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SALVAGE CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, DOXORUBICIN, AND CISPLATIN (CAP) IN ADVANCED BREAST CANCER

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ABSTRACT

Twenty-one patients with advanced breast cancer(7 premenopausal and 14 postmenopausal women) were treated with a combination of cyclophosphamide, doxorubicin, and cisplatin (CAP). The median age of the patients was 43 years (range 36-61). This therapy was repeated every 3 weeks. Nine patients (group 1) received CAP as primary therapy for metastatic breast cancer, and twelve patients (group 2) received CAP as a second-line therapeutic agent. Of the 12 (57%) patients who responded, six (29%) had complete response (CR). The median disease-free survival (DFS) was 8 months. The response rate was highest for metastases in the pleura (83%) and lymph nodes (81%), followed by skin (64%), liver and breast (55%). The overall response rate was higher in previously untreated patients than in those previously treated (89% versus 33%, $p<0.01$). Complete response rates of 44% and 17%, and median DFS of 10.5 and 3 months respectively, were observed in the two groups of patients. The therapy was well tolerated, myelosuppression being the dose-limiting toxicity. The most frequent nonhematological toxicities were nausea, vomiting (100%), mucositis and stomatitis (38%), but these were rarely severe. Total alopecia occurred in only two patients. There were no toxic deaths or cardiotoxicity. Severe anemia occurred more frequently in group 2 patients. The present study suggests a role for CAP combination chemotherapy in the management of advanced breast cancer.

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Keywords: Breast cancer, combination chemotherapy, CAP regimen.

INTRODUCTION

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 five 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 have a median survival of 2.3 years, and those who achieve a complete response with standard dose therapy have a median survival of 2.5 years. Patients who have only small amounts of local disease (median>4 years) have a somewhat better prognosis.[2] Metastatic breast cancer therefore represents a public health problem as well as a frightening personal dilemma for women afflicted with the disease.

From the 1960s through the mid-1970s, clinical researchers developed chemotherapy regimens for metastatic

TABLE I: Novel agents for the treatment of metastatic breast cancer

Agent	Dose	Response rate	Reference no.
Mitoxantrone	14mg/m² every 3 wk	35/99 (35%)	6
Epirubicin	120mg/m² every 3 wk	15/22 (69%)	8
Cisplatin	30mg/m² qdx4 every 3wk	9/19 (47%)	10
Carboplatin	400mg/m² every 3 wk	4/20 (20%)	7
Navelbine	30mg/m² every 3 wk	10/19 (52%)	9
Amonafide		6/26 (23%)	13
CI -941		20/31 (64%)	14

breast cancer. While these regimens differed in terms of both number and type of chemotherapeutic agents employed, they shared common characteristics (representative combinations are shown in Table I). These regimens were based on the superiority of combination therapy over single agent therapy in the laboratory in decreasing the emergence of drug resistance,[3,4] and using agents with nonoverlapping toxicities. Generally administered in an out-patient setting, regimens were designed to achieve maximal objective clinical response rates with acceptable toxicity.

Standard dose chemotherapy regimens, whether doxorubicin (e.g., 5-fluorouracil, adriamycin, cyclophosphamide-CAF) or methotrexate (e.g., cyclophosphamide, methotrexate and 5-fluorouracil-CMF, or CMF-vincristine, prednisone-CMF-VP) based, have more similarities than differences. In previously untreated patients, these regimens produce 40% to 75% objective response rates of 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 rates than methotrexate-based regimens, although their toxicity is greater.[5,21]

Combination chemotherapy used as a second-line form of therapy in failed breast cancer (salvage therapy) gives substantially lower response rates (between 20% to 35%). Very few of these responses are complete remission and the duration tends to be short (2 to 3 months).[11]

In this article we report our experience with cisplatin used in combination with cyclophosphamide and doxorubicin (CAP) as first and second-line chemotherapy for the management of advanced breast cancer.

PATIENTS AND METHODS

Twenty one patients attending the Hematology/Oncology Unit of Seyyed-al-Shohada Hospital of Isfahan University of Medical Sciences from July 1985 to December 1990 with

TABLE II: Patients characteristics

	Previously untreated	Previously treated
No. of patients	9	12
Median age (range)	41 (36-61)y	45 (37-59)y
Premenopausal	3	4
Postmenopausal	6	8
Initial stage at diagnosis:		
2B	2	3
3A	1	1
3B	1	2
4	4	6
unknown	1	0
Primary therapy received:		
Surgery	7	11
Adjuvant RT	7	12
Adjuvant CT	6	10
Tamoxifen	7	11
Ovarian ablation with RT	0	2
Median DFS before metatasis	12 (7-24)m	22 (13-41)m
Predominant metastatic site:		
Soft tissues	9	12
Visceral organs	6	7
Bone	3	4
Skin	4	6

RT: radiation therapy
DFS: disease-free survival
CT: chemotherapy
m: month

TABLE III. Schedule of CAP chemotherapy

Drug	Dose	Day 1	2	3	4	5
Cyclophosphamide	200mg/m² IV	*		*		*
Doxorubicin	40mg/m² IV	*		-		-
Cisplatin	30mg/m² IV	*		*		*

TABLE IV. Response according to site.

Site	Previously untreated			Previously treated			All patients			N: 21
	No.	CR	RR	No.	CR	RR	No.	CR	RR	%
Lymph node	7	4	7	9	3	6	16	7	13	81
Bone	3	1	2	4	0	1	7	1	3	43
Liver	5	1	3	6	1	3	11	2	6	55
Lung	2	0	1	5	0	1	7	0	2	29
Pleura	2	0	2	4	0	3	6	0	5	83
Skin	5	1	3	6	1	4	11	2	7	64
Breast	5	1	3	6	1	4	11	2	6	55

No: number
CR: complete response.
RR: response rate (CR+PR).
PR: partial response.

histologically-proven breast carcinoma and distant metastases were entered in this trial. Details of patient characteristics are given in Table II. The median age was 43 (range 36 to 61) years. 14 patients were postmenopausal and 7 premenopausal. Patients were treated with a combination of cisplatin 30 mg/m² for three alternate days; doxorubicin 40 mg/m² as a single dose; and cyclophosphamide 200 mg/m² on three alternative days (CAP) (Table III). This therapy was repeated every 3 weeks. Nine patients (group 1) received CAP as primary therapy for metastatic breast cancer, and twelve patients (group 2) received CAP as second-line therapy, 8 of whom had failed to respond to a methotrexate-based combination chemotherapy (CMF), and 4 patients to the CAF regimen (cyclophosphamide, doxorubicin and 5-fluorouracil). All patients who were estrogen receptor-positive had failed a previous trial with tamoxifen (hormone therapy).

Patients who received a minimum of three cycles of CAP chemotherapy were considered evaluable. The twenty-one patients received a mean six cycles of CAP (range 3-12 cycles). All patients were required to have measurable, histologically proven advanced breast cancer along with normal renal and cardiac function. The CAP schedule was administered every 3 weeks if the total leukocyte count (TLC) was≥2,500/μL and the platelet count was≥100,000/μL. If the counts were lower, chemotherapy was delayed. Toxic effects were monitored regularly. Blood urea and serum creatinine were monitored before each cycle of chemotherapy. Patients who achieved CR continued to receive CAP for a total of twelve cycles.

Treatment duration and cross-over

Patients who achieved an objective response as defined by standard UICC criteria[15] continued to undergo twelve courses. Patients who developed progressive disease or had stable disease, but had failed to achieve symptomatic relief after two courses were changed to a cross-over regimen (i.e. vinblastin and mitomycin)[26] if this was clinically appropriate. Likewise, responding patients received the cross-over regimen at relapse.

Dose modification

Treatment was only given if the peripheral white blood count was≥2,500/μL and the platelet count≤100,000/μL at the start of the second or subsequent courses. Otherwise, treatment was delayed until these parameters had recovered. After two delays the dose of all drugs was reduced by 25% of the original dose. Further delays led to the treatment being stopped. If any patient developed a neutropenic infection the dose of all drugs in subsequent courses was reduced by 25%.

Anti-emetics

All patients received prophylactic anti-emetic coverage, usually comprising of metoclopramide 20 mg IV and dexamethasone 8 mg IV, or orally before chemotherapy. If nausea or vomiting occurred, oral metoclopramide 20 mg, 4-6 hourly was continued after the initial injection and if necessary, lorazepam 1 mg, 4-6 hourly was added as a third agent.

Investigation and response assessment

Specific investigations to document and assess tumour sites including chest x-ray, radiological skeletal survey, ultrasound or computed tomography, bone scan, and other radiologic or isotope studies or bone marrow aspiration and biopsy (when clinically indicated) were carried out prior to treatment, after three courses, at the completion of six courses, and at the end of treatment or progression of disease. Palpable lesions were assessed at each course of treatment and earlier assessment of other disease sites was carried out if clinically indicated. Response was assessed according to standard UICC criteria. Physical examination, peripheral blood count, plasma urea, creatinine, electrolytes, calcium, phosphorus, ECG and liver function tests were

carried out before each treatment. Bone marrow aspiration and biopsy examination were performed in patients who had myelosuppression for more than 6 weeks after any cycle of chemotherapy, to exclude tumor invasion as the cause of pancytopenia.

Toxicity

As shown in Table V, all patients experienced nausea and vomiting. Stomatitis or frank oral ulcerations were recorded in two patients, but mild to moderate mucositis was common. Total alopecia occurred in two patients(14%). Thinning of the hair that did not require use of a wig occurred in 15 patients (71%) and was completely reversible. No patients developed clinical features suggestive of cardiac toxicity in this study. Three patients had changes evident on ECG after completing four cycles of therapy, with minor T-wave changes occurring in two and sinus tachycardia without evidence of cardiac ischemia in one. 57% of patients developed anemia (mean Hb, 7.8g/dL); and 38% developed leukopenia (Table V). Severe anemia (hemoglobin<6.5g/dL, WHO grade 4) occurred more frequently in previously treated than untreated patients (1 of 9 versus 2 of 12 patients). Other toxicities were similar in the two groups. There were no chemotherapy deaths.

TABLE V. Chemotherapy toxicity

Toxicity	No. of patients	%
Vomiting (WHO grade 2/3)	21	100
Mucositis, Stomatitis	8	38
Ototoxicity	3	14
Peripheral neuropathy	2	9
Supraventricular tachycardia	1	5
Anemia (WHO grade 1/2/3/4)	12(2/4/3/3)	57
Thrombocytopenia (WHO grade 1/2/3/4)	3(2/0/1/0)	14
Leukopenia (WHO grade 1/2/3/4)	8(2/3/2/1)	38
Alopecia (severe)	2	9
Chemotherapy-induced deaths	0	0
Cardiotoxicity	0	0

TABLE VI. Response rate according to groups of patients

	Group 1	Group 2	All patients
No. of patients	9	12	21
RR	8(89%)	4(33%)	12(57%)
CR	4(44%)	2(17%)	6(29%)
DFS(range)	14(3-30)m	6(3-9)m	8(3-30)m

RR: response rate CR: complete response
DFS: disease-free survival m: month

RESULTS

Among 21 evaluable patients, twelve (57%) responded. From patients who responded, six (29%) achieved complete response (CR) and six (28%) achieved partial response (PR). The median disease-free survival (DFS) was 8 months (range 3-30 months). Partial response lasted for a median of 3.5 months (range 2-5 months). Of the six patients with complete response, three relapsed after 3,4, and 6 months. Each of these patients had liver and bone metastases. The complete response for three patients continues at 9,19 and 30 months. The response rates at different sites of disease are shown in Table IV. The response rate was highest for metastases in the pleura (83%) and lymph nodes (81%), followed by skin (64%), liver and breast (55%). No patient with lung and pleural metastases achieved complete response. The overall response rate was higher in previously untreated than in previously treated patients (89% versus 33%). Complete response rates of 44% and 17%, and a median disease free-survival of 14 and 6 months respectively, were observed in the two groups of patients. Patients with visceral-dominant tumor sites (lung and liver) experienced a complete response rate of 9%, lower than the group as a whole (29%).

Response to this treatment program was relatively rapid. Among patients who responded, 7 patients whose tumors were easily measurable by physical examination (three patients), or radiographs (four patients) showed a mean 90% (10% standard error) tumor volume reduction during the first 2 months of chemotherapy administration.

Relapses tended to occur in sites of prior bulky disease, visceral disease relapsed at visceral sites and soft-tissue disease at soft-tissue sites. Central nervous system relapse occurred in only one patient. No patient had CNS disease when treatment began. Patients who recurred in bony sites had significantly shorter survival rates than patients with soft-tissue recurrences.

The characteristics of two groups of patients are shown in Table II. Patients with no prior therapy for metastatic disease were younger (median age 41 versus 45) with shorter disease-free intervals after initial management (12 versus 22 months) compared to those who had been treated for metastatic disease. These differences, however, were not statistically significant ($P>0.05$) because the total number of patients was small. Other characteristics, including menopausal status, stage at initial diagnosis, initial curative therapy and predominant metastatic sites were similar in the two groups. The response rate was higher in previously untreated than in previously treated patients (89% versus 33%, $P<0.01$).

DISCUSSION

The role of intensive chemotherapy for metastatic breast cancer is a subject requiring considerable investigation.

Conventional ambulatory treatment produces complete response in only a small fraction of patients, and such patients are often continued on maintenance therapy because rapid relapse is the common outcome if therapy is discontinued.[19] Without a major increase in the percentage of complete responses achieved, prolonged survival for premenopausal women with metastatic breast cancer is unlikely. It is not clear at present whether new chemotherapeutic regimens are superior to conventional regimens for metastatic breast cancer.

Cisplatin, tested extensively in the 1970s and 1980s in heavily pretreated metastatic breast cancer, demonstrated significant activity as single agent therapy, with response rates equivalent or superior to those of currently used agents in metastatic breast cancer.[24] In combination therapy, it has been demonstrated to achieve response rates and overall survival times comparable to those of other standard chemotherapy regimens.[10,23,28]

In previously untreated patients, however, it demonstrated higher activity, producing response rates of 41-54%[10] which are similar to rates associated with other active agents[6,17,25] such as doxorubicin (39%) and mitoxantrone (35%). Response rates of 68% and a response duration of 2.5-7 months were observed[10] when cisplatin was combined with other chemotherapeutic agents in previously treated metastatic or locally advanced breast cancer.

Our experience in this study with 12 previously treated patients is similar in that 33% responded to CAP. The duration of partial response with disease-free survival (CR+PR) was 3-9 months, with a median of 6 months. Kolaric et al.[28] and Sledge et al.[10] have reported that cisplatin combinations in previously untreated patients are associated with higher overall response rates (49-83%) and a higher complete response rate(36%). In the present series 8 of 9 (89%) previously untreated patients responded, and 4(44%) achieved CR. The response rate was clearly better in previously untreated patients (89% versus 33%, Table VI). That the site of metastatic disease may influence treatment outcome was suggested in a study by Kolaric et al.[28] in which a CAP regimen produced higher responses in lung and liver metastases. In the present study however, none of the eleven patients with lung and pleural metastases achieved CR. However, responses were seen in lymph nodes, skin, breast and liver. Since the number of patients in the present study as well as in other reported series is small, it is difficult to draw conclusions regarding responses based on the site of metastases.

It is not clear at present whether cisplatin-containing regimens are superior to conventional regimens for metastatic breast cancer. Inclusion of other active agents such as doxorubicin and cyclophosphamide in the present study makes it difficult to comment on the role of cisplatin in the achievement of better response rates.

Three recent studies have investigated the role of cisplatin in combination chemotherapy as first-line therapy for metastatic breast cancer. Mechl and Sopkova[27] reported objective responses in six of 13 evaluable patients treated with cyclophosphamide, adriamycin and cisplatin (CAP). Kolaric et al,[28] have performed a prospective, randomized trial comparing CAP to FAC. While the overall response rates for the two arms of this study were similar, patients receiving CAP had a statistically significant increase in CR. A report from the Mayo Clinic compared the combination of cyclophosphamide, fluorouracil and prednisone (CFP) to CAP, and demonstrated a 49% response rate. Patients in the Mayo Clinic trial received lower doses of both cyclophosphamide and cisplatin than patients in the trial of Kolaric et al. This lower dosage may have impaired the overall response rate.

The results of this and other trials suggest that cisplatin should be considered as an active agent in the treatment of metastatic breast cancer, and as an attractive component of new combination chemotherapy in first-line regimens. Dose schedules that employ more convenient cisplatin scheduling (e.g. cisplatin administered on one day of every cycle), or test the ability of cisplatin analogs as first-line therapy, may increase the usefulness of platinum compounds in combination therapy. The relative efficacy of such schedules should he the subject of future clinical trials.

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