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Single-Drug vs Combination Cytotoxic Chemotherapy in Advanced Breast Cancer: A Randomized Study*

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Abstract—*One hundred and thirty-five patients with advanced breast cancer were randomized to receive either a five-drug combination consisting of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone (study group) or a single agent, 5-fluorouracil alone (control group). Objective responses were seen in 69% of the patients in the study group (47/68) and 18% of patients in the control group (12/67). The median duration of response (12.5 vs 6 months) and the median survival were significantly greater in the study group. The toxicity was somewhat greater with the multiple drug regimen compared with the single-drug.*

INTRODUCTION

PROSPECTIVE randomized clinical trials of single vs multiple drug therapy in the treatment of advanced breast cancer published in recent years have yielded conflicting results concerning the possible superiority of combination cytotoxic chemotherapy.

Lemkin and Dollinger [1] obtained results showing a similar efficacy for 5-fluorouracil compared to a five drug regimen including 5-fluorouracil, methotrexate, chlorambucil, vincristine and prednisone (5-FU, MTX, CMB, VCR and PNS). Similarly, Rubens, Knight and Hayward [2], comparing cyclophosphamide (CPP) alone with cyclophosphamide, 5-fluorouracil, methotrexate and vinblastine (CPP, 5-FU, MTX and VBL) found no significant statistical differences in the results, although the number and duration of remissions were greater in patients receiving the four drug combination.

However, Canellos *et al.* [3] demonstrated the superiority of a schedule of a combination cytotoxic chemotherapy including CPP, MTX and 5-FU over melphalan (MPL) alone. More recently, Mouridsen *et al.* [4] reported another prospective study demonstrating the superiority of a combination comprising CPP, MTX and 5-FU, VCR and PNS vs CPP alone.

The most extensively studied antimetabolite on the treatment of breast cancer is 5-FU giving a response rate of about 26% in advanced disease [5]. The present prospective and controlled clinical trial was designed to evaluate a single-drug treatment using 5-FU alone vs a modification of Cooper's regimen of combination cytotoxic chemotherapy including CPP, MTX, 5-FU, VCR and PNS in patients with advanced breast cancer.

MATERIALS AND METHODS

Patients

One hundred and thirty-five women, with advanced breast carcinoma in progression and refractory to endocrine therapy and irradiation, were entered in the study. All of them had histologically proven metastatic and measurable disease, were ≦75 yr, had normal hepatic and renal functions, a performance status equal to or more than 20% according to Karnofsky's criteria [6], and a minimum total white blood count of 3000 cells/mm^3. Before starting cytotoxic chemotherapy a full physical examination was carried out and all

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Abbreviations used: MTX, methotrexate; 5-FU, 5-fluorouracil; VBL, vinblastine; VCR, vincristine; CPP, cyclophosphamide; CMB, chlorambucil; PNS, prednisone; MPL, melphalan.

palpable or superficial lesions were measured in two perpendicular diameters. Photographs of all visible lesions were taken. Base line studies included hematological and biochemical screens and a radiological hepatic scan.

The physical examination was repeated before each subsequent course of therapy. Relevant radiographs were repeated at 2-month intervals and the isotopic liver scan at 3 months.

The patients were randomly allocated to one of two groups: 68 received a 5-drug combination (study group), CMFVP, a modification of Cooper's regimen comprising 5-FU—300 mg/m^2 i.v., MTX—15 mg/m^2 i.v. and VCR—0.65 mg/m^2 i.v., weekly for 20 weeks, together with CPP—75 mg/m^2 p.o. daily for 2 weeks, alternating with a 2-week rest period, and PNS—20 mg/m^2 p.o. daily, with diminishing dose (remission–induction period). The maintenance regimen was 5-FU—500 mg/m^2 i.v., MTX—15 mg/m^2 i.v. and VCR—0.65 mg/m^2 i.v. given on days 1, 8 and 15, together with CPP—75 mg/m^2 p.o. on days 1–15, with a 3-week rest period between courses.

The other 67 patients (control group) received 5-FU alone 500 mg/m^2 i.v., days 1–5 (loading dose), and then 500 mg/m^2 i.v., weekly.

Before randomization patients were stratified according to menopausal status, disease free interval and predominant lesions.

The selection of Cooper's regimen was determined by the known high percentage of objective remissions obtained with it. In spite of this, some modifications were introduced to avoid an anticipated severe toxicity due to the weekly administration of 5-FU, MTX and VCR, and the daily use of CPP. The maintenance regimen employed, with 3-week intervals off treatment, allowed a more adequate recovery between the courses and a beneficial psychological effect to the patients. Cytotoxic chemotherapy was continued either until progression of disease after a response or evidence of failure to respond to therapy. If myelotoxicity developed, i.e., total white cell count <2500 cells/mm^3 and platelet count $<100{,}000$ elements/mm^3, the interval between the cycles was increased (mainly or specially in study group); however, this interval was never more than 2–3 weeks, since this allowed enough time for the complete recovering of bone marrow. Some of the patients, in the control group, who failed to respond did receive subsequently CPP $\pm$ PNS $\pm$ MTX, but objective regressions were not achieved. Usually, after treatment failure, the patients were selected for phase I–II trials. The treatments were compared by response rate, response duration, survival and toxicity. Objective responses were assessed using the system recommended by the U.I.C.C. [7].

Complete response. Total disappearance of all known disease (CR). With osteolytic lesions these must be shown radiologically to have calcified.

Partial response. A $\geqq 50\%$ decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions (PR) and without appearance of new lesions.

No change. Less than 50% decrease or less than 25% increase in the size of all measurable lesions (NC).

Progression. $>25\%$ increase in the size of measurable lesions or appearance of new lesions (P).

To avoid the possibility of a withdrawal response patients were not entered into this trial until at least 4 weeks after the cessation of ablative hormone treatment. The duration of response was determined from the start of cytotoxic chemotherapy until the data progression of disease was documented. Survival was dated from beginning of treatment to death. The response duration and survival have been analysed by the life table method. The significance of differences between responses were determined by the chi-squared test and the log rank method was used to study the differences between duration of response to treatment and survival [8]. The records of all patients in this trial were reviewed by two extra-mural observers.

RESULTS

Sixty eight patients were randomized to receive the CMFVP protocol (study group) and 67, 5-FU alone (control group). The clinical characteristics of each treatment group are shown in Table 1. The patients randomly allocated to each of two groups were comparable with regard to age at diagnosis, time from diagnosis to start of cytotoxic chemotherapy, degree of axillary involvement, performance status, disease-free interval, menopausal status and dominant lesions.

Anti-tumor effects

The results of treatment are shown in Table 2. The percentage of objective responses in

Table 1. Clinical characteristics

	Number of patients	
	Study group	Control group
Number of patients	68	67
Median age at diagnosis (yr)	47.5	50
Median time from diagnosis to chemotherapy (months)	24.5	24
Previous treatment:		
Mastectomy ± radiotherapy (Stage I and II)	38	40
Axillary involvement N+	30	31
Axillary involvement N−	8	9
Primary radiotherapy ± mastectomy (Stage III)	28	23
Oophorectomy	35	31
Androgens and/or oestrogens	68	67
Median performance status (range) %	50 (20–90)	60 (20–90)
Disease free interval		
none	21	20
<2 yr	23	22
≧2 yr	24	25
Menopausal status		
0–1 yr (pre-menopausal)	19	19
1–5 yr	19	17
>5 yr	30	31
Predominant sites		
soft tissue	15	13
osseous	14	14
visceral: Lung/pleura	23	20
Liver	10	12
Ascites	6	8

Table 2. Objective responses

	Number of patients			
	Study group		Control group	
Objective regression				
Complete response	14 (20, 5%)	47 (69%)	3 (4%)	12 (18%)
Partial response	33 (48, 5%)		9 (14%)	
Median (months)	12.5		6	
Range	4–43 months		2–32 months	
Median survival (months)	16		5	
	$\chi^2 = 33.92$;		$P < 0.001$	

the study group was 69%, compared with 18% of the control group ($\chi^2 = 33.92$; $P < 0.001$). The median duration of response was 12.5 months (range 4–43) in the study group and 6 months (range 3–32) in the control group.

All patients in the single-drug group have died. In the study group (CMFVP Cooper's modification) 19 were still alive at the end of the trial with 12 remaining in remission.

The survival life-table curve is shown in Fig. 1. The median survival is 16 months for the study group and 5 months for the control ($P < 0.001$).

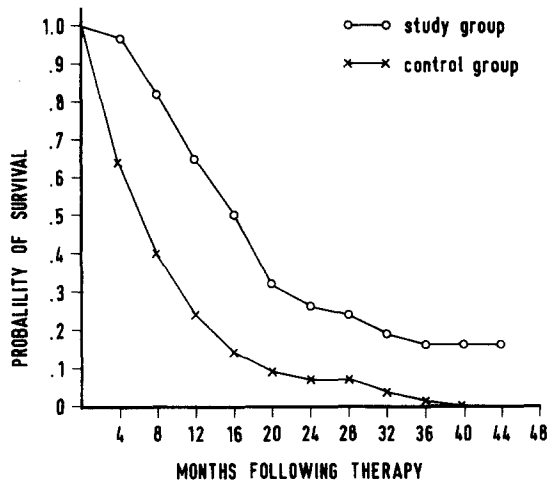

Fig. 1. *Overall survival of the two treatment groups: study group*—16 months, *control group*—6 months. (*Life-table method.*)

Toxicity

The toxicity of both schedules, summarized in Table 3, was significantly different, but tolerance to both treatments was generally good.

Table 3. *Toxicity*

	Number of patients (%)	
	Study group	Control group
	(n=68)	(n=67)
Neurotoxicity	64 (94)	—
Alopecia		—
Mild	3 (4)	
Severe and/or total	59 (87)	—
Leukocytes		
4000–3000	15 (22)	—
2999–2000	28 (41)	—
1999–1000	7 (10)	—
Platelet count:		
<100,000	—	—
Stomatitis	—	27 (40)
Nausea and/or vomiting	30 (44)	67 (100)
Diarrhoea	—	27 (40)
Diabetes mellitus	4 (6)	—
Sepsis	4 (6)	—
Cystitis	3 (4)	—
Secondary hyperadreno-corticalism	2 (3)	—

In the study group there are, mainly, two side effects, alopecia (mild—not requiring a wig: severe and/or total—requiring a wig) and peripheral neuropathy. Both reactions were minimized: the first, alternating the cycles of CPP, being alopecia less evident and with faster recovery; the second, witholding the administration of VCR once the neurotoxicity reached grade I (mild weakness, paresthesia, myalgia, numbness and tingling), according the criteria by Holland *et al.* [9], and until complete regression of the neurological symptoms. In the maintenance period, the interval between the courses was sometimes sufficient enough to correct this. Myelosuppression in this group was not severe and only in 7 patients did the leukocyte count go below 2000 cells/mm^3.

Four cases of diabetes mellitus and two with secondary hyperadrenocorticalism were also detected in the study group, but were easily controlled after stopping the corticotherapy. Three cases of toxic cystitis, the duration of which never exceeded 3 weeks, were reversed on stopping cyclophosphamide. Four cases of septicaemia were treated sucessfully and the cytotoxic chemotherapy was, subsequently, resumed.

In the control group tolerance to treatment was better, some stomatitis, nausea and/or vomiting being the most frequent reactions, and mild diarrhoea being observed only with the initial loading dose of 5-fluorouracil. The weekly administration of this drug did not give rise to unpleasant side effects.

DISCUSSION

In this prospective clinical trial, which was designed to assess the value of a schedule of combination cytotoxic chemotherapy vs single-agent treatment, it was demonstrated that the overall response rate, duration of response and survival, were significantly greater for the combination of CPP, MTX, 5-FU, VCR and PNS (study group) compared to the control group using 5-FU alone. We also observed objective response of osteolytic metastases with radiological complete recalcification, not seen in other series [3, 10–2]. As reported previously [13], a rapid complete regression of disseminated pulmonary metastases was observed in several cases. If the pulmonary parenchyma is the first capillary net to be crossed by i.v. drugs, we can postulate that the action of cytotoxic substances may be particularly effective at that site.

This study confirms the greater efficacy of using multiple drugs in combination over the use of single agents in the treatment of advanced breast cancer. The greater toxicity of the combination, as compared with single agent chemotherapy, did not detract from its therapeutic superiority. The few cases of sepsis,

diabetes mellitus and cystitis were successful treated or controlled and there were no drug related deaths. The results obtained suggest that the introduction of the maintenance regimen did not lead to an earlier progression of the disease compared to the continuous treatment as at the original regimen described by Cooper.

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