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CAP (cyclophosphamide, adriamycin, platinum) vs CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisolone) combination chemotherapy in untreated metastatic breast cancer

A preliminary report of a controlled clinical study

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Summary. *The prospective controlled phase III clinical trial compared the therapeutic value of the cis-platinum – adriamycin – cyclophosphamide combination (CAP) and that of the combination of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisolone (CMFVP) in untreated metastatic breast cancer. Seventy-two patients (> 2 cycles) were evaluated: 36 had received CAP and 36, CMFVP. An objective response (CR+PR) to CAP combination chemotherapy was achieved in 75% of patients (27 of 36), with a high rate (42%) of complete remissions. In terms of metastatic site, the response rate appeared to be particularly high in soft tissue and visceral organ (lung, liver) metastases. In the CMFVP group, an objective response was noted in 16 of 36 patients (44%) with 19% complete remissions. Overall therapeutic response and the complete remission rate were better with CAP regimen (statistically significant; $P < 0.01$). The duration of remissions was 4–16+ months (M = 12) for CAP and 2–12+ months (M = 8) for CMFVP. Toxic side-effects were more pronounced in the CAP group, particularly myelosuppression, and anemia was prevalent. Side-effects of CMFVP treatment were mild. In 11 CMFVP-resistant cases CAP was administered as second-line treatment, and an objective response was observed in 45% of cases (5 of 11). The preliminary results of this controlled trial show the advantage of the CAP combination in the treatment of metastatic breast cancer.*

Introduction

Thus far breast cancer has not been studied in sufficient detail as far as the antitumorigenic acitivity of *cis*-platinum (*cis*-DDP) is concerned.

A few reports discuss phase II *cis*-DDP trials, but only in previously heavily treated breast cancer patients [3, 6, 7, 11–13]. The few reports available have supported the current view that breast cancer is not chemosensitive to *cis*-DDP. However, very recently we have reported a phase II clinical trial of *cis*-DDP in previously untreated metastatic breast cancer [8]. This trial showed an objective response rate (CR+PR) in 54% (19 of 35) of patients treated, with a high complete remission rate (37%) particularly in soft tissues and visceral organs (lung, liver). Following these results we have incorporated *cis*-DDP into combination chemotherapy with two other drugs very active in breast cancer, adriamycin and cyclophosphamide (giving CAP) and studied the antitumorigenic activity of this drug combination vs that of the frequently used combination of cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisolone (CMFVP). The preliminary results of this phase III controlled randomized trial are presented.

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Patients and methods

Up to 1 February 1984 a consecutive series of 78 pre- and postmenopausal patients with metastatic breast cancer who had not previously been treated with cytostatic drugs entered the trial. The criteria for inclusion were as follows: maximum age 70 years; pathohistological evidence of disease; measurable disease; performance status > 40 (Karnofsky index); normal bone marrow, liver, and renal function tests (creatinine < 1.5 mg/100 ml serum); no additional primaries or severe cardiac disease; and expected survival > 6 weeks. Prior radiotherapy or hormone therapy were not considered to be criteria for exclusion.

The patient characteristics are shown in Table 1. It shows a slight prevalence of postmenopausal patients in the CMFVP treatment modality. In all 47 patients had previously been treated with radiotherapy, and 14 with hormone therapy. The

Table 1. Patient characteristics

	Total no. of patients	CAP	CMFVP
Patients entered on trial	78	38	40
Evaluable patients (> 2 cycles)	72	36	36
Age			
Range	30–70	30–67	32–70
Average	54	52	55
Premenopausal patients	29	19	10
Postmenopausal patients	43	17	27
Previous radiotherapy	47	20	27
Previous hormone treatment	14	4	10
Performance status (Karnofsky)			
40– 70	35	17	18
80–100	37	19	18
Predominant metastatic site			
Soft tissue	26	15	11
Visceral organs	36	15	21
Bones	10	6	4

performance status was 40–70 in 35, and 80–100 in 37 patients. Prior to randomization the patients were stratified according to predominant metastatic sites; thus, 26 patients presented metastases in soft tissues, 36 in visceral organs, and 10 in bones.

Within the CAP protocol *cis*-DDP was given at a dose of 30 mg/m^2 as an IV infusion on days 1, 3, and 5, along with the frequently used forced diuresis with 2,000 ml 5% glucosaline and 500 ml 10% mannitol. Adriamycin was given at a dose of 40 mg/m^2 IV on day 1, and cyclophosphamide at a dose of 200 mg/m^2 IV on days 1, 3, and 5. The CMFVP treatment consisted in cyclophosphamide, 200 mg/m^2 IV on days 1, 2, 3, 4, and 5; methotrexate, 20 mg/m^2 IV on days 2 and 4; 5-fluorouracil, 500 mg/m^2 IV on days 1, 3, and 5; vincristine, 1 mg/m^2 IV on days 1 and 5; and prednisolone, 40 mg PO daily on days 1–5. The rest periods between cycles were 3–4 weeks.

All the toxic side-effects were monitored regularly, particularly any effects on blood count and serum creatinine, ototoxicity, cardiotoxicity, and neurotoxicity.

In cases of complete clinical remission therapy was discontinued after 10 cycles, and the patients were followed-up regularly. In cases of partial remissions and stable disease therapy was sustained until signs of disease progression were observed. To study the antitumorigenic activity of the CAP regimen as a second-line treatment, the CAP schedule was administered in all patients showing no primary response to the CMFVP protocol or cases with disease progression following remission. Only patients given at least two cycles of the planned chemotherapy were evaluated. The criteria recommended by the WHO/UICC Committee were applied in the evaluation of treatment results and toxicity.

Results

Of the 78 patients entered on trial, 72 received more than two chemotherapy cycles and could be evaluated during an observation period of 22 months. Of the 36 patients treated according to the CAP protocol, 27 (i.e., 75%) responded to therapy. The latter group presented a complete remission rate of 42% (15 patients). Partial remission was observed in 12 patients; the disease progressed in six patients and was stable in three. In the group treated with CMFVP the response rate was 44%, with seven complete remissions (19%) and nine partial remissions. In 16 cases the disease progressed and in four it was stable. The differences between the two groups in both overall response and complete remission rate were statistically significant ($P < 0.01$). The duration of remission was 4–16+ months (M = 12+) for the CAP protocol, and 2–12+ months (M = 8+) for the CMFVP schedule during a median follow-up period of 16 months. It should be mentioned that 12 of the 15 patients achieving complete response with CAP completed the planned 10 chemotherapy cycles. Following treatment, the disease relapsed in only one case (bone disease), while the others are still in remission 2–6 months after the discontinuation of therapy. The complete responses have now lasted 6+ to 18+ months (median 14+ months).

The analysis of response as related to metastatic sites and the number of affected organs (Table 2) shows a high response rate to the CAP schedule in soft tissues (75%, 24 of 32) and lungs (70%; 11 of 15). Comparison with the CMFVP schedule revealed a statistically significant difference ($P < 0.01$).

On the other hand, the effect of the menopause, prior radiotherapy, and prior hormone therapy on treatment results showed no major differences between the two patient groups. Patients with a 40–70 performance status had a poorer response than those with 80–100, but only in the CMFVP group (3 of 18 vs 13 of 18).

Table 3. Toxic side-effects (CAP vs CMFVP)

	CAP (36 patients)	CMFVP (36 patients)
Anemia	14 (39%)	–
Grade I	3	
Grade II	4	
Grade III–IV	7	
Leukopenia	6 } 56%	6 (17%)
Grade I	1	4
Grade II	2	1
Grade III–IV	3	1
Thrombocytopenia		
Grade I	1	–
Creatinine	3 (142, 174, 158) mMol/l	–
Neurotoxicity	1	1
Ototoxicity	–	–
Vomiting	32/36 (89%)	7/36 (19%)
Alopecia	30/36 (83%)	15/36 (42%)
ECG changes	2/36 (5%)	–
Stomatitis	–	2/36 (5%)

Table 2. Response with regard to localization of metastases and number of affected organs[a]

Localization	Complete response		Partial response		Stable disease		Progression		Objective response	
	CAP	CMFVP	CAP	CMFVP	CAP	CMFVP	CAP	CMFVP	CAP	CMFVP
Skin, subcutaneous tissue, primary tumor	5	1	5	4	3	5	2	6	10/15	5/16
Lymph nodes	9	2	5	6	1	3	2	3	14/17	8/14
Lung/pleura	7	3	4	4	2	3	2	11	11/15	7/21
Liver	2	1	3	2	1	1	3	4	5/9	3/8
Bones	–	1	2	–	1	3	4	5	2/7	1/9

Comparisons: Soft tissue and lymph nodes (CAP) 24/32 (75%) vs soft tissue and lymph nodes (CMFVP) 13/30 (43%): $P < 0.01$; lung/pleura (CAP) 11/15 (70%) vs lung/pleura (CMFVP) 7/21 (33%): $P < 0.01$

The analysis of response referred to the predominant metastatic site shows an obvious therapeutic difference where the visceral organs are concerned: whereas 13 of 15 patients (86%) responded to CAP, the rate was 33% (7 of 21) for CMFVP. The difference was statistically significant ($P < 0.01$).

Due mention should also be made of the five remissions observed in 11 patients (response rate 45%) in whom the CMFVP schedule failed to produce results and CAP was administered as second-line treatment. One complete remission was observed in a case of pleural effusion and lung metastases, and four partial remissions in soft tissue and lung metastases.

As shown in Table 3, CAP proved to be much more toxic in terms of side-effects. The most pronounced side-effect was myelosuppression, observed in as many as 56% of patients. Marked anemia, present in 39% of patients, is attributed to the specific toxic effect of *cis*-DDP on red blood cells. Leukopenia was also pronounced, whereas thrombocytopenia was present in only one case. Creatinine levels were continuously high in three patients, albeit below 200 mMol/l, permitting the completion of therapy (10 cycles). Alopecia was present in 83% of cases, and transitional ECG changes in 5%. Toxic side-effects produced by the CMFVP schedule were mild.

Discussion

Our preliminary observations concerning the effect of CAP combination chemotherapy in breast cancer appear to be encouraging, and to justify incorporation of *cis*-platinum into the treatment of this disease. Here it is necessary to mention that besides platinum, our regimen contained two of the other drugs most active in breast cancer, i.e., adriamycin and cyclophosphamide. The overall response rate to the CAP regimen was 75%; moreover, particular emphasis should be placed on the observed high rate of complete remissions (42%); these patients are also the only candidates for long-term survival. A similarly high response rate was obtained in visceral organ and soft tissue metastases. Let us also point out that there has been only one case of relapse (in the bones), among the 12 complete remission cases during the observation period. Accordingly, the preliminary results of our trial indicate the pronounced therapeutic value of the CAP schedule compared with the CMFVP protocol we have used. In connection with our results with the CMFVP protocol, mention should be made of the response rates ranging from 20% to 70% (average 47%) with short-term intermittent five-drug regimens reported elsewhere [2, 4, 10]. Considering the CMFVP dosage we have used, we did not find any major differences from the other five-drug intermittent schedules, except the original Cooper protocol. We would like to emphasize that the other adriamycin-containing regimens (CAF, FAC, AC, ACMF) are also superior in response rate (but not in survival) to the CMF and the CMFVP protocols [1, 5, 9].

The toxic side-effects of the CAP schedule are not negligible, particularly with regard to bone marrow suppression, i.e., mainly anemia. As the trial proceeded, however, we reduced the total platinum dose after three induction cycles to 60 mg/m^2 per cycle. Preliminary results have already shown that this modification of the CAP schedule reduces myelosuppression considerably without affecting the antitumorigenic effect. Moreover, our initial observations regarding the antitumorigenic effect of the CAP schedule as a second-line treatment have also been favorable. A response was observed in five of 11 CMFVP-resistant cases.

It is necessary, however, to stress that other adriamycin-containing second-line protocols (AV, AVP, AVP-16) also yielded practically the same response rate (25%–40%).

The trial is still under way. The final results will show whether the CAP schedule used might provide a more successful approach to combination chemotherapy in metastatic breast cancer.

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