Phase II Trials of Baker's Antifol, Bleomycin, CCNU, Streptozotocin, Tilorone, and 5-Fluorodeoxyuridine Plus Arabinosyl Cytosine in Metastatic Breast Cancer

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A total of 202 patients with advanced breast cancer were entered into two prospectively randomized Phase II trials conducted by the Eastern Cooperative Oncology Group, in an effort to identify promising agents and combinations for previously treated cases. Patients in Study 1 received bleomycin, CCNU, or streptozotocin and those in Study 2 received tilorone, Baker's antifol, or a combination of 5-fluorodeoxyuridine plus arabinosyl cytosine. Partial responses were seen only with bleomycin, Baker's antifol, and 5-fluorodeoxyuridine plus arabinosyl cytosine. The median times to treatment failure ranged from 3.6 weeks to 5.7 weeks, and the median survival times, from 8 weeks to 25 weeks for tilorone and bleomycin, respectively. Toxic reactions was primarily hematologic and gastrointestinal, but skin, neurologic, respiratory, and renal abnormalities were noted in some treatment arms. The treatment schedules outlined and the toxic effects noted provide background information that might prove useful in designing complex new chemotherapeutic programs, since there is pharmacological rationale for incorporating some of the agents tested into present standard combination chemotherapy regimens.

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THE CHOICE OF AGENTS for the initial use of cytotoxic combination chemotherapy in patients with metastatic breast cancer is usually not difficult. The use of alkylating agents and antimetabolites with or without Adriamycin, vincristine, or prednisone in a variety of chemotherapeutic regimens has resulted in improved response and survival rates for patients not previously exposed to chemotherapy. The selection of appropriate single agents and combinations for cases proven refractory to these regimens is considerably more difficult. In an effort to identify promising agents and combinations for previously treated cases of meta-

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static breast cancer, the Eastern Cooperative Oncology Group (ECOG) performed prospective randomized Phase II trials involving a group of such cases.

In this report, we present a detailed analysis of these studies, evaluating the single agents Baker's antifol, bleomycin, CCNU, streptozotocin, and tilorone and the combination of 5-fluorodeoxyuridine and arabinosyl cytosine for antitumor activity and for information on the toxic effects of these treatments. Preliminary observations of these results have already been reported.[1,5]

Materials and Methods

Patient Selection

Eligible patients were those who had histologically confirmed metastatic breast carcinoma no longer amenable to conventional therapy and with evidence of progressive disease. Each had measurable disease. A pretreatment leukocyte count of at least 4000/mm^3 was necessary, although for a time any patient with a count of less than 5000/mm^3 was included in a nonrandomized fashion and directly assigned to receive tilorone. No patient was totally bedridden, and none had undergone prior treatment with any of the agents studied. Every patient had to have recovered from the effects of previous chemotherapy, wide-field radiation therapy, or major surgery, and could have no significant infections at the time of entry into study. At least four weeks had to have elapsed from the cessation of medical hormonal therapy and eight weeks from any surgical hormonal manipulation.

A total of 88 patients entered the protocol evaluating bleomycin, CCNU, and streptozotocin (Study 1). A total of 114 postmenopausal patients entered the study involving Baker's antifol, tilorone, and 5-fluorodeoxyuridine plus arabinosyl cytosine (Study 2).

Drug Treatments

Patients in Study 1 were randomized to receive bleomycin, 15 mg/m^2, intramuscularly once weekly; or CCNU, 130 mg/m^2 orally as a single dose every six weeks, or streptozotocin 0.5 g/m^2, (originally 1.25 g/m^2) intravenously once weekly in Study 1. Three patients received CCNU at a lower dosage, 100 mg/m^2, and all but three patients on streptozotocin received the lower dosage because of anticipated or encountered excessive toxicity. Treatment was discontinued when progressive disease became evident.

Patients in Study 2 were stratified according to performance status (ambulatory vs. nonambulatory) and dominant metastatic site (visceral > osseous > local or soft tissue) prior to randomization. Patients were randomized to receive either 5-fluorodeoxyuridine, 1.5 mg/m^2 over 2 hours by intravenous infusion followed by arabinosyl cytosine, 100 mg/m^2 as a 1-hour intravenous infusion given daily for five days at monthly intervals from April 1974 to January 1977; or tilorone, 340 mg/m^2 orally daily from April 1974 to November 1975; or Baker's antifol, 250 mg/m^2 as a 1-hour infusion given daily for three days every three weeks from February 1976 to January 1977. Thus, a greater distribution of patients received either 5-fluorouracil plus arabinosyl cytosine or Baker's antifol because tilorone was dropped before the conclusion of the study and Baker's antifol was included in the randomization after the study began. Therapy was stopped at the time of progression. Dosage modifications for hematologic, gastrointestinal, or renal toxicities were incorporated into each study.

Evaluation

Each patient had standard pretreatment and follow-up examinations, including a complete history and physical examination, hematologic and serum chemistry profile, x-rays of the chest and skeleton, and a radioisotopic liver scan, as well as other studies deemed appropriate for evaluating and following suspected metastatic development. Levels of response were defined as: complete response, disappearance of all measurable disease with no new lesions developing and recalcification of osteolytic lesions; and a partial response, when there was a decrease within an organ of at least 50% in the product of the two largest perpendicular diameters of measurable lesions and/or there was no change or partial recalcification of bone metastases. A patient was considered to be a partial responder if at least half of all organ sites were in partial response. Both partial and complete responses had to last at least four weeks. Progression was defined as an increase of at least 25% in the same product, the occurrence of new lesions, and/or the progression of bone metastases. A no change category represented a decrease of less than 50% or an increase of less than 25% over original measurements with no change in osseous lesions that lasted for at least eight weeks. Patients were classified as unevaluable if they were without objective response or progression and went off study or died within the first eight weeks of treatment. Such patients were considered nonresponders in the analysis. The ECOG toxicity criteria was used in each case and recorded as mild, moderate, severe, or lifethreatening.[6]

TABLE 1. Prior Therapy for Patients with Metastatic Breast Cancer

	Bleomycin	CCNU	Streptozotocin	Baker's antifol	Tilorone	FUdR + ARA-C	Total
Mastectomy	82%	77%	90%	91%	88%	97%	88%
Primary radiation (definitive)	0%	9%	5%	0%	8%	3%	4%
Radiation to metastases	73%	77%	79%	74%	88%	72%	77%
average no. of sites	1.5	1.4	1.5	1.4	1.6	1.5	1.5
Hormone therapy	46%	55%	74%	60%	88%	72%	66%
Ablative surgery	36%	32%	42%	29%	24%	34%	32%
Additive agents	27%	41%	63%	60%	68%	69%	56%
Average no. of therapies	0.7	0.8	1.2	1.2	1.2	1.4	1.1
Response if had hormonal therapy							
Yes	20%	33%	43%	29%	21%	32%	30%
Unknown	30%	33%	14%	33%	26%	25%	26%
No	50%	33%	43%	38%	53%	43%	44%
Chemotherapy	100%	100%	100%	100%	100%	100%	100%
Average no. of regimens	1.7	1.2	2.5	2.5	2.2	2.5	2.2
Average no. of drugs	4.0	3.0	4.1	5.1	4.7	4.8	4.4
Immunotherapy (all BCG)	0%	0%	0%	3%	4%	0%	1%

Results

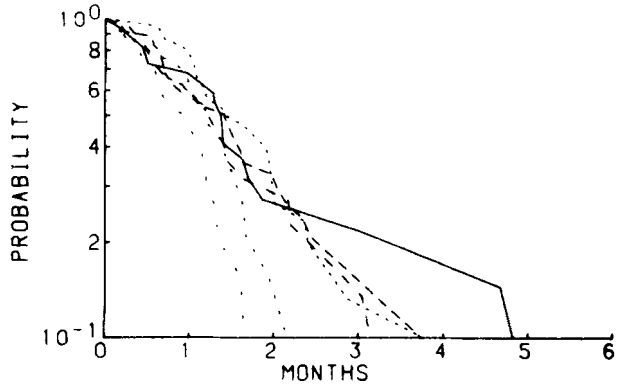
The distribution of patients according to age, prior therapy, performance status, and organ involvement was generally similar in each treatment group. Only approximately 55% of the patients were ambulatory and visceral involvement was present in 65–73% of the cases. These patients had already undergone extensive therapy, as shown in Table 1. The average number of prior chemotherapeutic agents used was 4.4. Twenty-three percent (47) of the 202 patients entering on the two studies, 47 (23%) were not included in this analysis because of treatment cancellations (seven patients), no prior chemotherapy (25 patients), or failure to satisfy eligibility requirements (15 patients).

The results observed are shown in Table 2. No complete responses were seen. Among the six treatment programs, there were four partial responses and 36 patients had stabilization of their far-advanced disease. No treatment arm was significantly better or worse than any other in terms of response rate. Partial responses were achieved with bleomycin, Baker's antifol, and 5-fluorodeoxyuridine plus arabinosyl cytosine. Disease stabilization was noted in all treatment arms except for that involving tilorone.

The patients who achieved partial responses included a 61-year-old woman with liver metastases who achieved an eight-week response with weekly bleomycin; a 50-year-old with stable bone lesions and skin recurrences that cleared for 26 weeks on monthly five-day cycles of 5-fluorodeoxyuridine plus arabinosyl cytosine; and a 59-year-old with skin recurrence and a 63-year-old with liver metastases, both of whom responded to Baker's antifol for 19 and 29 weeks, respectively. The bleomycin responder had been treated previously with phenylalanine mustard. The 5-fluorodeoxyuridine plus arabinosyl cytosine responder had previously received 5-fluorouracil with cyclophosphamide and methotrexate (CMF). One of the Baker's antifol responders had previously received CMF plus

TABLE 2. Response of Breast Cancer Patients to Various Agents

Number of patients	Bleomycin	CCNU	Streptozotocin	Baker's antifol	Tilorone	FUdR + ARA-C
Entered	29	30	29	39	28	47
Cancelled (never got drug)	1	0	0	0	0	6
With no prior chemotherapy	3	5	7	0	3	7
Ineligible	3	3	3	4	0	2
Analyzed	22	22	19	25	25	32
With partial response	1 (5%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	1 (3%)
With no change	6 (27%)	6 (27%)	3 (16%)	10 (29%)	0 (0%)	11 (34%)
With progression	13 (59%)	12 (55%)	12 (63%)	17 (49%)	11 (44%)	12 (38%)
Nonresponders who were on study for less than 8 weeks and did not have objective progression	2 (9%)	4 (18%)	4 (21%)	6 (17%)	14 (56%)	8 (25%)
Early death	2	4	4	4	9	4
Refused further treatment	0	0	0	0	3	3
Withdrawn because of toxic reaction	0	0	0	0	1	1
Withdrawn because of subjective worsening	0	0	0	2	0	0

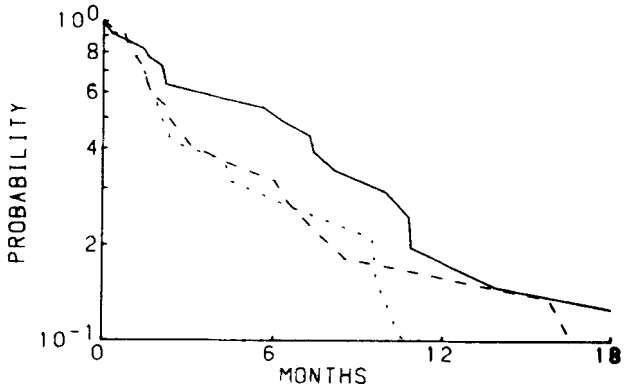


TREATMENT CODE	NOPRG	PROG	TOTAL	MEDIAN
—— BLEOMYCIN	3	19	22	1.4
· · · STREP	0	19	19	1.2
– – CCNU	2	20	22	1.2
····· FUDR-ARAC	2	30	32	1.4
– – – BAK-ANTIFOL	1	34	35	1.4
· · TILORONE	4	21	25	0.9

FIG. 1. Time to treatment failure for patients receiving bleomycin (——), streptozotocin (- - -), CCNU (– –), FUdR-Ara-C (-----), Baker's antifol (– – –), or tilorone (· ·). The median times to treatment failure were 1.4, 1.2, 1.2, 1.4, 1.4 and 0.9 months, respectively.

vincristine and also Adriamycin and the other responder had received only 5-fluorouracil.

The median times to treatment failure are shown in Figure 1. They ranged from 3.6 weeks for tilorone-treated cases to 5.7 weeks for patients treated with bleomycin, attesting to the refractory state of disease in the majority of patients. The median survival patterns seen in each study are shown in Figures 2 and 3. They ranged from eight to nine weeks for tilorone-



TREATMENT CODE	ALIVE	DEAD	TOTAL	MEDIAN
—— BLEOMYCIN	1	21	22	6.2
· · · STREP	0	19	19	2.0
– – CCNU	2	20	22	2.3

FIG. 2. Survival for patients receiving bleomycin (——), streptozotocin, (- - -), or CCNU (– –). The median survival times were 6.2, 2.0, and 2.3 months, respectively.

streptozotocin cases to 25 weeks for bleomycin-treated cases.

The toxic reactions were primarily hematologic and gastrointestinal, as expected, but skin, neurologic, respiratory, and renal abnormalities were noted in some of the treatment arms. A summary of these details is presented in Table 3. Severe and life-threatening myelosuppression was seen with CCNU, Baker's antifol, and 5-fluorodeoxyuridine plus arabinosyl cytosine, and streptozotocin, but not with the other two agents. One patient receiving CCNU and one receiving 5-Fluorodeoxyuridine plus arabinosyl cytosine had life-threatening infections. Moderate to severe nausea and vomiting was most prominent in patients receiving either streptozotocin, Baker's antifol, tilorone or 5-fluorodeoxyuridine plus arabinosyl cytosine. One patient had a severe skin reaction on both the hands and feet and another experienced a severe cough and dyspnea associated with severe stomatitis; in both cases, these reactions occurred after treatment with bleomycin. Two patients had moderate renal toxic reactions after receiving streptozotocin. Moderate to severe neurologic toxic reactions were encountered in eight instances after treatment with tilorone. Additionally, two patients receiving tilorone experienced keratopathy. Similar lesions have been noted by others,[8] and randomization to this arm was discontinued.

Discussion

These prospective randomized Phase II trials were designed to identify and evaluate promising agents and combinations for antitumor activity in patients with metastatic breast cancer. It is difficult to select appropriate chemotherapy programs for cases refractory to standard treatments, as has been shown by the results of these studies. Only four partial responses were observed and 36 patients achieved stabilization of their disease. No treatment was significantly better or worse than any other in terms of response rate, time to treatment failure, or survival, but the median survival times ranged from 2.0 months to 6.2 months, as shown in Figures 2 and 3. It is difficult to determine if this relative difference reflects antitumor activity in this large group of patients with far-advanced disease, where responses are not seen frequently.

Certainly none of the treatments studied offers any advantage to breast cancer patients if used alone, but there might be pharmacologic rationale for incorporating some of the agents into more standard combination chemotherapy regimens. This might be particularly pertinent to bleomycin, Baker's antifol, and 5-fluorodeoxyuridine plus arabinosyl cytosine, the three arms in which partial responses were noted and the ones

TABLE 3. Toxic Reactions of Breast Cancer Patients to Various Agents

Number of patients	Bleomycin	CCNU	Streptozotocin	Baker's antifol	Tilorone	FUdR + ARA-C
Analyzed	22	22	19	35	25	32
With hematologic toxicity						
Mild	1	6	5	16	3	3
Moderate	0	8	0	6	0	13
Severe	0	3	1	1	1	3
Life-threatening	0	0	0	2	0	4
With gastrointestinal toxicity						
Mild	3	7	3	14	7	10
Moderate	0	3	5	12	7	9
Severe	0	1	5	3	6	6

with the longest median survival times (Figs. 2 and 3). Bleomycin is nonmyelosuppressive and might be added to standard programs for treating metastatic breast cancer without overlapping toxicity. Baker's antifol demonstrated only mild hematologic toxicity in most instances (Table 3), using a three day schedule repeated every three weeks. The mechanism by which this agent is transported into cells differs from that of methotrexate and it can potentially concentrate even in cancer cells demonstrating inhibition to methotrexate transport.[7] Conceivably, Baker's antifol might be substituted for methotrexate in conventional regimens for patients whose tumors are shown to be methotrexate resistant. 5-Fluorodeoxyuridine preceeding arabinosyl cytosine has been shown to be synergistic to leukemic cells by one or more mechanisms.[3] This combination is different from those using standard agents and, thus, theoretically it might have some role in programs utilizing cell-cycle-active agents.[4]

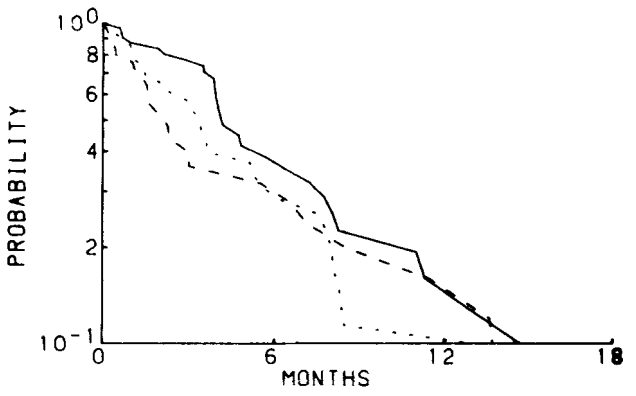


FIG. 3. Survival for patients receiving FUdR-Ara-C (——), Baker's antifol (- - -), and tilorone (– –). The median survival times were 4.1, 3.4, and 2.1 months, respectively.

All of these theories, however, would have to be tested in randomized controlled clinical trials and the results compared to those achieved with standard combinations before determining whether the agents and combination reported here offer any potential benefit over present therapy for metastatic breast cancer.[2] The treatment schedules outlined and the toxic effects noted provide important background information that might prove useful in designing complex new chemotherapeutic programs for treating this disease.

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