

COMBINATION CHEMOTHERAPY AND ADRIAMYCIN IN PATIENTS WITH ADVANCED BREAST CANCER

A Southwest Oncology Group Study

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In January, 1972, the Southwest Oncology Group initiated two randomized studies for patients with advanced breast cancer. The study for patients with prior chemotherapy showed a 33% response rate with adriamycin. The study for patients without previous chemotherapy consisted of three treatment regimens: a weekly repeated combination of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone; these same five drugs given in courses of 5 days repeated every 4 weeks; and adriamycin as a single agent every 3 weeks. For the 283 evaluable patients, the response rates were: weekly combination 63/106 (59%); intermittent combination 39/98 (40%); and adriamycin 31/79 (39%). The median duration of response was 8 months for weekly combination, 10 months for intermittent therapy and only 4 months for adriamycin. Leukopenia was the dose-limiting toxicity with all three regimens. The weekly combination is the most effective therapy for patients with advanced disease. Extensive trials of combinations that include adriamycin are underway.

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MANY ANTICANCER DRUGS HAVE BEEN TESTED in patients with advanced breast cancer and the results compiled and updated systematically.¹⁰ Of the 28 drugs used thus far, the efficacy of only eight has been clearly established. Greenspan⁷ was the first to use

active agents in combinations and subsequently Cooper³ combined five commercially available drugs into a new regimen. Although a subsequent evaluation of Cooper's records did not support the 88% complete response rate he reported, his initiative nevertheless has stimulated an intensive use of the combination throughout the world.

In 1971, the Southwest Oncology Group established a Breast Cancer Study Committee and in January, 1972, the Group initiated two studies for patients with advanced disease, one for those who had received prior chemotherapy and the second for those without such therapy. In both studies, adriamycin, the new antitumor antibiotic, was compared with two other modes of therapy. The first study, since reported, demonstrated a response rate of 33% for adriamycin, which was far superior to the rate for either CCNU or methyl CCNU, 12 and 3%, respectively.⁷

In the second study, the results of which are reported in this paper, the efficacy of adriamycin in the "fresh" patient was compared with that of the five-drug combination Cooper regimen and with the same five drugs given intermittently in courses at 4-week intervals.

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The choice of the intermittent therapy of this randomized study was based on the success of the well-known MOPP therapy in Hodgkin's disease.⁵ The intermittent therapy with intensive courses of a drug combination had never been tested in patients with breast cancer. The preliminary results of this study have been presented previously.¹⁰ This paper reports results with respect to response only. An analysis of the prognostic value of certain patient characteristics and of the survival will be included in a later report.

MATERIALS AND METHODS

The first patient was entered into the study on January 9, 1972 and the last one on February 19, 1974. Entry into the study was restricted to patients with measurable metastatic breast cancer, who, except for hormones, had not received prior cancer chemotherapy. We required that patients with previous hormone treatment have clearly progressive disease and that their hormone treatment was started at least 2 months before entering the study. We were careful that a withdrawal response did not occur when such hormones were suddenly discontinued. Irradiation of ovaries, if done, had to be completed at least 2 months before entering the study and, again, progressive disease had to be present.

Prior irradiation of other areas was permitted, provided the patient had active progressive disease outside the radiation field.

There was no limit on age or sex, renal function had to be normal,⁴ and informed consent in accordance with institutional policies had to be obtained. Patients with a history of myocardial disease or an abnormal ECG were only randomized for combination chemotherapy.

The design of the study is outlined in Table 1. Initial chemotherapy in Phase I consisted of randomization into three treatment groups, called "intermittent combination," "weekly combination," and "adriamycin," and following either relapse or failure to respond, a non-compulsory randomized crossover was provided in Phase II.

The intermittent combination was repeated at 4-week intervals and after three courses the vincristine was discontinued. From then on the other four drugs were given orally. After 70 days and increasing disease, the patient could go to Phase II.

The weekly combination was given eight times; then the vincristine was deleted, and the other four drugs were given orally. Again after 70 days and increasing disease, the patient could go to Phase II.

Adriamycin could be discontinued when the patient failed to respond after three doses. A total dose limit of 500 mg/m² was strictly observed to prevent the occurrence of myocardial toxicity reported with increased frequency at higher doses.⁸

Parameters to evaluate the patients for extent of disease, response, and toxicity con-

TABLE 1. Randomization Schedule

Phase I	Failure or relapse →	Phase II
1. Intermittent combination CTX 120 mg/m ² /iv/d × 5 MTX 4 mg/m ² /iv/d × 5 5-FU 180 mg/m ² /iv/d × 5 VCR 0.625 mg/m ² /iv/d 1 & 5 PRED 40 mg/m ² /d × 5 Repeat courses every 28 days		Adriamycin
2. Weekly combination VCR 0.625 mg/m ² /iv/wk MTX 15 mg/m ² /iv/wk 5-FU 300 mg/m ² /iv/wk CTX 60 mg/m ² /po/daily PRED 30 mg/m ² /d × 14 20 mg/m ² /d × 14 10 mg/m ² /d		Adriamycin
3. Adriamycin 60 mg/m ² /iv every 3 weeks		Intermittent combination or Weekly combination

CTX = Cyclophosphamide MTX = Methotrexate PRED = Prednisone 5-FU = 5-Fluorouracil VCR = Vincristine

sisted of evaluation of performance, bone marrow, complete blood counts, BUN, creatinine, calcium, alkaline phosphatase, SGOT, x-rays of chest, spine, pelvis, and painful areas, electrocardiogram, and tumor measurements. A special Breast Cancer Prestudy Form was designed, which asked for more information. The data obtained from these forms are being analyzed with regard to response and survival and will be the subject of a future report. There was no difference in the incidence of visceral, osseous, and soft tissue involvement in the three treatment groups.

Criteria for response and relapse are provided in detail since these are often the cause of controversy.

All tumor sizes were determined by the measurement, in centimeters, of the longest diameter and its perpendicular through the widest portion of the tumor. Both measurements had to be entered on the flow sheets.

Complete remission (CR): Disappearance of all clinical evidence of active tumor for a minimum of 4 weeks was considered complete remission. This did not necessarily mean normalization of involved skeleton, but required that x-rays showed improvement, all lytic lesions had reossification, and patient was free of any pain.

Partial remission (PR): Fifty percent or greater decrease in the sum of the products of the diameters of measured lesions for a minimum of 4 weeks was considered partial remission, with no simultaneous increase in size of any lesion or appearance of new lesions. Where skeleton was involved there had to be improvement. Hypercalcemia had to be controlled without any other aid.

Improvement (IMP): Some reduction in tumor size but less than 50%, or in patients with only skeletal metastases, a disappearance of the lesions on x-ray or a steady state, were considered improvement, with no in-

crease in size of any lesion or appearance of new lesions.

No response (NR): Failure to improve but no obvious progression of disease was classified as no response.

Increasing disease (ID): Unequivocal increase of at least 50% in size of any measured lesion, appearance of new lesion, uncontrolled hypercalcemia and/or clearly progressive skeletal involvement, were classified as increasing disease.

Early death (ED): Death as a result of any cause within 4 weeks from start of therapy. This rather arbitrary time was chosen because it meant that patients could not start a second course of intermittent therapy.

Relapse: The following conditions were considered as relapse: appearance of new lesions; reappearance of old lesions in patients who achieved a complete remission; for patients in partial remission, an increase of 50% or more in the product of the diameters of any of the measured tumors over that which was obtained at the time of maximum regression, e.g., tumor of 25 cm² diminished to 8 cm² during partial remission and increased to 14 cm² at time of relapse; appearance or recurrence of hypercalcemia; new or progressive skeletal involvement; or appearance of abnormal clinical or laboratory observations proven to be secondary to active disease.

RESULTS

A total of 297 patients entered Phase I of the study. Of these, seven were declared non-evaluable because there were major protocol violations, and seven others, because the investigator provided inadequate data to permit an evaluation of the records. Of the remaining 283 evaluable patients in Phase I, 97 were subsequently crossed over to Phase II of the study (Table 2). Due to a temporary short-

TABLE 2. Results of Therapy in Phases I and II

	No. of cases	CR	PR	Results (%)		ID	ED
				IMP	NR		
Phase I							
Intermittent	98	8	32	14	12	23	10
Weekly	106	19	40	10	12	13	6
Adriamycin	79	4	35	10	19	24	8
Phase II							
Intermittent	24	4	21	8	38	25	4
Weekly	24	8	38	8	8	29	8
Adriamycin	49	—	20	8	23	33	16

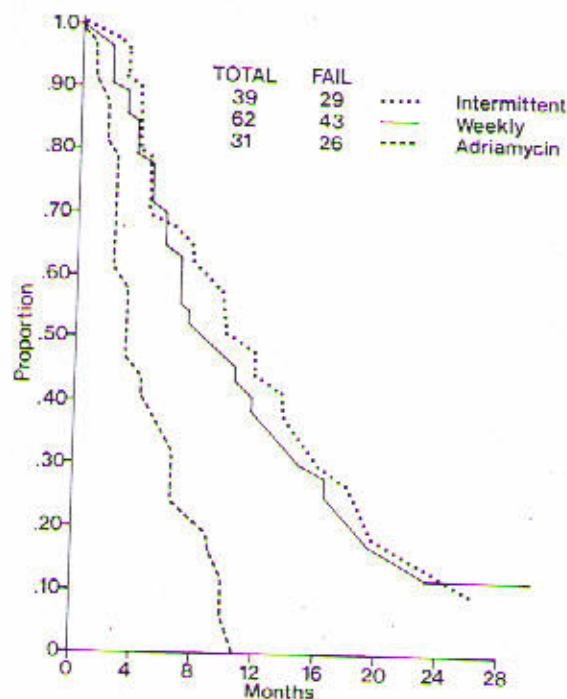


Fig. 1. Duration of response (CR + PR) by treatment.

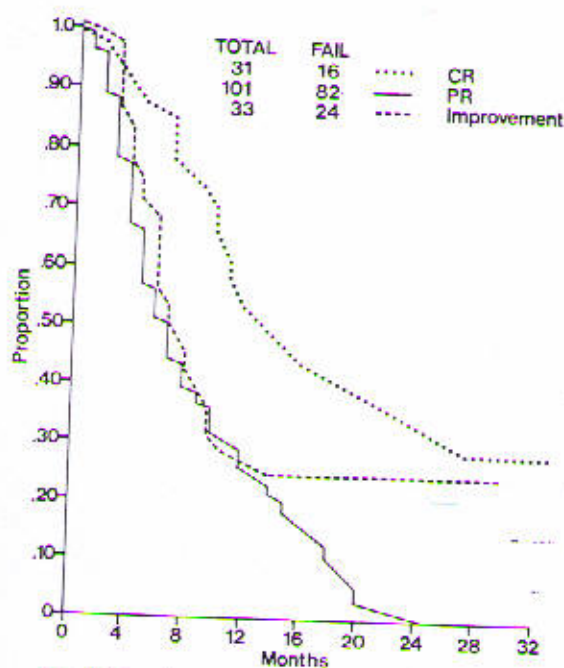


Fig. 2. Duration of CR, PR, and improvement.

age of drug the number of adriamycin-treated patients is less. The response rate of 59% of the weekly combination is clearly superior to the rates of 40% and 39% of the other two treatment arms ($p < .05$) for complete and partial remissions. When only complete remissions are considered the level of significance in the difference between weekly combination results (19%) and those of intermittent and adriamycin treatment combined (6%) is even higher ($p < .01$). This same trend is observed in Phase II of the study, when the weekly treatment, with 40% responses, is compared with the other two regimens combined (22%), although this is not as statistically significant ($p = .09$).

The time elapsed for response differed for the three treatment regimens. The weekly combination resulted in the fastest responses: 75% of these occurred within 2 months as compared with 3 months for the intermittent combination and 2½ months for adriamycin, which for this last drug means after four injections. At the end of 3 months the percentage of initial responses occurring in patients ultimately going into remission on the three treatment regimens was 74% for intermittent, 94% for weekly combination, and 84% for adriamycin. Of course, it took much longer to achieve a complete remission.

In Phase II of the study, the two combinations performed less well after prior adriamycin, but this difference did not approach statistical significance. The rate of response to adriamycin after combination chemotherapy (21%) was nearly significantly less ($p = .06$) than the initial result after no prior chemotherapy (39%). The overall response in Phase I (47%) is significantly better ($p < .05$) than the overall response in Phase II (28%).

The duration of response to the three treatment arms is shown in Fig. 1. The median remission durations induced by the combinations are significantly longer than those induced by adriamycin ($p < .01$), about 9 months vs. 4 months. As can be expected, the median duration of all CR's (13 months) was significantly longer ($p < .01$) than that of the PR's (7 months), but there was no difference at all between PR's and improvements (Fig. 2). This seems to justify our criteria for improvement as used in this study. The median survival times were 14 months for the two combination treatment arms and 11 months for the adriamycin group, a difference that is not statistically significant.

TABLE 3. Criteria and Degree of Toxicity

Type	Degree			
	1	2	3	4
Leukopenia (WBC/mm ³)	3,000-3,999	2,000-2,999	1,000-1,999	<1,000
Thrombocytopenia (/mm ³)	75,000-99,999	50,000-74,999	25,000-49,999	<25,000
Gastrointestinal				
stomatitis	erythema	ulcers-able to eat	ulcers-unable to eat	
nausea + vomiting	nausea only	vomiting can be prevented	vomiting in spite of antiemetics	
Neurologic	DTR decreased or paresthesias	DTR absent, weakness, tolerable pain	incapacity, paresis, intolerable pain	
Cardiac	EKG changes	Arrhythmias	CHF, ventricular tachycardia or pericarditis	
Alopecia	Hair loss when combing	Noticeable thinning	bald	

TOXICITY

The criteria and degrees of toxicity used in the evaluation of this study are shown in Table 3. Four degrees are used for hematologic toxicity and three for all other types. These criteria are almost identical to those proposed by the Combination Chemotherapy Subcommittee of the Breast Cancer Treatment Program of the NCI. The percentages of patients with toxicity, by type of toxicity, treatment, and degree of toxicity, are given in Table 4.

Noticeable is the degree of leukopenia caused by adriamycin, which is about the same as for the two combinations. None of the

treatments resulted in much thrombocytopenia. Adriamycin in particular appears to have a platelet-sparing effect. The patients having a severe depression (3%) were cases with marked tumor infiltration of their bone marrow. The gastrointestinal side effects of adriamycin are marked and almost all patients require antiemetics. Even with these, the vomiting, usually lasting 24-48 hours, was not controlled in 22% of the patients. Adriamycin also results in marked alopecia, which is complete in 60%. Hair loss was not reported in 24 patients, six because they had an early death, some because they failed to respond while still having hair, and others probably because their investigator failed to report it.

TABLE 4. Type and Degree of Toxicity for each Treatment Group

Type	Treatment	Degree of Toxicity (%)				
		0	1	2	3	4
Leukopenia	I	29	8	22	30	11
	II	26	21	25	23	5
	III	22	24	22	29	3
Thrombocytopenia	I	65	13	8	5	9
	II	72	12	9	5	2
	III	90	5	1	1	3
G.I. toxicity	I	64	15	17	4	
	II	71	17	10	2	
	III	35	10	33	22	
Alopecia	I	68	11	15	6	
	II	67	2	19	12	
	III	28	—	12	60	
Neurologic	I	84	5	10	1	
	II	69	11	19	1	
Cardiac	III	95	1	3	1	

I = Intermittent Combination. II = Weekly Combination. III = Adriamycin.

In addition to the side effects listed in Table 4, there were 11 patients with cyclophosphamide-induced cystitis, all but one as a result of the daily treatment. Two of these were severe enough to require blood transfusions. Cardiac toxicity due to adriamycin was present in four patients whose total dose ranged from only 180 to 485 mg/m². In three, the EKG changes or arrhythmias were present on two occasions after a dose and in the fourth patient congestive heart failure occurred. This patient received a total of 485 mg/m² and she remained in failure until death from her malignancy. The ages of these patients ranged from 49 to 59 years.

The causes of early death and the degrees of toxicity in such cases are given in Table 5. No less than 15 of the 22 patients had massive liver involvement and in nine of these, it was the direct cause of death. Three patients with massive liver metastases died with severe myelosuppression and gram-negative septicemia. Fatal bleeding occurred in two, and a third had massive emboli with asso-

ciated thrombocytopenia. Although the overall degree of leukopenia in patients with liver metastases was not significantly worse than those without, in 14% of these patients the WBC dropped to below 1000/mm³, as compared with 5% of the other patients.

DISCUSSION

After an appropriate dose and schedule of a new agent has been determined in a Phase I study, the agent is then tried in Phase II studies. Only patients with prior chemotherapy are used routinely, a practice with several disadvantages: a) there is a high percentage of incomplete trials due to early deaths; b) the drug dose is frequently too low because of prior bone marrow damage; c) patient and physician enthusiasm is at a low key, which may lead to early removal from study; d) too many disease symptoms are judged to be due to drug toxicity; and e) valuable time is lost in the correct evaluation of the drug. These disadvantages are removed when one employs

TABLE 5. Details of Patients with Early Deaths

Treatment	Age (years)	Day of death	Liver metast. ^a	Leukopenia	Thrombocytopenia	Cause of death
Intermittent	28	25	0	4	4	Hemorrhage
	53	13	3	4	2	Gram-negative sepsis
	70	27	3	4	3	Gram-negative sepsis
	50	26	0	4	3	Gram-negative sepsis
	47	21	3	4	4	Tumor
	70	23	0	3	0	Tumor
	58	22	0	0	4	Pulmonary emboli
	39	20	3	—	—	Tumor
	54	15	3	—	—	Tumor
	73	6	0	—	—	Tumor
Weekly	65	14	3	4	4	Gram-negative sepsis
	59	27	3	4	4	Hemorrhage
	65	17	3	0	0	Tumor
	61	22	1	0	0	Tumor
	74	7	3	—	—	Tumor
	45	12	3	0	1	Tumor
Adriamycin	71	16	3	0	0	Unknown
	46	18	1	4	2	Tumor
	34	27	3	1	0	Tumor
	59	4	3	—	—	Hypercalcemia
	32	21	3	0	0	Tumor
	69	17	3	0	0	Tumor

^a 0 = none; 1 = mild; 2 = moderate; 3 = massive.

the new agent as the first drug. On the other hand, it is frequently argued that the use of new agents in patients who have received no prior chemotherapy may be unethical since it exposes them to a potentially inferior therapy first. Yet in the field of cancer chemotherapy there are sufficient examples to contradict this argument. Remission maintenance with a placebo in children with acute leukemia did not compromise the subsequent survival.⁶ In a combination radiation-chemotherapy study of Stage III Hodgkin's disease, the median remission duration for chemotherapy alone was 1 month as compared with over 24 months for the combination, yet there is no difference in subsequent survival.¹¹

Breast cancer is a relatively slow disease and permits a cross-over to established effective therapy after failure with the new agent or relapse where a remission had been obtained. Adriamycin had shown an important lead for possible activity in this disease in its Phase I studies and thus was chosen in this Phase III study as the new agent to be tested.

The best results for remission induction, 59%, were obtained with the weekly combination. This is similar to the 69% (11/16) and 67% (6/9) rates of responses already reported in patients without prior chemotherapy.^{4,10} The median duration of our responses, 250 days, compares well with the median of 150 days reported by Davis et al.⁴

The results with the intermittent five-drug combination are disappointing. Once obtained, the responses lasted a median of 310 days.

SWOG now has experience with adriamycin as a single agent in 315 patients with breast cancer.¹² In patients with prior chemotherapy, we reported a mean of 30% responses in three studies^{7,13,14} with a median duration of response of 4 months. The response rate did not appear to be dose-related. Ahmann et al.¹ found 50% (10/20) responses to primary therapy with adriamycin, but in a cross-over after a combination program, only one among nine patients responded. In our study 20% of the cases had a remission with adriamycin as the second line treatment, 16% with the weekly and 25% with the intermittent combination (Table 2). The good result with the weekly five-drug regimen, an effective program, again supports our belief that a new mode of chemotherapy can be tested without added risk, provided effective treatment is available as a backup.

With respect to future studies, especially the adjuvant chemotherapy trials, the time required to obtain a remission in this study may be important. For the best combination in this study weekly, 3 months is quite adequate. Of the patients responding to adriamycin, 80% did so with the fourth dose. O'Bryan et al.¹⁵ found that 90% of their patients who responded did so with the fourth dose and one could therefore advocate interruption of this drug at that time and keep the remaining doses in reserve for future use.

Of interest is the identical duration of the partial responses and the improvements. The latter group consisted mainly of patients whose disease was confined to the skeleton, an area of involvement in which response is difficult to measure. As far as the response rate in Phase II is concerned, one could ask whether patients who had already responded once in Phase I did better than the nonresponders plus those with increasing disease. This was not the case since the response rates of such patients in Phase II were 29 and 27%, respectively.

The two combinations were quite comparable as far as overall myelosuppressive effect was concerned, but the 5-day course was associated with more life-threatening leukopenia and three such patients had a fatal gram-negative sepsis. Adriamycin caused hardly any thrombocytopenia, confirming all previous reports. Most other toxicity was acceptable. A special word of caution is needed for patients with severe liver involvement. Benjamin et al.² have already reported the higher incidence of toxicity with adriamycin in such patients, but this can also be true for patients treated with combination schedules. One may do well to start with a lower drug dose when most of the liver is replaced by tumor and to advocate starting chemotherapy as soon as liver involvement is detected.

This study showed that the weekly combination chemotherapy program is superior in efficacy for advanced breast cancer to an intermittent program of adriamycin. In patients without prior chemotherapy this last drug induced a higher response rate than that reported with any other single agent. However, the responses are of short duration and it appears thus far that adriamycin can best be used for remission induction. Studies of combinations with other agents are in progress.

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APPENDIX

Institutions Participating in the Study

Institution	No. of evaluable patients
Wayne State University School of Medicine, Detroit, MI	71
The University of Kansas Medical Center, Kansas City, KS	65
Tumor Institute of the Swedish Hospital Medical Center, Seattle, WA	50
University of Texas Medical Branch at Galveston, TX	27
Scott and White Clinic, Temple, TX	24
University of Mississippi Medical Center, Jackson, MS	23
Brooke Army Medical Center, Fort Sam Houston, TX	19
Cleveland Clinic, Cleveland, OH	16
Ohio State University Hospitals, Columbus, OH	15
University of New Mexico School of Medicine, Albuquerque, NM	11
Oklahoma Medical Research Foundation, Oklahoma City, OK	10
Wilford Hall USAF Medical Center, Lackland AFB, San Antonio, TX	9
Albert Einstein Medical Center, Philadelphia, PA	8
University of Arkansas Medical Center, Little Rock, AR	8
Mountain States Tumor Institute, Boise, Idaho	8
Baylor College of Medicine, Houston, TX	6
V. A. Research Hospital, Chicago, IL	4
University of Arizona Medical Center, Tucson, AZ	2
Borgess Medical Center, Kalamazoo, MI	2
Henry Ford Hospital, Detroit, MI	1
M. D. Anderson Hospital and Tumor Institute, Houston, TX	1

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