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A randomized trial of two regimens of cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone in advanced breast cancer

J. Carmo-Pereira, F. Oliveira Costa, Elvira Henriques, and Valentim Carvalho

Instituto Portugues de Oncologia de Francisco Gentil, 1093, Lisboa, Codex, Portugal

Summary. One-hundred evaluable patients with progressive advanced breast carcinoma untreated by cytotoxic chemotherapy but resistant to hormone therapy and irradiation were randomly allocated to receive either a combination of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), 5-fluorouracil (600 mg/m^2) IV every 3 weeks and prednisone 20 mg/m^2 PO daily, with diminishing doses (intermittent group), or a combination of cyclophosphamide (100 mg/m^2 PO on days 1–15, alternating with a 15-day rest period), methotrexate 20 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV weekly for 20 weeks and prednisone 20 mg/m^2 PO daily, with diminishing doses in the remission induction period, followed by a maintenance regimen of cyclophosphamide 100 mg/m^2 PO on days 1–15, methotrexate 20 mg/m^2 IV on days 1, 8, and 15, 5-fluorouracil 500 mg/m^2 IV on days 1, 8, and 15, and prednisone 20 mg/m^2 PO on days 1–15, with a 3-week rest period between the courses (intensive group). Entry was from 1 December 1982 to 30 November 1983. Objective responses were seen in 20/49 (41%) patients in the intermittent group and 34/51 (67%) in the intensive group ($\chi^2 = 6.72$; $P < 0.01$). The estimated median duration of response was 11 months in the intermittent group and 14 months in the intensive group. The estimated median survival was greater in the intensive group, but the difference was not statistically significant, although this parameter can be influenced with alternative additional chemotherapy. Toxicity was similar in both groups. These data suggest there are no therapeutic and survival advantages to the 3-weekly IV protocol compared with our previous regimen CMFP.

Introduction

In the last few years, some progress has been made in the treatment of advanced breast carcinoma. The use of combination cytotoxic chemotherapy regimens is widely accepted as an appropriate method to achieve a larger number of objective remissions and a longer survival time than are possible when agents are used singly [1, 2, 9].

Since 1976, we have been using a modification of Cooper's regimen as first-line treatment [3]. The results obtained have been satisfactory, with 65% objective responses, and similar to those achieved with the classic CMF [5]. The inclusion of prednisone in this schedule was intended to increase the wellbeing of the patients and to stimulate the bone marrow [11].

Recently, several attempts have been made to increase the interval between the administration of the cycles of chemotherapy, with the aim of minimizing the distressing psychological effects of a weekly or a 2-weekly schedule of IV treatment and avoiding the gastrointestinal intolerance that some patients experience with oral cyclophosphamide. To address these questions, we have carried out a trial to compare the efficacy of our CMFP regimen with a modified schedule including the same drugs, but with 3-weekly IV administration of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) combined with prednisone (P) by mouth. The purpose of this trial was to assess the objective response rate, the duration of response and survival, and the toxicity of these two schedules.

Patients and methods

One-hundred seven patients with biopsy-proven breast carcinoma, who had evaluable disease in progression that was resistant to endocrine treatment but had not previously been subjected to cytotoxic chemotherapy, were recruited from 1 December 1982, to 30, November 1983 (last followup 31 March 1985). The patients were aged ≤ 75 years and had adequate hepatic and renal function, a performance status of at least 20% (Karnofsky scale) [8], white blood cell count ≥ 4000 cells/mm^3, and platelet count $\geq 100\,000$ cells/mm^3; at least 4 weeks had elapsed since they had stopped additive or ablative endocrine treatment. Patients with osteoblastic bone lesions, brain metastases, and pleural effusions as the sole manifestations of disseminated disease were excluded. Before each course of cytotoxic chemotherapy a full physical examination was carried out, with a full blood count, including platelets. Lesions were measured and photographs taken when appropriate. An assessment of baseline lesions included an hepatic ultrasonogram, a chest X-ray, a bone scan, and radiographs of areas of increased uptake of isotope. These were repeated after a 3-month interval if appropriate.

Each patient was randomly allocated to one of the two treatment groups, and before randomization the patients were stratified according to dominant site of disease, disease-free interval, and menopausal status.

The intensive group received the CMFP regimen previously described [3], comprising cyclophosphamide

Offprint requests to: J. Carmo-Pereira

100 mg/m^2 PO daily (maximum 150 mg) for 15 days, alternating with a 15-day rest period, methotrexate 20 mg/m^2 IV and 5-fluorouracil 500 mg/m^2 IV weekly for 20 weeks, and prednisone 20 mg/m^2 PO daily (full dose for 3 weeks, diminishing doses for 2 weeks more, and then a maintenance dose of 10 mg on alternate days, if possible), followed by a maintenance regimen of cyclophosphamide 100 mg/m^2 (maximum 150 mg) PO on days 1–15, methotrexate 20 mg/m^2 IV on days 1,8, and 15, 5-fluorouracil 500 mg/m^2 IV on days 1, 8, and 15, and prednisone 20 mg/m^2 PO on days 1–15, with a 3-week rest period between the courses.

The intermittent group received a combination of cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 IV every 3 weeks, and prednisone 20 mg/m^2 PO daily, at the full dose initially, and then at diminishing and alternating doses, according to the schema reported above for this compound. This schedule of cytotoxic chemotherapy was continued until either there was evidence of failure to respond to treatment or relapse occurred after a response, other non-cross-resistant chemotherapy regimens subsequently being given if appropriate.

The following dose modifications (except for prednisone) were adopted in the presence of bone marrow suppression. For grade 1 toxicity (WBC 2000–3999/μl and/or platelet count 80 000–99 999/μl), 50% of the projected dose was given. For grade 2 toxicity WBC ≤ 1999/μl and/or platelet count ≦ 79 999/μl) cytotoxic drugs were omitted until grade 1 was reached.

The courses of cytotoxic chemotherapy were usually administered on an outpatient basis, and at least three cycles of treatment were given, both arms being used.

The treatments were compared for objective response rate, duration of response, survival time, and toxicity. The response to cytotoxic chemotherapy was assessed according to the criteria recommended by the UICC [6]. The categories of response, confirmed by at least two sequential observations made not less than 4 weeks apart, are as follows:

Complete response. Disappearance of all known disease. In the case of lytic lesions these must be shown radiologically to have calcified.

Partial response. A 50% or more decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions, without appearance of new ones.

No change. Lesions unchanged (i.e., less than 50% decrease or less than 25% increase in the size of measurable lesions).

Progressive disease. An increase by 25% or more in the size of measurable lesions and/or appearance of new lesions. When some lesions regress while others progress or new lesions appear (mixed response) this is deemed progressive disease.

All patients studied in this protocol in whom no change was recorded were classed as nonresponders.

The duration of response was dated from the beginning of chemotherapy to the date of documentation of progressive disease.

Survival was recorded as the time treatment was started to death, or to date of last followup (31 March 1985) for patients still alive. The response duration and survival were analyzed by the life-table method, and the significance of differences between responses was calculated by the chi-square test; the log rank method was used to study the differences in duration of response to treatment and survival. The records of all patients in this trial were reviewed by an external observer.

Results

One-hundred seven patients were entered in this prospective controlled clinical trial. Seven patients were excluded from the final analysis: Four in the intermittent group, because they refused to go on with treatment after the first course of therapy, and three in the intensive group, because protocol violations had occurred. In all 100 evaluable patients were analyzed in this study, 51 of whom were randomized to the intensive group and 49 to the intermittent group. The clinical characteristics of the patients in each group are shown in Table 1 and are comparable re-

Table 1. Characteristics of patients

	Intensive group	Intermittent group
Number of patients	51	49
Median age at diagnosis (years)	52 (range 26–74)	54 (range 27–75)
Median time from diagnosis to chemotherapy (months)	21 (range 1–156)	22 (range 1–153)
Previous treatment:		
Mastectomy ± radiotherapy (stage I and II)	26	25
Axillary involvement N+	18	18
Axillary involvement N−	8	7
Primary radiotherapy ± mastectomy (stage III)	25	24
Oophorectomy	16	12
Androgens and/or antiestrogens	51	49
Median performance status		
20%–50%	24	23
≧60%	27	26
Postoperative disease-free interval		
None	4	5
<2 years	12	11
≧2 years	10	9
Menopausal status		
0–1 year (premenopausal)	11	9
1–5 years	15	13
> 5 years	25	27
Predominant sites involved		
Soft tissue	19	20
Osseous	8	10
Visceral		
Lung/pleura	18	13
Liver	5	4
Ascites	1	2

Table 2. Objective responses

	Number of patients			
	Intensive group (51)		Intermittent group (49)	
Objective regressions				
Complete response	10 (20%)	34 (67%)*	2 (4%)	20 (41)*
Partial response	24 (47%)		18 (37%)	
Duration of response				
Median (months)	14		11	
Range	4–28+		4–28+	
Median survival (months)	21		17	

* $X^2 = 6.72 : P < 0.01$

Table 3. Toxicity

	Number of patients	
	Intensive group (51)	Intermittent group (49)
Total white blood cell count		
≧4000/μl	4	7
3999–3000/μl	9	10
2999–2000/μl	25	22
1999–1000/μl	13	10
Platelet count		
≦100 000/μl	2	0
Alopecia		
Mild	13	14
Severe and/or total	38	35
Stomatitis	3	5
Diabetes (induction)	5	2
Nausea and/or vomiting	49	48
Sepsis	2	1
Duodenal ulcer	2	1

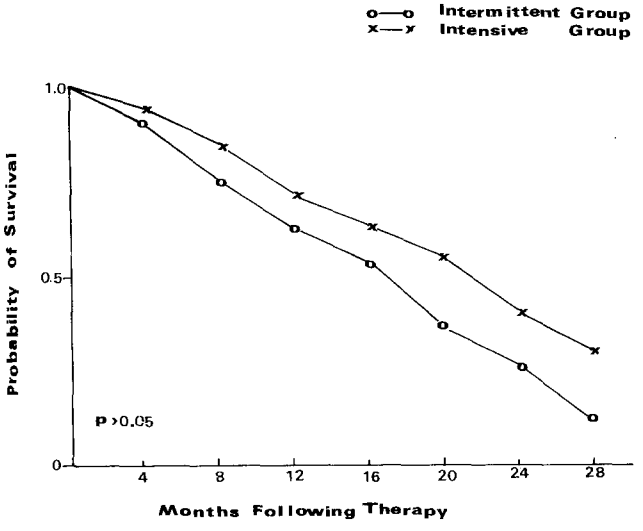

Fig. 1. Survival (months) of all patients: O———O, intermittent group (17 months); ×———×, intensive group (21 months). Life-table method

garding age at diagnosis, median time from diagnosis to initial chemotherapy, previous treatments, axillary involvement, median performance status, postoperative disease-free interval, menopausal status, and predominant sites involved.

Antitumor effects

The results of treatment obtained in both groups of patients are shown in Table 2. Of the 51 patients treated in the intensive group, 34 (67%) achieved an objective response, including 10 with complete remissions (20%). In the intermittent group, of 49 patients treated 20 (41%) achieved an objective regression, with 2 achieving complete responses (4%). There was a significant difference between these response rates ($\chi^2 = 6.72$; $P < 0.01$) and the estimated median duration of response until the last followup (31 March 1985) was 14 months for the intensive group (range 4–28+) and 11 months for the intermittent group (range 4–28+). Survival is documented in Fig. 1. There was a difference (not significant) between the two groups, as analyzed according to the log rank method: 21 months for the intensive group and 17 months for the intermittent group.

Toxicity

The toxic effects of treatment are summarized in Table 3. The tolerance to cytotoxic chemotherapy was generally moderate and acceptable in both groups of patients and very similar regarding nausea and/or vomiting, myelossupression, alopecia, stomatitis, diabetes induction, and septicemia. Seven cases of diabetes mellitus were well resolved after stopping prednisone (5 in the intensive group and 2 in the intermittent group). No cases of cystitis were detected and only two cases of sepsis were observed in the intensive group and one in the intermittent group; these were sucessfully treated with antibiotics. No drug-related deaths occurred. No difference in the tolerance to the cytotoxic drugs was detected in favor of the modified schedule group.

Discussion

The main purpose of this study was to assess the therapeutic value and the toxicity, in advanced breast carcinoma, of a Cooper's regimen modification, CMFP, which has previously been tested by ourselves [3] (intensive group), in

comparison with another schedule including the same cytotoxic drugs administered IV 3-weekly, except for prednisone (intermittent group). Fifty-one patients were studied in the intensive group, where an objective response rate of 67% (with 20% complete remissions) was achieved, as against 41% objective regressions (with 4% complete) obtained in 49 patients in the intermittent group. The difference is statistically significant. The higher response rate achieved with the intensive program may be attributed to the more constant administration of the drugs. We observed in this trial that in two patients receiving the intermittent schedule, after relapse it was still possible to obtain a partial remission using the more intensive regimen.

No significant differences were seen in duration of regression or median survival, as in the studies by Hoogstraten et al. [7] and Smalley et al. [10] using a Cooper's regimen versus a schedule including the same five drugs administered in an intermittent fashion. In the present study, the results we have obtained, showing no significant benefit in survival, can be altered by giving other chemotherapy regimens (non-cross-resistant drugs) on disease progression.

The toxicity of the two regimens was similar, and no significant differences were found with regard to gastrointestinal complaints or distressing psychological effects.

The results in the intensive group are consistent with the preliminary data we reported previously [4]. Comparison of the earlier results with those recently obtained reaffirms the greater effectiveness of our intensive CMFP regimen. Therefore, for ethical reasons we closed the recruitment of patients to this protocol on 30 November 1983. However, the results presented appear to conflict with those obtained by Smalley et al. [10] who were not able to demonstrate a difference when this combination of drugs was used either continuously or intermittently.

The present prospective randomized clinical trial demonstrates a disadvantage for the intermittent regimen in comparison with our previous CMFP regimen, which continues to be the most useful first-line schedule for treatment of patients with advanced breast carcinoma in our center.

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