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A Pilot Evaluation of Alternating Preoperative Chemotherapy in the Management of Patients with Locoregionally Advanced Breast Carcinoma

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BACKGROUND. This prospective trial was conducted to evaluate the outcome of patients treated with preoperative and postoperative chemotherapy, mastectomy, and irradiation for locoregionally advanced breast carcinoma.

METHODS. Between June 1986 and September 1990, 71 patients received 2 cycles of doxorubicin that alternated with 2 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil prior to mastectomy; irradiation was administered when the tumor was not amenable to surgical resection. Additional chemotherapy and tamoxifen, in hormone receptor-positive tumors, was used after mastectomy. Postoperative irradiation was given on a selective basis for patients at high risk for locoregional disease recurrence.

RESULTS. Although 5 patients (7%) had disease progression, clinical partial or complete tumor response to preoperative chemotherapy was noted in 46 patients (65%). Sixty-eight patients (96%) underwent mastectomy. With a median follow-up of 52 months, the relapse-free and overall survival rates at 5 years were 42% and 57%, respectively. Locoregional tumor recurrence occurred in 14 patients (20%), and 28 patients (39%) developed metastatic disease. Menopausal status, clinical presentation (noninflammatory vs. inflammatory), and American Joint Committee on Cancer clinical stage were independent covariates associated with patient outcome.

CONCLUSIONS. Preoperative alternating chemotherapy, with the selective use of irradiation, resulted in significant locoregional disease regression and the successful integration of mastectomy into the therapeutic strategy. Locoregional tumor control and relapse-free and overall survival estimates for the approach described herein compared favorably with other contemporary reports for this condition.

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KEYWORDS: breast neoplasms, chemotherapy, mastectomy, neoplasm recurrence, pathology, prognosis, prospective studies, radiotherapy, survival rate.

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For patients managed with mastectomy or irradiation (RT) for locoregionally advanced breast carcinoma (LABC), disease relapse has been a common occurrence.¹⁻³ As a result, treatment of this condition evolved toward the integrated use of surgery, RT, and systemic therapy (e.g., chemotherapy). Although these treatments have been combined in different ways, the administration of systemic therapy prior to ablation of locoregional (LR) tumor (i.e., neoadjuvant therapy) has several possible advantages. With this approach, there existed the potential to provide prompt treatment of occult systemic disease (i.e., micrometastases), to reduce LR tumor burden to enhance the efficacy of surgery and/or RT, and to eliminate concern regarding stimulated micrometastatic tumor growth after surgical removal of the primary tumor.⁴ On the basis of these principles, neoadjuvant chemotherapy was introduced into the management of LABC, and the initial experience with this approach resulted in favorable tumor response and patient outcome.^{1,5-7} Furthermore, the results achieved with neoadjuvant chemotherapy may be enhanced by the use of additional chemotherapy after surgical or radiotherapeutic treatment of the LR disease process.⁸

During this time, the concept of alternating noncross-resistant therapy emerged as a possible method to improve treatment efficacy.⁹ This concept was based on the hypothesis that spontaneous somatic mutation of tumors occurred during the course of treatment. As a derivative of this hypothesis, an inverse relationship between tumor volume and the likelihood of cure with chemotherapy was assumed. This led to the conclusion that a combination of noncross-resistant chemotherapy used in a rapidly alternating fashion would have the greatest probability of eradicating all tumor cells within a heterogeneous population, and that the malignancy should be treated as early as possible to increase the chance for cure.

In the context of these observations, the North Central Cancer Treatment Group, in association with the Mayo Clinic, embarked upon a prospective trial that employed alternating noncross-resistant chemotherapy as the initial treatment of LABC. The selection of chemotherapy was based on the results achieved with doxorubicin in the management of metastatic breast cancer,¹⁰ and the experience with the combination of cyclophosphamide, methotrexate, and 5-fluorouracil in the adjuvant setting.¹¹ After preoperative chemotherapy, mastectomy was incorporated because of the likelihood for residual LR disease,¹² which might increase the risk of LR tumor recurrence and the emergence of chemotherapy-resistant tumor cells. RT was used to enhance LR disease control in patients with inflammatory carcinoma, and was selectively inte-

grated into the treatment strategy for patients with noninflammatory disease on the basis of the histologic findings from the mastectomy specimen.

PATIENTS AND METHODS

Patient Characteristics

Between June 1986 and September 1990, 71 women with histologically confirmed LABC were enrolled in a prospective study conducted by the North Central Cancer Treatment Group (NCCTG) in collaboration with the Mayo Clinic. These patients had one or more of the following clinical findings: tumor more than 5 cm in diameter; tumor involvement of chest wall (ribs or intercostal or serratus anterior muscles) or skin (ipsilateral cutaneous edema, ulceration, or satellite nodules); clinically evident inflammatory carcinoma,¹³ ipsilateral fixed axillary adenopathy; or histologic evidence of ipsilateral internal mammary or supraclavicular lymph node involvement. Additional criteria for trial eligibility included: age younger than 70 years; performance score of 0-1¹⁴; adequate hepatic and renal function; and evaluable or measurable disease.¹⁴ The presence of any of the following conditions precluded study entry: prior breast cancer therapy; bilateral breast cancer; metastases to sites other than ipsilateral regional or supraclavicular lymph nodes; a leukocyte count of less than 4000/ μ L; a platelet count of less than 100,000/ μ L; concurrent pregnancy or lactation; or previous malignancy exclusive of nonmelanomatous skin carcinoma. Patients were considered technically operable if, in the opinion of the surgeon, all disease could be removed with primary closure (without cutaneous or muscular transposition) without anticipated microscopic or gross tumor residua.

Of the 71 patients enrolled in this trial, all were included in the present analysis. No patient was excluded due to trial ineligibility, cancellation, or loss to follow-up. The pretherapy clinical characteristics of the study group are summarized in Table 1.

Evaluation and Treatment

Prior to trial entry, patient evaluation was comprised of history, physical examination, complete blood cell count, chemistry profile, electrocardiography, chest radiography, mammography, radionuclide bone scan, and pregnancy test (if indicated). Treatment began (Fig. 1) after informed consent was obtained as specified by Department of Health and Human Services and institutional guidelines.

Preoperative chemotherapy was comprised of intravenous doxorubicin, 75 mg/m², followed 3 weeks later by the administration of cyclophosphamide (C), methotrexate (M), and 5-fluorouracil (F). The CMF regimen consisted of cyclophosphamide, 600 mg/m²,

TABLE 1
Patient Characteristics

Characteristic	Inflammatory		Noninflammatory	
	No. of patients	%	No. of patients	%
All patients ^a	31	44	40	56
Menopausal status				
Premenopausal	16	52	20	50
Postmenopausal	15	48	20	50
Clinical lymph node involvement				
None	6	19	6	15
Mobile axillary	20	65	23	58
Fixed axillary	5	16	10	25
Supraclavicular	2	6	2	5
Clinical chest wall/skin extension				
No	0	0	25	63
Yes	31	100	15	38
Clinical stage ^b				
IIB	0	0	3	8
IIIA	0	0	20	50
IIIB	29	94	15	38
IV	2	6	2	5
Technically operable				
No	27	87	25	63
Yes	4	13	15	38
Tumor grade				
1-2	8	26	10	25
3-4	21	68	27	68
Unknown	2	6	3	8
Estrogen receptor content				
<10	4	13	11	28
≥10	13	42	13	33
Unknown	14	45	16	40

^a Median age, 50 years (range, 35-68 years).

^b American Joint Committee on Cancer (AJCC) Staging System.¹³

methotrexate, 40 mg/m², and 5-fluorouracil, 600 mg/m², administered intravenously on the first and eighth days of each 4-week cycle. Patient status was assessed at each chemotherapy session as specified by World Health Organization (WHO) guidelines.¹⁴ Accordingly, clinical response was defined as follows: complete response, disappearance of all known disease; partial regression, 50% or greater decrease in tumor area or size; no change, less than partial regression without progressive disease; and progressive disease, 25% or greater increase in tumor size or appearance of new lesions. The WHO criteria were used to grade the acute toxicity of preoperative chemotherapy.¹⁴ Treatment in accordance with protocol specification was discontinued if disease progression occurred.

Dosage modification of all chemotherapeutic agents was made for severe nausea or vomiting (20% reduction), and for hepatic or hematologic toxicity. At the time of scheduled retreatment, therapy was de-

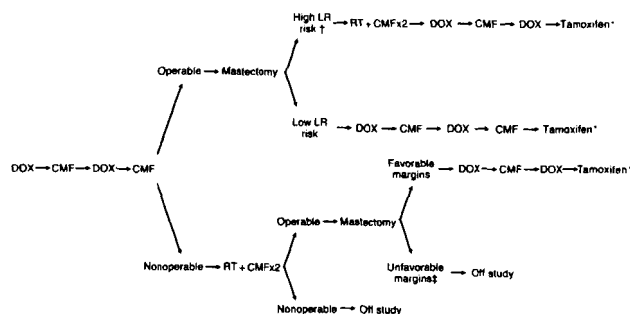


FIGURE 1. Treatment scheme. DOX: doxorubicin, CMF: cyclophosphamide, methotrexate, 5-fluorouracil, RT: irradiation. †Inflammatory presentation; or residual tumor >5 cm diameter; or involvement of skin, fascia, ≥4 axillary lymph nodes, or surgical margin(s). ‡Gross residual disease or microscopic involvement of surgical margin(s). *If hormone receptor positive.

layed if serum aspartate aminotransferase was more than 3 times the upper normal value, if serum total bilirubin was more than twice the upper normal value, if the leukocyte count was < 3000/μL, or if the platelet count was < 100,000/μL. Modifications according to the hematologic nadir value of preceding cycles included a 20% dosage increase for a leukocyte count of > 3000/μL and a platelet count of > 100,000 μL, a 20% decrease for a leukocyte count of 1000/μL to 1500/μL or a platelet count of 25,000/μL to 75,000/μL, and a 30% decrease for a leukocyte count of < 1000/μL or a platelet count of < 25,000/μL. In addition, the dosage of doxorubicin, methotrexate, and 5-fluorouracil was reduced for moderate (20% reduction) or severe (30% reduction) stomatitis or diarrhea. The dosage of methotrexate was reduced or discontinued in the presence of renal toxicity.

After two cycles of doxorubicin that alternated with two cycles of CMF, disease status was re-evaluated, and modified radical mastectomy (MRM) was performed in those patients regarded as technically operable. Patients with inflammatory presentation or those with histologic evidence of residual tumor that measured more than 5 cm in diameter, or with involvement of skin, fascia, 4 or more axillary lymph nodes, or surgical margin(s) in the MRM specimen were considered at high risk for LR disease recurrence. For these patients, RT concurrent with two cycles of CMF was administered and followed with additional doxorubicin and CMF chemotherapy (Fig. 1). For patients considered at low risk for LR recurrence, two postoperative cycles of doxorubicin that alternated with two cycles of CMF were given.

When the tumor was not considered amenable to complete surgical resection after preoperative chemotherapy, RT concomitant with two cycles of CMF was

used (Fig. 1). Thereafter, if MRM was performed with favorable margins (no evidence of gross tumor residua or microscopic involvement of surgical margins), three additional cycles of chemotherapy were administered. When MRM could not be performed or when unfavorable margins existed after MRM, the patient went off study and was managed as indicated by clinical circumstance.

When given prior to mastectomy, the RT target volume consisted of the breast and chest wall, and the ipsilateral internal mammary, supraclavicular, and axillary lymph node regions. Megavoltage equipment was used to administer 50.4 Gray (Gy) in 28 daily fractions over 5.5 weeks; an additional 10–15 Gy in 5–8 treatments was given to clinically apparent supraclavicular or internal mammary adenopathy. Similar methods were used to administer postoperative RT, although the mastectomy scar received an additional 10 Gy in 5–6 daily treatments. All patients in whom RT was initiated completed treatment and received the intended irradiation dosage.

After completion of all therapy, patients were assessed every 3 months for 3 years, every 6 months during the next 2 years, and yearly thereafter. Sites of initial tumor progression were classified as local (ipsilateral chest wall), regional (ipsilateral supraclavicular, infraclavicular, axillary or internal mammary lymph nodes), or distant (all other sites). The classification for any patient with simultaneous local or regional and distant tumor relapse was distant.

Method of Analysis

Relapse-free survival (RFS) and overall survival (OS) were determined from the date of registration to the date of treatment failure or death. For analysis of RFS, an event was defined as recurrence of breast carcinoma, and patients who died without evidence of disease recurrence were censored; death from any cause was considered an event for evaluation of OS. The method of Kaplan and Meier was used to estimate the duration of RFS and of OS.¹⁵ In analysis of outcome, the observed (crude) rate for the event under consideration was determined for each factor, and univariate comparisons of end points were made with the log rank statistic.¹⁶ Multivariate analysis employed the Cox proportional hazard model to find the most significant factors related to outcome,¹⁷ and variables were retained on the basis of the backward elimination procedure. A two-sided *P* value of ≤ 0.05 was considered significant.

RESULTS

Toxicity of Preoperative Chemotherapy

Preoperative chemotherapy produced myelosuppression in all but 1 patient (99%). Although 46 patients

(65%) had a leukocyte nadir of $< 2,000/\mu\text{L}$ (Grade 3 or 4), only 3 patients (4.2%) had a minor-to-moderate (Grade 1 or 2) infectious complication and only 1 patient (1.4%) experienced a major (Grade 3) infection. Thrombocytopenia (a platelet count of $< 130,000/\mu\text{L}$) occurred in 32 patients (45%), but a platelet nadir of $< 50,000/\mu\text{L}$ (Grade 3 or 4) was noted in only 6 patients (8%) and no hemorrhagic complications developed. No deaths occurred as a result of hematologic toxicity. Significant nonhematologic side effects were limited to vomiting (61%) that was severe (Grade 3) in 4 patients (6%), and oropharyngeal mucositis and/or esophagitis that was evident in 33 patients (46%), but was moderate (Grade 2) in 8 patients (11%) and severe (Grade 3) in only 1 patient (1.4%). No life-threatening or lethal nonhematologic complications occurred. Among patients without tumor progression during preoperative chemotherapy (66 patients), 60 patients (91%) received $\geq 85\%$ of the intended doxorubicin dose (median, 99%), and $\geq 85\%$ of the planned amount of CMF chemotherapy was administered to 50 patients (76%) (median, 98%). This compared favorably with the percentage intended dose administered thereafter, which for doxorubicin and for CMF was $\geq 85\%$ in 69% of patients (median, 94%) and 63% of patients (median, 79%), respectively.

Response to Preoperative Chemotherapy

As shown in Table 2, partial or complete clinical response to preoperative chemotherapy was observed in 46 patients (65%). Among 52 patients considered unresectable at presentation, 40 (77%) were deemed operable after preoperative chemotherapy and underwent MRM, whereas 10 patients also received RT with 2 concurrent cycles of CMF prior to MRM. Eighteen of 19 patients amenable to surgical resection at presentation were able to undergo MRM after chemotherapy. However, disease progression occurred in 5 patients (7%), including 1 patient considered operable at the time of registration, and 3 patients with noninflammatory carcinoma went off study because the extent of LR disease progression (2 patients) or the development of distant metastases precluded surgical intervention (1 patient). Therefore, 68 of the 71 patients (96%) entered on the trial underwent MRM, and 53 patients (75%) were managed solely with chemotherapy prior to surgical resection. Among these 53 patients, the histologic findings of the MRM specimen placed 26 (49%) at high risk for LR tumor recurrence.

For the 40 patients with noninflammatory clinical presentation, 37 underwent MRM; of these, 29 (78%) had a partial or complete response to preoperative chemotherapy. However, 10 patients (35%) were at high risk for LR disease recurrence based on findings

TABLE 2
Clinical Response to Preoperative Chemotherapy

Response	Inflammatory		Noninflammatory		All patients	
	No. of patients	%	No. of patients	%	No. of patients	%
Complete	3	10	8	20	11	15
Partial	14	45	21	53	35	49
No change	12	39	8	20	20	28
Progression	2	6	3	8	5	7

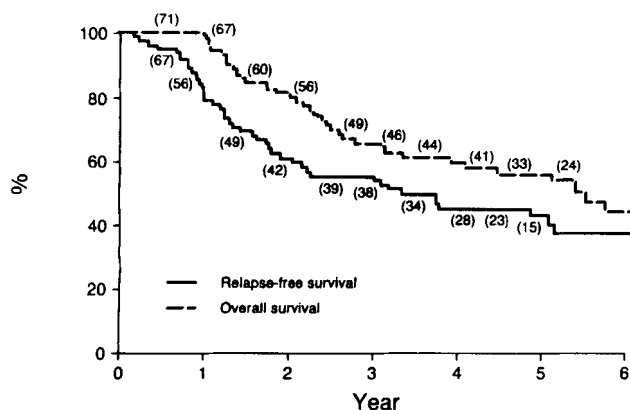


FIGURE 2. Relapse-free and overall survival of 71 patients with locoregionally advanced breast carcinoma. Numbers in parentheses represent number of patients at risk.

from histologic examination of the MRM specimen. Likewise, 8 patients (22%) had no change to preoperative chemotherapy, and 4 patients (50%) remained in the high risk category after MRM. Therefore, of the 37 patients with noninflammatory clinical presentation managed with MRM, 14 (38%) had histologic characteristics that placed the patient in the high risk category, and 13 patients received postoperative RT (one patient refused RT) on this basis.

Disease Outcome

With median follow-up of 52.2 months (range, 10.9 to 89.9 months), tumor relapse occurred in 42 patients (59%), and 37 patients (52%) had died. The actuarial estimate of RFS and OS for all patients at 5 years was 42% and 57%, respectively (Fig. 2). Fourteen patients (20%) had LR recurrence as the initial and sole site of treatment failure, whereas 28 patients (39%) had initial disease relapse at a distant site(s). The distribution of initial sites of treatment failure according to clinical presentation, clinical response to preoperative chemotherapy, and LR recurrence risk category are presented

in Table 3. Of note, the LR recurrence risk categories were not associated with LR tumor recurrence as an initial and sole site (perhaps because the high risk group received RT), but there was an association with metastatic disease relapse.

Patient and tumor-related characteristics were evaluated to determine the impact of selected pretherapy factors on treatment outcome. The variables selected for inclusion in a univariate analysis were menopausal status, clinical presentation, American Joint Committee on Cancer (AJCC) clinical stage,¹³ operability at presentation, and the presence of fixed axillary adenopathy. Estrogen receptor content was not included because the diagnostic biopsy did not recover a sufficient amount of tumor for quantification in a sizable proportion of patients (42%). Although operability and fixed axillary adenopathy were not associated with either RFS or OS, all other characteristics approached or met statistical significance as factors predictive of disease outcome, as shown in Table 4. A significant difference in outcome between AJCC Stage IIIA and Stage IIIB was maintained with exclusion of AJCC Stage IIB and IV disease categories (data not shown).

Multivariate analysis preserved the significance of menopausal status, clinical presentation, and AJCC clinical stage as independent covariates.

DISCUSSION

The overall tumor stage distribution of patients with breast cancer has changed over the last several years. Indeed, the proportion of patients with LABC (i.e., AJCC Stage III) has shown modest decline over time, and now accounts for approximately 7% of patients with newly recognized breast carcinoma.¹⁸ In addition to this relatively low incidence rate, LABC is also a heterogeneous condition in which patient characteristics and tumor-related factors have been predictive of disease outcome. For these reasons, prospective investigations of this condition have been somewhat limited, and the preferred management scheme for the

TABLE 3
Initial Sites of Disease Relapse in Locoregionally Advanced Breast Carcinoma

Characteristic	No. of patients	LR recurrence			Distant metastasis			Any relapse		
		No. of patients	%	P value	No. of patients	%	P value	No. of patients	%	P value
Clinical presentation										
Inflammatory	31	8	26	0.22	14	45	0.39	22	71	0.07
Noninflammatory	40	6	15		14	35		20	50	
Clinical response										
Partial or complete	46	3	7	0.003 ^a	21	46	0.23 ^a	24	52	0.33 ^a
No change	20	7	35		6	30		13	65	
Progression	5	4	80		1	20		5	100	
LR recurrence risk ^b										
Low	22	4	18	0.94	3	14	0.002	7	32	0.003
High	46	8 ^c	17		24	52		32	70	

LR: Locoregional.

^a Analysis restricted to partial or complete response versus no change; results not affected by inclusion of patients with disease progression (data not shown).

^b Three patients who did not undergo mastectomy were excluded.

^c All patients had inflammatory presentation.

TABLE 4
Impact of Pretherapy Disease Characteristics on Outcome in Locoregionally Advanced Breast Carcinoma

Characteristic	No. of patients	Relapse-free survival			Overall survival		
		5-yr, %	Median, mo	P value	5-yr, %	Median, mo	P value
Menopausal status							
Premenopausal	36	50	47.2	0.08	69	57.1	0.03
Postmenopausal	35	34	25.8		45	48.4	
Clinical presentation							
Inflammatory	31	26	25.3	0.06	48	46	0.15
Noninflammatory	40	54	60.5		64	76.3	
Clinical stage ^a							
IIB	3	33	15.2	0.0005	33	36.1	< 0.0001
IIIA	20	54	60.5		65	79.3	
IIIB	44	41	38.3		61	65.5	
IV	4	0	10.1		0	11.2	

^a American Joint Committee on Cancer (AJCC) Staging System.¹³

patient with LABC has not been defined through contemporaneous trials of a comparative study design.

The present study was conducted to prospectively evaluate a therapeutic approach predicated on the hypothesis that tumor mutation to a drug-resistant state may occur during treatment.⁹ Therefore, an alternating noncross-resistant chemotherapy regimen was incorporated into a multimodality program in an attempt to minimize the likelihood that treatment-refractory tumor clonogens would emerge. Furthermore, chemotherapy was administered as the initial component of a therapeutic approach designed to provide a

reduction in LR tumor burden and prompt treatment of potential micrometastases. Although this study could not determine the relative efficacy of this approach, the toxicity profile, clinical tumor response, and relapse-free survival and overall survival rates described herein were comparable to treatment programs that administer chemotherapy in a conventional manner¹⁹⁻²⁸ as well as in the setting of "hormonal synchronization."²⁹⁻³¹

The preoperative chemotherapy program used herein resulted in complete or partial tumor response in two-thirds of patients, which was comparable to

results achieved in similar studies of preoperative chemotherapy for LABC.^{19,24,26,27,29,32,33} Although an association between clinical response and LR tumor control was observed, the metastatic relapse rate was not affected by clinical appraisal of tumor response at the primary site (Table 3). However, these observations must be viewed with caution because clinical response criteria may not reliably predict ultimate disease outcome.^{26,34} Furthermore, a trial of larger scope would be required to accurately evaluate the association of primary tumor response with the metastasis free rate.³⁵ Nonetheless, it was noteworthy that tumor progression was uncommon (7%) during preoperative chemotherapy, and three-quarters of patients with inoperable disease responded to preoperative chemotherapy and the selective use of RT in a manner that allowed incorporation of mastectomy into the therapeutic scheme.

After initial chemotherapy (with or without preoperative RT), mastectomy was incorporated because it was believed residual LR disease^{12,34} might increase the risk for disease relapse. Although this approach produced satisfactory LR disease control, breast-conserving surgery may be a feasible alternative for the patient with a favorable response to the preoperative chemotherapy program,^{30,33,36} and merits consideration in future clinical trials for LABC. In an effort to improve disease control, RT was used in patients with clinical inflammatory breast cancer, and selectively on the basis of postmastectomy histologic findings in those with noninflammatory presentation. Although the number of patients available for analysis did not allow definitive conclusion, omission of RT in the low risk group did not result in an excessive rate of recurrence at a LR site(s). Similarly, use of RT in the high risk cohort appeared to achieve satisfactory LR tumor control. However, analysis of initial, solitary sites of disease relapse may underestimate the likelihood of residual LR disease and the risk for tumor recurrence.³⁷ Furthermore, all patients in the high risk group who experienced LR tumor recurrence presented with clinical inflammatory disease. Therefore, approximately one-quarter of those patients with clinical inflammatory breast carcinoma experienced LR recurrence as the first and only site of disease recurrence despite the combined use of chemotherapy, mastectomy, and RT. For this disorder, alternative methods of RT administration, such as accelerated hyperfractionation,^{37,38} or the use of innovative surgical or chemotherapeutic³⁹ approaches require investigation in an attempt to improve LR tumor control.

The influence of pretherapy characteristics on disease outcome was also of interest and was evaluated within the context of this clinical trial. The overall clin-

ical stage, assigned in accordance with the AJCC system,¹³ was the most striking factor associated with relapse-free and overall survival. This confirmed the observation of other investigators,^{23,29} and provided further support for subdivision of the Stage III category and consideration of ipsilateral supraclavicular adenopathy as a metastatic site.^{28,40} Likewise, the adverse impact of postmenopausal status and inflammatory clinical presentation on patient outcome confirmed the findings of prior investigations.^{5,21,24,25,29} These factors should be considered in the development and interpretation of clinical trials addressing newer therapeutic strategies for the management of LABC.

This study represents one of the few clinical experiences of alternating noncross-resistant chemotherapy in the care of patients with high risk breast cancer. Although the design of a Belgium trial was similar to that reported herein,³² the Eastern Cooperative Oncology Group (ECOG) study of partially noncross-resistant chemohormonal therapy for premenopausal patients with lymph node positive Stage II breast cancer⁴¹ was a prospective comparative trial that was in part based on assumptions central to the Goldie-Coldman hypothesis.⁹ Although the ECOG investigation suggested a therapeutic benefit with the alternating approach, the trial design included other variables that may explain this observation. Indeed, this finding may be attributed to the use of doxorubicin and/or flouxymesterone in the alternating, but not the conventional, regimen, rather than the method of treatment administration. Therefore, currently available clinical trials have not provided a definitive test of a hypothesis generated more than a decade ago.

Although this report described patient outcome that followed a therapeutic strategy predicated on a certain model of tumor growth and treatment responsiveness,⁹ other hypotheses to explain chemotherapy resistance have been put forth. An alternative model suggested that a tumor is comprised of subclones with varied growth kinetics and different profiles of chemotherapy resistance.⁴² Adherence to this model suggested that the initial treatment should be administered in a continuous (i.e., uninterrupted) fashion against the more rapidly growing tumor subclone(s). Thereafter, a noncross-resistant agent or combination effective against the slower growing and/or resistant subclone(s) should be given. Although this hypothesis has not been tested in the context of LABC, comparative clinical trials in lymph node positive, Stage II breast cancer have been conducted. The Cancer and Leukemia Group B (CALGB) demonstrated an improved outcome when a doxorubicin-based combination was administered after CMF with vincristine and prednisone.⁴³ However, as in the ECOG trial,⁴¹ the ben-

eficial effect noted with sequential therapy may have been due to the addition of doxorubicin and/or fluoxymesterone.

The Instituto Nazionale Tumori (Milan, Italy) provided a more direct test of the alternating versus sequential treatment approach and the assumptions derived from their respective biologic hypotheses.⁴⁴ This randomized study compared two sequences of non-cross-resistant chemotherapy, namely, CMF alternating with doxorubicin (alternating therapy) and doxorubicin followed by CMF (sequential therapy). Relapse-free survival and overall survival comparisons demonstrated improved results with the sequential therapy approach. Although both chemotherapy regimens included the same agents, dosages, treatment duration, and overall drug dose intensity, the doxorubicin dose intensity was higher for those patients assigned to sequential therapy. Therefore, the advantage attributed to the sequential approach may have been related to doxorubicin dose intensity rather than the sequence of noncross-resistant chemotherapy that was administered. The results of ongoing clinical research efforts may resolve questions of this nature.

In conclusion, the treatment strategy described herein provided a therapeutic outcome for patients with LABC that compared favorably with other contemporary investigations. Although this approach merits consideration for the care of these patients, further research efforts that adopt innovative surgical,^{33,36} radiotherapeutic,^{37,38} and systemic treatment^{39,45} measures are required to effect a much needed improvement for the outcome of patients with this condition.

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