Progress in Chemotherapy for Metastatic Breast Cancer

George W. Sledge, Jr and Karen H. Antman

APPROXIMATELY 45,000 women died of breast cancer in the United States in 1991, virtually all as a consequence of distant metastatic disease. Women with metastatic breast cancer are essentially incurable with standard therapy with a median survival of about 2 years after documentation of metastases.[1,2] The median survival of women with metastatic disease has not changed in the 5 decades for which statistics are available. While generally sensitive to initial chemotherapy regimens, metastatic breast cancer virtually always progresses with shorter and less complete remissions with subsequent regimens. Women with estrogen receptor positive tumors (median survival, 2.3 years), and those who achieve a complete response with standard dose therapy (median, 2.5 years) or who have only small amounts of local disease (median, >4 years) have a somewhat better prognosis.[2]

Metastatic breast cancer therefore represents a major public health problem as well as a frightening personal dilemma for women afflicted with the disease. For the physician caring for the patient with metastatic breast cancer, the disease represents a separate set of problems. What treatment goals should the physician strive for? Should medical efforts focus on the production of high clinical response rates? On prolongation of survival? On palliation of symptoms? On improvements in quantitatively elusive yet eminently real quality of life considerations?

The clinical researcher evaluating new cytotoxic therapy for metastatic breast cancer is faced with a parallel set of concerns. Should the physician-scientist (as well as cooperative oncology groups and research institutions) focus on issues affecting the therapeutic ratio of chemotherapy for metastatic breast cancer (maximize tumor response and minimize toxicity)? Or should the researcher view metastatic breast cancer as a model for regimens that might prove useful in an adjuvant (and potentially curative) setting? Finally, should the physician-scientist aim for the therapeutic "home run"—the cure of metastatic disease? Each of these approaches results in different, and sometimes mutually exclusive, research strategies. The problems and concerns listed above, frequently formulated as testable scientific hypotheses, have guided much of clinical research in the chemotherapy of metastatic breast cancer in recent years.

NEW AGENTS

In the past decade no new chemotherapeutic agents received FDA approval for the treatment of metastatic breast cancer. A positive new trend in phase II drug testing in patients with metastatic breast cancer is worth noting. Phase II agents had been routinely evaluated in heavily pretreated patients. Impaired performance status and previous marrow damage frequently limited administration of effective doses of drug to tumors with significant levels of multi-drug and other mechanisms of resistance. However several promising new agents (Table 1) have demonstrated significant clinical activity in phase II trials.[3-5,7-9] These new agents were tested in patients with no previous chemotherapy for metastatic disease. This clinical environment represents a more realistic setting for evaluation of new agents.

Anthracycline and Anthracene Analogs

Doxorubicin, generally considered the single most active agent in metastatic breast cancer, is limited primarily by its hemopoietic and cardiac toxicity. Two novel agents, the anthracycline epirubicin and the anthracene mitoxantrone, appear to have less cardiotoxicity than doxorubicin. Although mitoxantrone appears to be modestly less active with regard to response rate than doxorubicin in doses with equivalent myelo-

From the Department of Medicine, Indiana University School of Medicine, Indianapolis, IN; and the Department of Medicine, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA.

Supported in part by US Public Health Service Grant No. PO1CA-38493 and a grant from the Mather's Foundation.

Address reprint requests to George W. Sledge, Jr, MD, Indiana University Hospital, 926 W Michigan St, Room 1730, Indianapolis, IN 46202.

0093-7754/92/1903-0001$05.00/0

Table 1. Novel Agents for the Treatment of Metastatic Breast Cancer: Trials in Previously Untreated Patients

Agent	Dose	Response Rate	Reference
Mitoxantrone	14 mg/m² every 3 wk	35/99 (35%)	4
Epirubicin	120 mg/m² every 3 wk	15/22 (69%)	8
Cisplatin	30 mg/m² qd X4 every 3 wk	9/19 (47%)	10
Carboplatin	400 mg/m² every 3 wk	4/20 (20%)	7
Navelbine	30 mg/m² every wk	10/19 (52%)	3
Amonafide		6/26 (23%)	5
CL-941		20/31 (64%)	11

toxoicity, both as a single agent and in combination therapy, overall survival in prospective, randomized trials has not been compromised.[12-15] This lack of correlation between response rates and overall survival may represent the more general inability of standard breast cancer chemotherapy to significantly affect overall survival in patients with metastatic disease. Epirubicin is certainly at least equivalent to doxorubicin with regard to response rate and overall survival in prospective randomized trials when administered in doses with equivalent myelotoxicity.[16-20] Therefore, both agents represent reasonable alternative to doxorubicin in the patient with metastatic breast cancer, but are not commercially available in the United States.

CI-941 is an anthrapyrazole synthesized in an attempt to produce an agent with less cardiotoxicity than doxorubicin. CI-941 has a chromophore modification of the anthracenedione nucleus. The bis-hydroxyethylaminoalkyl side chains are identical to mitoxantrone replacing the glycone structure of doxorubicin. A phase II clinical trial of single agent CI-941 at a dose of 50 mg/m² given every 21 days in 31 patients with advanced breast cancer who had had no previous anthracycline or mitoxantrone. Fifteen had no previous cytotoxic chemotherapy and the remainder had had mainly cyclophosphamide, methotrexate, fluorouracil (CMF). Thirty patients were evaluable for response. Two patients (7%) had complete responses (of bulky intra-abdominal disease on computed tomography and of a soft tissue deposit on the anterior thoracic wall). The response rate in patients with and without previous chemotherapy was 63% and 64% respectively (95% confidence interval 46% to 81%). The median response duration was 28 weeks from start of treatment (range, 4 to 70+ weeks).[11]

Cisplatin and Platinum Analogs

Cisplatin, tested extensively in the 1970s and early 1980s in heavily pretreated metastatic breast cancer, demonstrated no appreciable clinical activity. In more recent trials in patients with no previous chemotherapy for metastatic disease, cisplatin has had significant activity, with response rates equivalent or superior to those of currently used agents in metastatic breast cancer.[9,21] In combination therapy, it has been demonstrated to achieve response rates and overall survival times comparable to those of other standard chemotherapy regimens.[22-25] Therefore, it can be considered a "new drug" in metastatic breast cancer. Its peculiar toxicities and relative inconvenience have limited its use in metastatic breast cancer, a disease traditionally treated in the outpatient clinic, although not in the setting of high-dose chemotherapy and autologous bone marrow transplantation (as discussed below). There is a somewhat smaller body of experience with the platinum analog carboplatin. As front-line chemotherapy, responses were observed in four of eight patients in one study and in four of 20 patients in the other.[7,26] As carboplatin's predominant toxicity is hematopoietic, it is a potential candidate for dose intensification with autologous stem-cell transplantation (as discussed below).

Three other agents, navelbene, amonafide, and taxol, have shorter pedigrees than those mentioned above, but are potentially quite promising. Navelbene, a vinca alkaloid, has been reported to have an objective response rate of 52% in previously untreated patients, higher than that of other vinca alkaloids.[3,27] Amonafide, a new imide derivative of napthalic acid and a DNA intercalator, has significant activity in previously untreated patients, with a response rate of 23%.[5] As this agent has primarily hematologic toxicity, it is a potentially interesting candidate for dose escalation. Taxol, an antimicrotubule agent, has produced a response rate of 56%.[6] Some of these responsive patients had prior anthracycline therapy. These agents will require confirmatory studies before routine application.

CONVENTIONAL CHEMOTHERAPY FOR METASTATIC BREAST CANCER

From the late 1960s through the mid 1970s clinical researchers developed chemotherapy regimens for metastatic breast cancer. While these regimens differed in terms both of number and type of chemotherapeutic agents employed, they shared common characteristics. (Representative combinations are shown in Table 1.) These regimens were based on the superiority of combinations over single agents in the laboratory to decrease the emergence of drug resistance,[28-31] and used agents with nonoverlapping toxicities. Generally administered in an outpatient setting, regimens were designed to achieve maximal objective clinical response rates with acceptable toxicity.

Standard dose chemotherapy regimens, whether doxorubicin (eg, 5-flourouracil, adriamycin, cyclophosphamide [FAC]) or methotrexate (eg, cyclophosphamide methotrexate 5-flourouracil [CMF] or CMF vincristine prednisone [VP]) based, have more similarities than differences. In previously untreated patients, these regimens produce 40% to 75% objective response rates complete response [CR] and partial response [PR], with median durations of response and survival of 6 to 12 months and 12 to 24 months, respectively. These regimens frequently palliate the symptoms of metastatic breast cancer, but do not substantially extend the median survival and virtually never result in the cure of patients with metastatic breast cancer. Doxorubicin-based regimens generally have somewhat higher overall response rate than methotrexate-based regimens, although at greater cost in toxicity.[32]

The results reported for standard chemotherapy should be considered in context. The majority of trials included a defined subset of patients with metastatic breast cancer. Clinical trials regularly exclude patients with coexisting medical and psychological illnesses, poor performance status, organ system dysfunction, or older age. Furthermore, reported results for standard regimens initially were, and largely still are, derived in populations with no previous adjuvant chemotherapy. Thus, many patients with predictably poor response rates or survival are excluded from reported clinical trials, but present very real therapeutic challenges in the physician's office. The real world of metastatic breast cancer treatment is therefore frequently even more disheartening than the already dismal statistics reported in clinical trials.

OLD WINE IN NEW BOTTLES

Although there is general, if incomplete agreement as to what constitutes conventional chemotherapy for metastatic breast cancer, there is little agreement as to how such therapy should be used. Recent research has studied the best means of using standard chemotherapy regimens. Such research has focused on two salient questions in cancer chemotherapy: duration of therapy and dose intensity.

Duration of Therapy

An important question regarding standard therapy is the optimal duration of chemotherapy. Should chemotherapy be administered continuously (ie, until disease progression), or intermittently (with treatment only until maximum response, followed by retreatment at time of progression)? Opponents of continuous therapy argue that treatment past a predefined goal (such as an objective remission, or palliation of symptoms) results in impairment of quality of life secondary to cumulative drug toxicity. Because metastatic breast cancer is incurable with standard chemotherapy, intermittent treatment (at such time as there is clear disease progression or symptomatic worsening) would avoid such toxicity. Conversely, opponents of intermittent therapy argue that continuous therapy might delay relapses, increase overall response rates (hence improve palliation of disease), and potentially prolong survival.

Three recently-reported trials have addressed this question (Table 2). The Australia-New Zealand Breast Cancer Trials Group randomized patients to receive standard chemotherapy regimens (doxorubicin and cyclophosphamide or cyclophosphamide, methotrexate, fluorouracil, and prednisone) either intermittently or continuously.[33] Intermittent therapy, comprised of three cycles of therapy, with re-treatment upon progression, proved inferior to continuous therapy with regard to overall response rates, although survival was not adversely affected.

Table 2. Randomized Trials of Treatment Duration in Metastatic Breast Cancer

Regimen	Randomization	TTP	OS	*P* Value	Reference
D 50 mg/m²	Continue to progression				33
C 750 mg/m² every 21 days	*v*	6 mo	10.7 mo		
or	3 cycles; re-treat upon				
C 100 mg/m² daily for 14 days	progression			0.19	
M 40 mg/m² days 1 and 8					
F 600 mg/m² days 1 and 8		4 mo	9.4 mo		
Pr 40 mg/m² daily for 14 days every 28 days					
C 600 mg/m²	18 mo	52 wk	67 wk		34
E 60 mg/m² every 3 wk	*v*			0.068	
F 600 mg/m²	6 mo	39 wk	58 wk		
+					
T 30 mg orally each day					
Mx 14 mg/m² every 3 wk for 4 courses	Retreat upon progression	26 wk	52 wk		35
	v			NS	
	Continue to progression				
		22 wk	49 wk		

Abbreviations: D, doxorubicin; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil; Pr, prednisone; T, tamoxifen; Mx, mitoxantrone; TTP, time to progression; OS, overall survival.

However, quality of life was superior in patients receiving continuous therapy. A similar trial by the Danish Breast Cancer Cooperative Group randomized patients with estrogen and progesterone-receptor-negative cancers to receive cyclophosphamide, epirubicin, and fluorouracil every 3 weeks for either 6 or 18 cycles.[34] All patients also received tamoxifen. The median time to progression was significantly longer (and survival marginally longer) in the group receiving continuous therapy.

In a similar trial, Harris *et al* treated patients with four cycles of single-agent mitoxantrone.[35] Responding patients were then randomized to either continuous therapy with mitoxantrone, or to re-treatment upon progression. Patients on continuous mitoxantrone averaged seven cycles of therapy. There was no survival advantage for patients receiving continuous therapy; quality of life was not assessed in any systematic fashion. This result must be viewed cautiously because the overall response rate to four cycles of single-agent mitoxantrone (30%) and the number of additional cycles was sufficiently low that any survival benefit or palliation of symptoms might be difficult to demonstrate. Similarly, Glaholm et al have pointed out that this trial lacked the statistical power to demonstrate even moderate survival benefits.[36]

These three studies suggest that prolonging duration of therapy is likely to have at best a marginal effect on overall length of survival for women with metastatic breast cancer, but may improve the quality of that time, by diminishing breast-cancer-related symptoms and delaying relapse. The appropriate duration of therapy must be considered still an open issue. The Eastern Cooperative Oncology Group is completing protocols in which maintenance therapy after establishment of complete remission is randomized. These protocols should provide additional information regarding the duration of therapy.

Dose Intensity

A relationship between dose and clinical response has long been recognized, for both individual and combination chemotherapeutic agents.[37] Laboratory models have been recently reviewed.[38] Systematic analysis of dose-response relationships in the clinic has proven problematic, and until recent years few attempts had been made to quantify dose-response relationships in patients with metastatic breast cancer.

In 1984 Hryniuk and Bush introduced the concept of dose intensity for the purpose of quantifying dose-response effects, using meta-

static breast cancer as a clinical model.[39] They argued that quantitation of dose-response effects required that dose be viewed as a function of the time (ie, dose intensity). In their analyses, dose intensity is expressed arbitrarily as units of drug administered per square meter per week. In trials in which multiple agents were used, Hryniuk and Bush expressed the dose intensities of individual drugs compared with those of a standard regimen. These relative dose intensities are then added and divided by the number of drugs in the regimen to produce the average relative dose intensity for a regimen. These average dose intensities are then compared with those of an arbitrary "standard" regimen (eg, the Cooper regimen for methotrexate-based regimens, or Bull and Tormey cyclophosphamide, doxorubicin, fluorouracil (CAF) for doxorubicin-based regimens.

In metastatic breast cancer, the Hrynuik-Bush dose intensity analysis suggested that dose intensity correlated strongly with response, and that response in turn correlated significantly with survival. This relationship was seen for both methotrexate- and doxorubicin-based regimens. Based on this analysis, the authors suggested that chemotherapy regimens should be designed to maximize dose intensity. This provocative thesis has had a profound influence on the design of both individual regimens and group trials. Emphasizing overall dose administered over time, rather than the peak dose, has led to the development of regimens in which complex scheduling and repetitive therapy replace high-dose, single bolus infusions. This approach stands in contrast to the philosophy underlying high-dose chemotherapy and autologous bone marrow transplantation, as discussed below. Two such dose-intensive regimens (the Duke AFM regimen and the Johns Hopkins 16-week regimen) are shown in Table 3.[39,41]

The dose-intensity hypothesis and methodology have been debated extensively based on both practical and theoretical concerns.[13,42] Dose intensity, as calculated by Hryniuk and Bush, necessarily oversimplifies a complex problem by making numerous assumptions. These include (1) that all drugs in a given regimen are therapeutically equivalent in dose-intensity calculations; (2) that synergy and cross-resistance between drugs play no role; (3) that peak drug concentrations are not so important as the area under the curve (AUC); (4) that scheduling has no importance other than as it relates to total dose intensity; and (5) that duration of therapy is inconsequential. Furthermore, the Hryniuk-Bush retrospective analysis relies heavily on the assumption that all reported studies are comparable with regard to entrance criteria, prognostic variables, and analysis of response and survival.

Table 3. High Dose Intensity Chemotherapy Regimens

AFM Regimen: Cycles repeated every 21 days
Fluorouracil 750 mg/m² CI for 5 days
Doxorubicin 25 mg/m² days 3-5 IV
Methotrexate 250 mg/m² day 15 IV
Folinic acid 12.5 mg orally q6h X 6 D15
Hopkins Regimen: Cycles repeated every 14 days
Cyclophosphamide 100 mg/m² orally for 7 days
Doxorubicin 40 mg/m² IV day 1
Vincristine 1 mg IV day 1
Methotrexate 100 mg/m² IV day 1
Fluorouracil 600 mg/m² day 2
Leucovorin rescue
Fluorouracil 300 mg/m² by CI days 8 and 9

Abbreviations: CI, continuous infusion; IV, intravenously.

Given the concerns regarding the methodology in Hryniuk-Bush type of retrospective analysis, it seems appropriate to consider results from randomized clinical trials in which dose intensity is the sole or most important variable.[43-51] Some of these trials are shown in Table 4.

These trials are difficult to interpret because the increased doses planned varied from 10% to two- to threefold over the low dose arms. Because the serum levels for a given dose of drug commonly vary fivefold, the serum levels of drug achieved on these trials must overlap considerably. In addition, the actually delivered dose (frequently not included in the manuscript) is often not significantly different from that delivered on the lower dose arm.

In many cases, these trials have shown an increase in response rates for regimens with greater dose intensity. Only two trials show a significantly increased overall survival. In a trial by Tannock et al, randomization resulted in an excess of patients with brief durations between initial diagnosis and relapse on the low-dose-intensity arm causing the authors to advise caution in the interpretation of their observations.[49] Carmo-Pereira et al demonstrated a

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.