Mitoxantrone, 5-Fluorouracil, and High Dose Leucovorin (NFL) versus Intravenous Cyclophosphamide, Methotrexate, and 5-Fluorouracil (CMF) in First-Line Chemotherapy for Patients with Metastatic Breast Carcinoma

A Randomized Phase II Trial

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BACKGROUND. Previous Phase II studies using the combination of mitoxantrone, 5-fluorouracil, and high dose leucovorin (NFL) in the treatment of metastatic breast carcinoma have shown this regimen to be active and well tolerated. In this randomized Phase II study, the authors compared the NFL regimen with a standard CMF regimen in the first-line therapy of patients with metastatic breast carcinoma.

METHODS. One hundred twenty-eight women receiving their first chemotherapy for metastatic breast carcinoma were entered into this randomized study. Sixty-four patients were treated with NFL: mitoxantrone 12 mg/m^2 IV on Day 1; leucovorin 300 mg IV over 30–60 minutes on Days 1, 2, and 3, immediately preceding administration of 5-fluorouracil; and 5-fluorouracil 350 mg/m^2 IV bolus on Days 1, 2, and 3. Sixty-four patients received CMF: cyclophosphamide 600 mg/m^2 IV on Day 1; methotrexate 40 mg/m^2 IV on Day 1; and 5-fluorouracil 600 mg/m^2 IV on Day 1. Both regimens were repeated at 21-day intervals; responding patients received at least 8 courses.

RESULTS. Patients treated with NFL had a higher response rate than patients treated with the CMF regimen (45% vs. 26%, respectively; $P = 0.021$). Median duration of response was 9 months with NFL and 6 months with CMF ($P = 0.10$); 11 patients had long responses (>12 months) with NFL versus 4 patients with CMF ($P = 0.06$). Median survival was similar for both groups. Both regimens were well tolerated, with infrequent Grade 3 or 4 toxicities.

CONCLUSIONS. NFL is an active, well-tolerated regimen for the treatment of metastatic breast carcinoma; it produced a higher response rate than the CMF regimen used in this study. Although more intense CMF regimens or regimens containing doxorubicin would likely increase the response rate, they would almost certainly do so with the consequence of greater toxicity as compared with NFL. NFL is an excellent initial palliative treatment option for elderly patients or patients who have exhibited poor tolerance for other chemotherapy regimens. ***Cancer* 1997; 79:740–8.** © *1997 American Cancer Society.*

KEYWORDS: metastatic breast carcinoma; mitoxantrone, 5-flourouracil, and leucovorin (NFL) regimen; cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimen.

Metastatic breast carcinoma remains an incurable illness, although systemic therapy can provide effective temporary palliation for many patients. Hormonal therapy remains the most effective pallia-

tive treatment in sensitive patients; however, all patients eventually become refractory, thereby becoming candidates for systemic chemotherapy. Although several antineoplastic agents have moderate activity in the therapy of breast carcinoma, combination regimens, such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) and cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF), have been the most commonly used first-line regimens for the last 20 years. Toxicity with these regimens is moderate; side effects most frequently encountered include nausea and vomiting, alopecia, fatigue, and myelosuppression. Regimens containing doxorubicin have produced higher response rates as well as increased toxicity; however, survival differences have not been evident in most comparative trials.

Recently, a combination regimen including mitoxantrone, 5-fluorouracil, and high dose leucovorin (NFL) has been tested in several Phase II trials.[1–5] The two components of this regimen, mitoxantrone and 5-fluorouracil/high dose leucovorin, both show marked single agent activity while avoiding some of the toxicities traditionally associated with doxorubicin and cyclophosphamide.[6–9] In our previously reported Phase II study, responses were achieved with NFL in 65% of patients with metastatic breast carcinoma, most of whom had not received doxorubicin previously and were receiving second-line therapy for metastatic disease.[1] In addition, this regimen was well tolerated by most patients, with infrequent alopecia, nausea, vomiting, and other gastrointestinal toxicity. Comparable results have been obtained by other investigators with similar combination regimens.[2–4]

Based on these encouraging Phase II results, we initiated a randomized Phase II comparison of NFL versus a standard CMF regimen in first-line chemotherapy of metastatic breast carcinoma. The CMF regimen, rather than CAF, was chosen due to its continued widespread usage and its broader applicability in the treatment of elderly patients. In this report, the efficacy and toxicity of these two combination regimens are compared in the first-line treatment of metastatic breast carcinoma.

PATIENTS AND METHODS

Between July 1991 and November 1994, 128 patients were entered onto this study by 18 participating investigators. Eight-three patients (65%) were entered by the authors from their respective institutions. Patients were randomly allocated to receive either NFL or CMF by a random card system.

Patients eligible for this study had biopsy-proven metastatic breast carcinoma and had received no previous chemotherapy for metastatic disease. Patients who had received previous adjuvant chemotherapy more than 6 months prior to the development of metastases were eligible. Previous doxorubicin as a component of adjuvant therapy was acceptable, as long as the cumulative dose was less than 350 mg/m^2. Patients with measurable or evaluable disease were eligible. In addition, patients with bone metastases who had only abnormal bone scans were eligible, but they were stratified and analyzed using different response criteria, as described below. Patients with prior hormonal therapy and palliative radiation therapy for metastatic disease were allowed. Patients with congestive heart failure or cardiac ejection fraction $<45\%$ were excluded. Additional entry criteria included the following: leukocytes $\geq 3{,}000/\mu$L; platelets $>100{,}000/\mu$L; serum creatinine ≤ 1.5 mg/dL; serum bilirubin less than twice the normal upper limits; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; and expected survival of more than 10 weeks. Pregnant patients were excluded, as were patients with a history of a second malignancy within 3 years of study entry. All patients gave informed consent prior to entering this study, and the study was approved by the institutional review boards of all participating institutions.

At the time of study entry, all patients underwent the following routine laboratory and staging procedures: complete blood counts, differential, chemistry profile, electrolytes, urinalysis, chest radiograph, and electrocardiogram. Computerized tomography was employed as necessary to obtain objective tumor measurements. Baseline performance status was recorded for all patients. For all patients with a history of any cardiac disease, and for all those who had received previous doxorubicin, a baseline nuclear medicine ejection fraction was obtained. Prior to randomization, patients were stratified by age (≤ 50 years vs. >50 years) and sites of metastases (visceral vs. soft tissue/regional lymph nodes/bone).

The treatment regimens are shown in Table 1.

TABLE 1
CMF and NFL Regimens[a]

Agents	Doses
CMF	
Cyclophosphamide	600 mg/m^2 i.v. Day 1
Methotrexate	40 mg/m^2 i.v. Day 1
5-Fluorouracil	600 mg/m^2 i.v. Day 1
NFL	
Mitoxantrone	12 mg/m^2 i.v. Day 1
5-Fluorouracil	350 mg/m^2 i.v. bolus Days 1, 2, and 3
Leucovorin	300 mg i.v. Days 1, 2, and 3[b]

i.v.: intravenously.

[a] Both regimens were repeated at 21-day intervals.

[b] Leucovorin was given over 30–60 minutes immediately prior to 5-fluorouracil.

Both regimens were administered every 21 days, for a total of 8 courses. In responding patients who received eight courses, continued treatment with the same regimen was given at the discretion of the treating physician.

After receiving two courses of therapy, patients were reassessed for response. Objective remeasurements of tumors were obtained by repeating appropriate physical examination or radiographic studies. Patients with objective response or stable disease continued therapy every 3 weeks until progression occurred or until a total of 8 courses were administered. During treatment, restaging tests were performed every 2–3 courses of therapy. At the time of disease progression, patients were removed from the study and monitored until the time of death. Further therapy was given at the discretion of the treating physician.

If patients had received no doxorubicin previously and had normal ejection fractions, repeat determinations of ejection fraction were not required until a total mitoxantrone dose of 140 mg/m^2 was reached. For those who had received doxorubicin previously, ejection fractions were determined after a total ''doxorubicin-equivalent'' dose of 450 mg/m^2, and then after every other course. Calculation of ''doxorubicin-equivalents'' = total doxorubicin dose (mg/m^2) + 5 $\times$ total mitoxantrone (mg/m^2).

Dose reductions were based on blood counts on the day of scheduled treatment, as follows: white blood cell count (WBC) $>$3500/μL and platelets $>$125,000/μL, full dose given; WBC 2500–3500/μL or platelets 100,000–125,000/μL, 75% dose; WBC 2000–2500/μL or platelets 75,000–100,000/μL, 50% dose; WBC $<$2000/μL or platelets $<$75,000/μL, treatment delayed 1 week, counts rechecked, and same parameters used to determine the dose. No dose reductions were made on the basis of nadir counts. No dose escalation was planned in this study. Dose reductions included mitoxantrone and 5-fluorouracil; the leucovorin dose was not reduced.

For patients with measurable or evaluable disease, complete response was defined as the complete disappearance of all objective evidence of disease for at least 4 weeks. Partial response was defined as a decrease of $\geq$50% in the sums of products of diameters of measurable lesions, or objective improvement in evaluable lesions with accompanying symptomatic improvement. Stable disease was defined as a decrease of $<$50% or increase of $<$25% in the sums of products of diameters of measurable lesions, or no change in evaluable lesions, with no new lesions appearing. Disease progression was defined as an increase of $\geq$25% in the sums of products of diameters of measurable lesions, worsening of evaluable lesions, or appearance of new lesions. For patients with disease limited to the skeletal system, complete response was defined as the resolution of all symptoms with normalization of the bone scan. Partial response was defined as improvement or resolution of symptoms for at least 3 months, with either an improved bone scan or a stable one. Stable disease was defined as no change in symptoms for at least 3 months, without the development of any new symptoms or the appearance of new lesions on bone scan. Disease progression was defined as worsening of symptoms with either a stable bone scan or the appearance of new lesions on bone scan.

Myelosuppression was assessed by measuring blood counts prior to each course of treatment. Nonhematologic toxicity was also assessed by the treating physician and by the research nurse prior to each course of therapy.

Comparisons of response rates and toxicities in the two treatment groups and in subsets were accomplished using the two-sided chi-square test. Actuarial survival curves were constructed using the Kaplan–Meier method and compared using Wilcoxon's rank sum test. The number of evaluable patients in this study was sufficient to detect an increase in the response rate from 25% to 50% with power 90% and using a significance test of size 0.05.

Patient Characteristics

The characteristics of the patients in each of the two study groups are summarized in Table 2. Patients in the CMF and NFL treatment arms were comparable with respect to potentially important prognostic characteristics. The median age of patients in this study was 58 years, and 72% of patients were postmenopausal, reflecting the age distribution of patients with metastatic breast carcinoma. The majority of patients in each treatment group had one or more visceral sites of metastases. Twenty-two patients (13%) had bone metastases only. Only 46 patients (36%) had received previous adjuvant chemotherapy. Thirty-nine of these 46 patients had received previous CMF or CMF-variant regimens, whereas 7 had received regimens containing cyclophosphamide and doxorubicin. Twenty-seven patients (42%) in the NFL group had received previous adjuvant chemotherapy versus 19 patients (30%) in the CMF group ($P = 0.14$). Seventy-nine patients (62%) had received previous hormonal therapy, either as adjuvant therapy or for metastatic disease.

RESULTS

Sixty-four patients received a total of 338 courses of CMF, and 64 patients received a total of 401 courses of NFL. The median number of courses of CMF received was 5.5 versus 7 courses of NFL. One hundred twenty-six of 128 patients were evaluable for response. Two patients (both receiving CMF) were inevaluable:

TABLE 2
Patient Characteristics (n = 128)

Characteristic	No. of patients	
	CMF (n = 64)	NFL (n = 64)
Median age, yrs (range)	59 (35–78)	57 (34–81)
Performance status		
0	16	13
1	32	38
2	16	13
Menopausal status		
Premenopausal	17	19
Postmenopausal	47	45
Sites of metastases		
Visceral	39	40
Nonvisceral	13	14
Bone only	12	10
Estrogen receptor		
Positive	35	27
Negative	17	20
Unknown	12	17
Previous adjuvant chemotherapy		
None	45	37
CMF + variants	14	25
CAF + variants	5	2
Previous hormonal therapy	41	38
No. of sites of metastases		
1	23	23
2	28	27
>2	13	14

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; NFL: mitoxantrone, 5-fluorouracil, and leucovorin; CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil.

TABLE 3
CMF vs. NFL: Comparison of Response Rates in the Entire Group and in Clinically Relevant Subsets

Patient group	No. of responses (%)		
	CMF (n = 62)	NFL (n = 64)	*P* value
Entire group	16 (26%)	29 (45%)	0.027
Age (yrs)			
<50	5/16 (31%)	10/20 (50%)	0.26
≥50	11/46 (24%)	19/44 (43%)	0.04
Previous adjuvant chemotherapy			
None	13/43 (30%)	16/37 (43%)	0.24
CMF or CAF	3/19 (16%)	13/27 (48%)	0.018
Sites of metastases			
Visceral	8/39 (21%)	12/40 (30%)	0.33
Nonvisceral	5/12 (42%)	13/14 (93%)	0.005
Bone only	3/11 (27%)	4/10 (40%)	0.54
Type of disease			
Measurable	9/33 (27%)	22/39 (56%)	0.013
Evaluable	7/31 (23%)	7/25 (28%)	0.64
Estrogen receptor status			
Positive	7/35 (20%)	12/27 (49%)	0.04
Negative	5/16 (31%)	10/20 (50%)	0.28
Unknown	4/11 (36%)	7/17 (41%)	0.80

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; NFL: mitoxantrone, 5-fluorouracil, and leucovorin; CAF: cyclophosphamide, doxorubicin, and 5-fluorouracil.

one patient died of sepsis while neutropenic, and one patient (with severe emphysema and lung metastases) developed a massive pulmonary embolism. All 128 patients were evaluable for toxicity, and all were included in the survival comparisons.

Seventy-eight percent of all CMF courses were administered at full dose versus 57% of NFL doses ($P < 0.001$). In most instances, a dose reduction to 75% was made based on a Day 21 leukocyte count between 2500 and 3500/μL. Only 4% of CMF courses and 11% of NFL courses required dose reductions to less than 75% of the initial planned dose ($P = 0.001$). Forty-one patients (64%) receiving CMF were able to receive full doses with each course, as compared with 18 patients (28%) receiving NFL ($P < 0.001$).

Response

Response rates to CMF and NFL are compared in Table 3. Sixteen of 62 evaluable patients (26%) receiving CMF had objective responses (14 partial, 2 complete), as compared with 29 of 64 patients (45%) receiving NFL (25 partial, 4 complete) ($P = 0.027$). In responding patients, the median duration of response with CMF was 6 months (range, 2–21 months) versus 9 months with NFL (range, 3–22 months). Four patients had responses lasting more than 1 year with CMF versus 11 patients with NFL ($P = 0.06$).

Table 3 also compares the response rates to NFL and CMF based on age, sites of metastases, and previous adjuvant chemotherapy. In most subsets, patients receiving NFL achieved higher response rates, and these differences reached statistical significance in several subsets. Of particular interest in these comparisons are the low response rates in patients receiving CMF after previous adjuvant chemotherapy and the high response rates in patients with nonvisceral disease receiving NFL.

Figure 1 compares the actuarial survival curves for patients receiving CMF and NFL. The median survival was 16 months for patients receiving CMF versus 19 months for those receiving NFL ($P = 0.48$).

Toxicity

Both chemotherapy regimens were well tolerated, and adverse events are compared in Table 4. Clinically significant myelosuppression was uncommon with both regimens. Nadir counts were not routinely measured, but hospitalization for treatment of neutropenia and fever occurred in only 2% of CMF courses and 4% of NFL courses ($P = 0.16$). Platelet transfusions were required for 1 patient receiving CMF and for no pa-

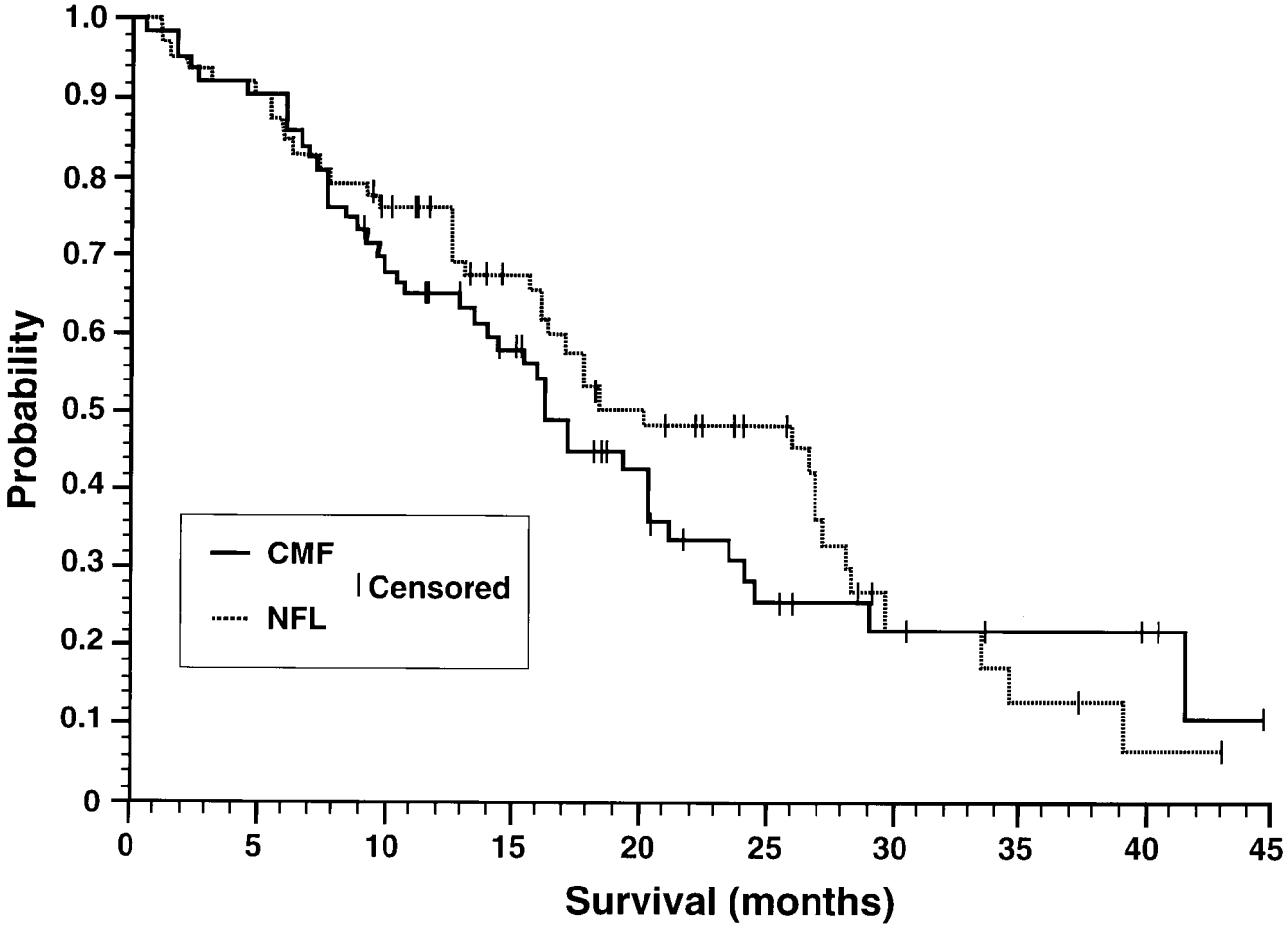

FIGURE 1. A comparison of the actuarial survival curves for patients receiving cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) versus mitoxantrone, 5-fluorouracil, and leucovorin (NFL). Median survivals were 16 and 19 months, respectively ($P = 0.48$).

tients receiving NFL. Thirteen patients required transfusion of red blood cells; 6 of these patients were receiving CMF and 7 were receiving NFL. By Day 21, the blood counts in the large majority of patients had increased to normal or near-normal levels; the leukocyte count remained below 2000 on Day 21 in only 2% of CMF courses and 4% of NFL courses.

No clinically significant cardiotoxicity was encountered in patients receiving NFL. The seven patients who had received doxorubicin previously had normal ejection fractions (51–71%) at study entry; these patients received 2–8 courses of NFL without clinical symptoms of congestive heart failure. Seven additional patients had baseline ejection fraction determinations made because of previous cardiac events. These 7 patients had ejection fractions ranging from 59–80%; 4 of 7 received NFL with no cardiac sequelae.

Other toxicities were also uncommon. Grade 2 through 4 nausea and vomiting was more frequent with CMF than with NFL ($P = 0.001$), whereas mucositis was more common with NFL ($P = 0.10$). Surprisingly, severe alopecia was uncommon in both groups, occurring in only 8 patients (13%) receiving CMF and 5 patients (8%) receiving NFL ($P = 0.25$). One patient (receiving CMF) died of clostridial sepsis while neutropenic.

DISCUSSION

The chemotherapeutic treatment of women with metastatic breast carcinoma has not changed substantially during the last 20 years. The most common regimens used at the time of relapse continue to be CMF, CAF, or variants of these regimens. All standard combination regimens for metastatic breast carcinoma are palliative, with low percentages of complete responses and median response durations in the range of 6–12 months. Although the toxicity produced by standard regimens for the treatment of breast carcinoma is moderate, these regimens frequently interfere with the quality of life of patients in a palliative setting. Common side effects include nausea, vomiting, alopecia,

TABLE 4
CMF vs. NFL: Treatment-Related Toxicity

Toxicity	No. of episodes (%)		
	CMF (338 courses)	NFL (401 courses)	*P* value
Myelosuppression			
Day 21			
WBC < 2000/μL	7 (2%)	18 (4%)	0.07
Platelets < 75,000/μL	3 (1%)	3 (1%)	0.83
RBC transfusions	6 (2%)	7 (2%)	0.98
Platelet transfusions	1 (0.3%)	0	0.28
Hospitalization, neutropenia/fever	8 (2%)	17 (4%)	0.16
Nausea/vomiting			
Grade 1	56 (17%)	94 (23%)	0.001
Grade 2	42 (12%)	27 (7%)	
Grade 3, 4	9 (3%)	2 (0.5%)	
Mucositis			
Grade 1, 2	21 (6%)	33 (8%)	0.10
Grade 3	2 (1%)	9 (2%)	
Diarrhea			
Grade 1	12 (4%)	34 (8%)	0.02
Grade 2, 3	7 (2%)	12 (3%)	
Conjunctivitis			
Grade 2, 3	1 (0.3%)	3 (1%)	0.40
Alopecia (no. of patients)			
Grade 3, 4	8 (13%)	5 (8%)	0.25
Treatment-related deaths	1	0	—

CMF: cyclophosphamide, methotrexate, and 5-fluorouracil; NFL: mitoxantrone, 5-fluorouracil, and leucovorin; WBC: white blood cells; RBC: red blood cells.

mucositis, and chronic fatigue. Regimens containing doxorubicin are associated with these toxicities more frequently than are CMF-type regimens. Although response rates are higher with regimens containing doxorubicin, changes in median survival have not been demonstrated in most comparative studies, even when dose intensity is increased up to twofold.[10–15]

The NFL regimen was originally designed in an attempt to achieve efficacy comparable to standard regimens while avoiding some of the side effects particularly bothersome to patients (e.g., alopecia, nausea, vomiting, and mucositis). In our initial Phase II study, these goals were apparently achieved; we obtained a 65% response rate in patients receiving first- or second-line therapy for metastatic breast carcinoma.[1] Myelosuppression was the most common toxicity, but it was easily manageable, and other toxicities were infrequent. Several subsequent Phase II studies have substantiated our observations, achieving response rates similar to other standard regimens with apparently less toxicity.[2–4] The doses and schedules of 5-fluorouracil and leucovorin differed substantially in these Phase II studies, making direct comparisons difficult. However, all regimens were well tolerated except those using very high doses of 5-fluorouracil and leucovorin.[5]

Although the Phase II results with NFL compared favorably with those reported with standard regimens, we felt that a prospective, randomized comparison was necessary before NFL could be recommended as first-line therapy for metastatic breast carcinoma. As a standard regimen, we selected a commonly used all-intravenous CMF regimen.[16] Compared with other CMF regimens, this regimen was easy to administer and relatively well tolerated. We selected a CMF regimen, rather than a regimen containing doxorubicin, for the following reasons: (1) CMF was the most commonly used first-line regimen at the time this study was initiated; (2) an intensive cyclophosphamide/doxorubicin regimen would not have been applicable to elderly patients, a group we were interested in including in this comparison; and (3) previous randomized studies had already shown significant differences in toxicity between doxorubicin and mitoxantrone used either alone or in combination regimens.[7,17] Although the response rates may have been higher with either a regimen containing doxorubicin or a more intensive CMF regimen, we felt that the extra toxicity was not justified in a palliative setting, particularly in the treatment of elderly patients.

In this randomized study, we have demonstrated a significantly higher response rate (45% vs. 26%) for NFL as compared with this CMF regimen. The median survival was similar in the two groups of patients (19 and 16 months), and similar median survivals have been reported in a number of other clinical trials. Both regimens were well tolerated, and severe toxicities were uncommon.

The response rate to NFL, although slightly lower than we reported previously, was similar to the response rates reported by other investigators.[2–4] The reported response rates with CMF regimens have varied from 25% to 68%, with response rate roughly correlated with the intensity of the CMF regimen employed.[10,12,13,18–22] Response rates similar to those achieved in our study have been reported with this particular CMF regimen, which uses relatively low dose intensities of the three chemotherapeutic agents.[20,22,23] A recent randomized trial documented lower response rates with this CMF regimen as compared with the original CMF regimen used by Bonnadonna et al., in which 14 days of oral cyclophosphamide were given (29% vs. 48%, respectively).[16,23] In addition, the median survivals of the two groups in this study also differed: 12 months for the all-intravenous CMF regimen versus 17 months for the classical CMF regimen ($P = 0.016$). However, more intensive CMF regimens are also more toxic with respect to myelosuppression, alopecia, nausea, vomiting, and mucosi-

tis. In addition, many reported series of patients treated with more intensive CMF regimens contained patients with median ages 5–10 years younger than in our series.[10,12,13,18,19] Although it is likely that the use of either a more intensive CMF regimen or a regimen containing doxorubicin would have resulted in a higher response rate than was achieved with the CMF regimen in this study, the added toxicity with such regimens would have then compared unfavorably with the toxicity observed with NFL. Based on the results of a number of previous studies, it seems unlikely that such intensification would have changed the median survival of patients substantially.

Since the initiation of this study, several trends in the systemic treatment of breast carcinoma have occurred that may effect the application of these results to clinical practice. The most important of these changes have occurred in adjuvant therapy. A larger overall percentage of women now receive adjuvant chemotherapy, including larger numbers of lymph node negative patients and also more postmenopausal women with lymph node positive disease. Regimens containing doxorubicin are increasingly used, rather than CMF, in the treatment of patients with lymph node positive breast carcinoma. Finally, the importance of dose intensity has now been demonstrated in randomized trials, and adjuvant regimens of increased dose intensity have found increasing acceptance in clinical practice.[24] Although retreatment with the same regimen has been useful for patients relapsing more than 12 months after adjuvant therapy,[25,26] it is likely that patients in general will have more treatment-resistant disease at the time of relapse. Patients who have received intensive adjuvant therapy containing doxorubicin may have increased resistance to mitoxantrone at the time of relapse, thereby lowering the efficacy of the NFL regimen.

Another recent change in the treatment of metastatic breast carcinoma relates to the availability of new and highly active agents, such as the taxanes (paclitaxel and docetaxel) and vinorelbine.[27–31] Several other new drugs, including gemcitabine and the topoisomerase I inhibitors, have also demonstrated single agent activity in the treatment of metastatic breast carcinoma.[32,33] Although the role of most of these new agents in breast carcinoma treatment remains undefined, the taxanes have been rapidly incorporated into standard therapy due to their activity in doxorubicin-refractory patients.[34–36] Short infusions (3 hours or less) of paclitaxel are relatively well tolerated by premenopausal and postmenopausal patients. However, alopecia occurs in all patients, and mild to moderate arthralgia, myalgia, and peripheral neuropathy are common. In addition, response rates to single agent paclitaxel (175 mg/m^2 given over 3 hours) are 25–35%,[37,38] and well-tolerated combination regimens for breast carcinoma have not been developed.[39]

In spite of the ongoing changes in the systemic treatment of breast carcinoma, a sizable percentage of women developing metastatic breast carcinoma will continue to be good candidates for palliative treatment with the NFL regimen. These include postmenopausal women relapsing after adjuvant hormonal therapy and many of the lymph node negative patients still treated routinely with adjuvant CMF regimens. For many of these patients, NFL may be a better choice for first-line therapy than either a regimen containing doxorubicin or single agent paclitaxel. In addition to these groups, patients who have previously exhibited poor tolerance of adjuvant chemotherapy may have the best results with NFL treatment.

Conversely, certain subsets of women may be more effectively treated with regimens other than NFL. Patients relapsing after adjuvant therapy containing doxorubicin, particularly within 12 months, are better treated with a regimen containing a taxane. In addition, high dose chemotherapy may be preferable in certain subgroups (i.e., age $<$55 years with limited tumor burden), because a minority can achieve prolonged unmaintained complete remissions and survival may be prolonged.[40]

In summary, the results of this randomized trial confirm the efficacy of the NFL regimen as compared with a commonly used CMF regimen. The results also duplicate previous Phase II data regarding the relatively mild adverse effects of NFL. Until new treatments are developed that substantially change the survival of patients with metastatic breast carcinoma, the NFL regimen will continue to provide clinicians with a well-tolerated, palliative therapy for these patients.

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