[2] declined to continue on study after the first day of the first course of neoadjuvant MVAC,[2] or received neoadjuvant chemotherapy other than

TABLE 2
Clinical Downstaging

Initial tumor size (cm)	
Median	7 × 8
Range	5 × 5 to 21 × 29
Pre-op tumor size (greatest dimension, in cm)	
Median	2.5
Range	0–10
Clinical complete response	16 (29%)
Partial response	33 (60%)
Progressive disease	0
No. of neoadjuvant MVAC courses	
Median	4
Range	3–5

MVAC: methotrexate, vincristine, doxorubicin, and cisplatin.

MVAC.[1] The median age of the 55 evaluable patients was 48 years (range, 29–68 years). All patients had LABC, 33% of them with advanced inoperable Stage IIIB or inflammatory carcinoma, without demonstrable distant metastases. One patient had involvement of ipsilateral supraclavicular lymph nodes.

Response to Induction Chemotherapy

After a median of 4 courses of neoadjuvant chemotherapy, 89% of patients achieved an objective response, including a 29% clinical CR and a 60% PR. No patient had progression of disease (Table 2). All 55 patients underwent modified radical mastectomy, 9 patients (17%) achieved pathologic CR, and another 6 patients had intraductal carcinoma only. Median maximum tumor size at mastectomy was only 0.6 cm (range, 0–10 cm), showing dramatic response of the primary breast carcinoma to chemotherapy. Axillary lymph node involvement after neoadjuvant therapy is presented in Table 3. Forty percent of patients were found to be lymph node negative, but 20% had >10 positive lymph nodes despite neoadjuvant chemotherapy. The stratification of the axillary lymph node involvement is somewhat different from the usual subgrouping of lymph nodes in breast carcinoma (i.e., 0, 1–3, 4–10, >10). This was necessary because the sample size in the 1–3 positive lymph node group was too small for adequate statistical analyses. ER and PR status could not be determined for 19 patients because of inadequate tissue for analysis due to either complete pathologic remission or only microscopic residual disease. Qualitative and/or quantitative ER and PR measurements were obtained for 36 patients: 18 were ER positive and 6 were PR positive, and 18 patients were both ER and PR negative.

Clinical evaluation did not correlate well with pathologic findings. Only 5 of 16 clinically undetectable cancers were indeed histopathologic CRs. Of the other 11 patients, 9 had residual breast tumor ranging from microscopic disease to 2.8 cm, which was largest tumor dimension (the median was 0.6 cm), and 2 had axillary lymph node involvement without residual cancer in the breast. A total of 8 patients had axillary lymph node involvement ranging from 1 to 31 lymph nodes (median, 9 lymph nodes). Conversely, only 5 of 15 pathologic CRs had been clinically assessed as complete responders, whereas the remaining 10 patients had palpable breast masses ranging from 3.0 to 9.0 cm that contained no residual cancer at the time of mastectomy. The likelihood of clinical or pathologic CR was independent of initial size; some remarkably large tumors achieved pathologic CR as readily as tumors < 10 cm in greatest dimension (Table 4). After induction chemotherapy and surgery, all 55 patients were rendered free of disease. Forty-four patients received radiation treatment to the chest wall at doses of 4500–5040 centigray (cGy), with optional scar boost using electron beam to 1800–2160 cGy. Eleven patients did not receive radiation therapy, 9 patients re-

TABLE 3
Histopathologic Findings

Findings	No. (%) of patients
Pathologic CR	9 (16%)
Intraductal carcinoma only	6 (11%)
Pathologic stage	
I	4 (7%)
IIA	21 (38%)
IIB	11 (20%)
IIIA	4 (8%)
Maximum tumor size (cm)	
Median	0.6
Range	0–10
Number of involved axillary lymph nodes	
0	22 (40%)
1–5	13 (24%)
>5	20 (36%)
Median no. of positive lymph nodes	2
Range	0–31
ER positive	18
PR positive	6

CR: complete response; ER: estrogen receptor; PR: progesterone receptor.

TABLE 4
Initial Tumor Size versus Pathologic Complete Response

Tumor size	No. of patients	Pathologic CR
5–10 cm	41	9 (22%)
>10 cm	14	6 (43%)

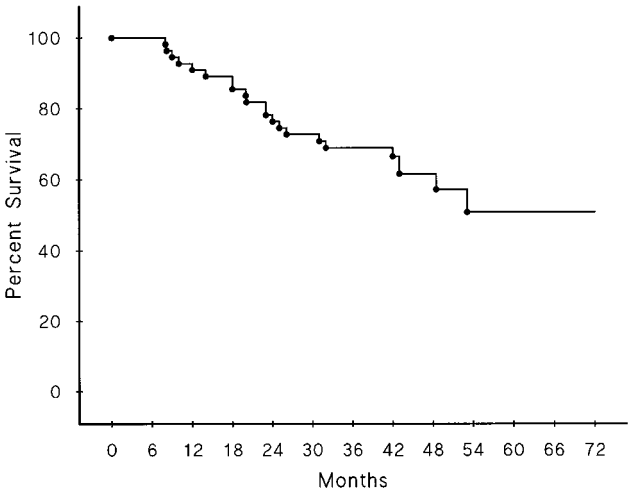

FIGURE 1. Disease free survival of the entire group, using Kaplan-Meier estimates, is shown (N = 55).

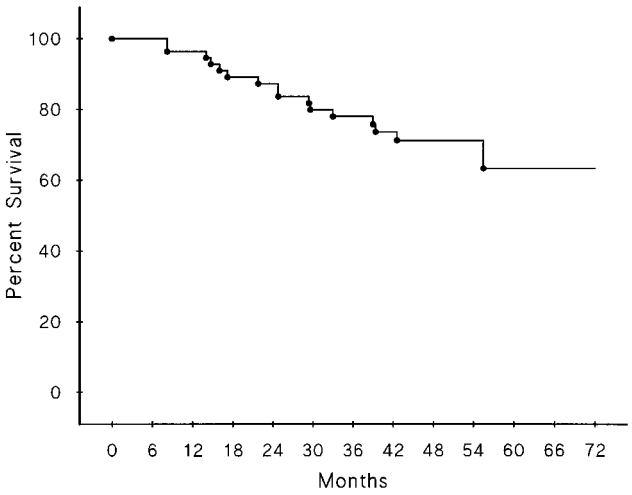

FIGURE 2. Overall survival of the entire group, using Kaplan-Meier estimates, is shown.

fused radiation, and 2 patients developed distant metastases before scheduled radiation therapy.

Patient Survival and Disease Recurrence

After a median follow-up of 47 months (range, 8–76 months), 31 patients are alive in remission, and 24 patients have relapsed (17 have died and 7 are alive with disease). The median DFS and overall survival have not been reached, with 51% free of disease at 5 years. The overall 3-year and 5-year survival were 78% and 63%, respectively. Kaplan-Meier plots of time to progression and overall survival are shown in Figures 1 and 2. Two patients with inflammatory breast carcinoma underwent high dose chemotherapy with autologous stem cell rescue in the adjuvant setting and were included in the disease free and overall survival analyses. There were only six locoregional recurrences (three Stage IIIA and three Stage IIIB): three in the chest wall, one axillary, and two supraclavicular. All six patients had PRs to neoadjuvant chemotherapy, with residual tumor measuring up to 5 cm and involvement of multiple lymph nodes. Four of these six patients received chest wall radiation after completion of adjuvant chemotherapy, but all 6 patients developed distant metastases within a few months of the first evidence of locoregional failure and died after a median of 26 months. Twenty-four patients developed distant metastases (Table 5), including central nervous system involvement in 5 of 24 (21%) but no hepatic involvement. Of the relapsed patients, 15 were Stage IIIA (41% of patients with Stage IIIA disease), and 9 were Stage IIIB or inflammatory (50% of patients had Stage IIIB or inflammatory cancer).

TABLE 5
Sites of Relapse

Sites	No. (%) of patients
Locoregional	6 (11%)
Chest wall	3
Axilla	1
Supraclavicular	2
Distant (first site of relapse)	24 (44%)
Bone	8
Lung/pleura	6
CNS	5
Neck	2
Other	3

CNS: central nervous system.

The failure rate was analyzed according to a variety of prognostic factors. The results of the univariate analyses are given in Table 6. Of the 6 factors evaluated for prognostic importance for DFS, age $\leq$50 years and number of positive lymph nodes were statistically significant. Decreasing DFS was associated in a linear trend with an increasing number of involved lymph nodes (Fig. 3). The multivariate analysis using a proportional hazards model identified the number of positive lymph nodes as the only prognostic variable. Initial clinical stage (IIIA vs. IIIB), clinical CR, and residual tumor size did not influence outcome significantly. Pathologic CR achieved a borderline predictive statistical significance. Of 15 patients who achieved pathologic CR (including 6 patients with residual intraductal carcinoma only), only 3 have experienced disease progression thus far. ER status was not analyzed as a prognostic factor because this information was not available for

TABLE 6
Univariate Analysis

Variable	N	DFS at 3 yrs	*P* value
Age (yrs)			
≤50	31	77%	0.013
>50	24	58%	
Initial clinical staging			
IIIA	37	73%	0.572
IIIB/Infl	18	61%	
Clinical CR			
Yes	16	75%	0.254
No	39	67%	
Pathologic CR			
Yes	15	87%	0.063
No	40	62%	
Residual tumor size			
≤1 cm	30	76%	0.134
>1 cm	25	60%	
Axillary lymph node metastases			
0	22	86%	0.004
1–5	20	77%	
>5	13	44%	

N: no. of patients; DFS: disease free survival; Infl: infiltrating; CR: complete response.

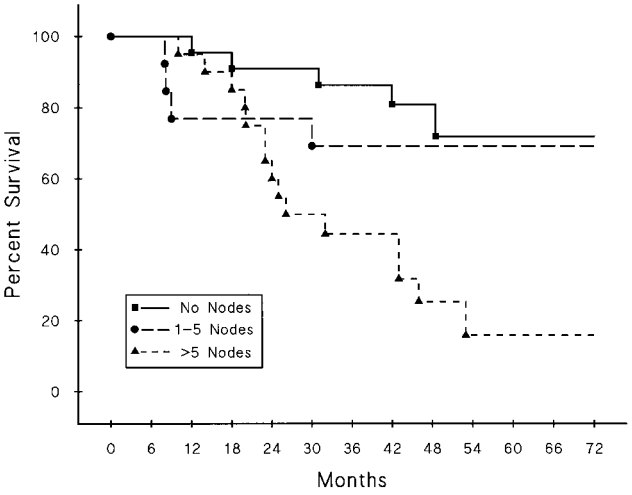

FIGURE 3. Kaplan-Meier estimates of disease free survival are shown, according to the number of lymph nodes involved after neoadjuvant chemotherapy. The difference between the curves of no lymph nodes versus >5 lymph nodes was statistically significant ($P < 0.005$).

one-third of the patients. A total of 23 patients were given tamoxifen after the completion of chemotherapy; 14 are alive without disease progression. Nuclear grade was not evaluated either, because the great majority (85%) of patients had poorly differentiated tumors.

Chemotherapy Toxicity

The main toxic effects of chemotherapy are shown in Table 7, according to World Health Organization recommendations.[20] A maximum degree of toxicity was selected for each patient. All patients developed complete alopecia. Myelosuppression was nearly universal, with 60% Grade 3–4 neutropenia. There were only two hospital admissions for neutropenic fever, and one patient developed *E. coli* sepsis without neutropenia. Eight other infections were documented: four cases of catheter-related sepsis, two cases of pneumonia, and two dental infections. Effects on platelet and red blood cell counts were less severe but still substantial. Approximately 40% of all patients experienced 1 or more treatment delays and/or dose reduction, largely due to neutropenia. Nausea/vomiting was the second most common toxicity, affecting 76% of patients. Only 31% of patients were able to complete all of the intended 6 adjuvant MVAC treatments, largely due to Grade 3–4 myelosuppression or gastrointestinal toxicity, and the median number of courses administered was 4. Eight patients developed Grade 2 neuropathy necessitating discontinuation of adjuvant MVAC. To complete a total of 6 courses of adjuvant chemotherapy, standard CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or CAF (cyclophosphamide, doxorubicin, and 5-fluorouracil) was given to those patients.

TABLE 7
MVAC Study Patient Toxicities (Total: 55 Patients)

	No. (%) of patients with grade:			
Type of toxicity	1	2	3	4
Neutropenia	4 (7)	12 (22)	31 (56)	2 (4)
Anemia	10 (18)	19 (35)	10 (18)	3 (5)
Thrombocytopenia	6 (11)	2 (4)	4 (7)	1 (2)
Nausea/vomiting	11 (20)	12 (22)	16 (29)	3 (5)
Mucositis	4 (7)	6 (11)	2 (4)	0
Anorexia	1 (2)	4 (7)	0	0
Diarrhea	2 (4)	4 (7)	0	0
Renal insufficiency	2 (4)	0	0	0
Fatigue/malaise	2 (4)	16 (29)	1 (2)	0
Neurosensory	5 (9)	8 (15)	0	0
CHF	0	1 (2)	1 (2)	0

MVAC: methotrexate, vincristine, doxorubicin, and cisplatin.

DISCUSSION

The results of this prospective study indicate that despite the large initial tumor volume, induction chemotherapy with MVAC prior to local therapy resulted in considerable tumor regression in 89% of patients, which is among the highest reported response rates for patients with LABC. The use of a variable number of neoadjuvant chemotherapy cycles to achieve maxi-

mum cytoreductive benefit before proceeding to local therapy differs from other studies in which a fixed number of courses was given.[1,7,8,21,22] Swain et al. used a similar approach to ours and reported a clinical response rate of 90% for Stage IIIA and 95% for Stage IIIB.[9] MVAC is not a commonly used chemotherapy regimen for the treatment of breast carcinoma. To our knowledge, there have been only two reports in the literature in which MVAC was given as a treatment for LABC or metastatic breast carcinoma.[23,24] Our study is the first in which MVAC was used as neoadjuvant and adjuvant therapy for LABC. Cisplatin is a highly active agent as a first-line chemotherapy for breast carcinoma, although its activity decreases to only approximately 10% response in previously treated patients. Recently, Smith et al.[25] reported a 98% response rate using neoadjuvant continuous infusion 5-fluorouracil with every 3-week course of epirubicin and cisplatin in patients with large primary cancers. Whether cisplatin is an essential component of this high response rate remains an important clinical question. By choosing MVAC, the dose of doxorubicin is less than standard for breast carcinoma therapy. It is unknown whether this could have had any impact on the final results.

Most clinical trials involving Stage III breast carcinoma treated with neoadjuvant chemotherapy followed by local treatment report median survivals of 36–66 months and overall 5-year survivals of 20–56%.[1,7,8,9,26,27] Our data show that more than half of patients with locally advanced and/or unresectable breast carcinoma remained progression free 5 years after the initiation of therapy, with overall 5-year survival of 63%. These results suggest that the clinical activity of a primary MVAC regimen could be higher than previously reported for combinations containing doxorubicin. The independence of clinical and pathologic responses from initial tumor size is a striking finding. In the study by Bonadonna,[28] the degree of tumor response was inversely proportional to the initial tumor size, such that with large tumor volume, complete pathologic remission was achieved in a small percentage of patients. In our series, however, the frequency of pathologic CR in patients with tumors measuring >10cm was twice as high as in those with tumors measuring 5–10 cm (43% vs. 22%). In fact, 1 patient with tumor measurements of 21 × 29 cm achieved a complete pathologic remission after 5 courses of neoadjuvant MVAC. Based on these data, MVAC seems to be an effective regimen for the treatment of locally advanced breast tumors, regardless of their initial size.

In many published clinical trials involving LABC, after initial chemotherapy, local therapy consisted of either radiation or surgery, and the latter was reserved for cases in which chemotherapy responses were less than CR.[9,29–32] Equivalent local control occurs after surgery or radiation therapy; however, recurrence rates as high as 50% can be observed when either modality is used alone,[8] whereas use of both modalities is substantially more effective.[26,33] In this study, all 55 patients underwent modified radical mastectomy with axillary lymph node dissection, and 80% of patients also received chest wall radiation after completion of adjuvant chemotherapy. This combined approach may explain the excellent local control rate obtained. It is noteworthy that all the locoregional recurrences occurred in patients who had residual tumor and multiple lymph node involvement after neoadjuvant therapy. It is therefore possible that patients with complete pathologic responses to primary chemotherapy may achieve optimal local control with only surgery or radiation therapy, as suggested by Jacquillat et al.[27]

The response of the primary tumor to neoadjuvant chemotherapy is usually considered to be a favorable prognostic factor, but several studies have failed to document any statistically significant survival advantage for patients with a major response to chemotherapy (a >50% decrease in tumor size).[34,35] Hortobagyi et al[31] observed significant improvement in survival for patients with Stage IIIB who achieved a CR to 3 cycles of primary chemotherapy, compared with those who had a lesser response. In the current study, pathologic CR, rather than clinical CR, correlated with improved DFS, and this result approached statistical significance ($P = 0.06$). Clinical lymph node staging remains a highly subjective evaluation, whereas axillary lymphadenectomy provides crucial information in identifying subgroups of patients with unfavorable prognoses. Even after complete histopathologic remission of the primary tumor, axillary lymph node metastases (1–11 involved lymph nodes) were still demonstrable in 4 patients. The results of the multivariate analyses demonstrate that meaningful prognostic information can be obtained only from the pathologic examination of the axillary lymph nodes, confirming other reports.[22,36–39] The univariate analysis of other potential prognostic indicators in Table 6 would require a larger sample size to detect differences among these subgroups. The response of LABC to the neoadjuvant chemotherapy can be heterogeneous, and relatively chemoresistant metastatic clones may be present at an axillary level. For these patients, a single chemotherapy regimen may not suffice to eradicate the regional as well as the occult distant disease.

The overall toxicity of the MVAC regimen was significant; only one-third of all patients were willing to

complete all six adjuvant courses. The main side effects that were responsible for decreased patient compliance were nausea/vomiting, fatigue, and sensory neuropathy, and these were probably secondary to the repeated use of cisplatin. How much this adjuvant chemotherapy added to the outcome after neoadjuvant and combined modality therapy is uncertain.

The main obstacle to effective treatment of Stage III breast carcinoma is control of distant micrometastases. The management of this disease almost invariably requires an aggressive multidisciplinary approach. The results obtained with primary chemotherapy are equivalent, and possibly superior, to those obtained with postoperative chemotherapy, but trends in favor of primary chemotherapy do not reach statistical significance. Recently, Scholl et al.[29] reported statistically significant improvement of survival in favor of neoadjuvant chemotherapy in a randomized trial involving 414 premenopausal patients with a largest tumor diameter of 3–7cm. Larger randomized clinical trials, such as National Surgical Adjuvant Breast Project B-18, are currently addressing the issue of the survival benefit of neoadjuvant chemotherapy versus that of the same chemotherapy given postoperatively.

It should be noted that this is a single-institution Phase II trial with a relatively small number of patients, and the results reported here should be confirmed by other prospective studies. Additional trials using this regimen could also evaluate patient quality-of-life issues, which are particularly important in the primary chemotherapy setting, especially because MVAC can be quite a toxic regimen.

Primary chemotherapy appears to be useful in defining a chemosensitive population, thereby potentially allowing drug intensification in the treatment of selected high risk patients who have a potential for cure. Results may be further improved by selecting responding patients to receive high dose adjuvant chemotherapy and stem cell rescue, an approach worth testing in a randomized trial.

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