Cancer Chemother Pharmacol (1983) 11: 108–112

Cancer Chemotherapy and Pharmacology

Phase II clinical trial of *cis*-dichlorodiammine platinum (*cis*-DDP) for antitumorigenic activity in previously untreated patients with metastatic breast cancer

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Summary. *A phase II clinical trial was set up in metastatic breast cancer patients who had not received previous cytotoxic drug therapy, involving the administration of cis-dichlorodiammine platinum (cis-DDP). Patients aged up to 75 years and with pathohistologically confirmed disease were entered on the trial. All patients had measurable disease, a performance status (Karnofsky) of > 40, and an expected survival of > 6 weeks. In all 38 patients entered the trial, and 35 have been evaluated. The predominating metastatic sites included soft tissues (19), visceral organs (12), and bones (7 patients). cis-DDP was administered in a daily dose of 30 mg/m² IV by a 4-h drip for 4 days, with customary hyperhydration. The results indicate a pronounced antitumorigenic effect of cis-DDP and a response rate of 54% (19/35), with 13 complete remissions (37%) and six partial remissions (17%). In terms of site the best response was obtained in soft-tissue processes (13/19; 68%), followed by visceral organs (4/10; 40%); the response rate was lowest in bones (2/6; 33%). The menopausal status and prior hormone therapy did not essentially influence the results of treatment, unlike previous irradiation. Patients with a lower performance status (40–70) had a significantly lower response rate (36% vs 63%; P < 0.05). Toxic side-effects were moderate and did not substantially affect the general condition of the patients. A transient increase of serum creatinine was observed in 4 patients, and neurotoxicity in 2 patients. The results of the trial warrant the conclusion that cis-DDP has a pronounced antitumorigenic effect in untreated metastatic breast cancer, particularly in soft-tissue metastases. These results call for additional clinical study of the cytotoxic effect of cis-DDP in untreated metastatic breast cancer.*

Introduction

As shown by clinical trials, *cis*-dichlorodiammine platinum (*cis*-DDP) has shown pronounced antitumorigenic activity in cancer of the testes, ovaries, lungs, urinary bladder, and tumors of the head and neck [7, 10, 11, 21–23, 25, 26]. A slight antitumorigenic effect of *cis*-DDP has also been noted in melanoma and osteogenic sarcoma, whereas in the case of squamous cell carcinoma of the esophagus reports appear to be conflicting [1, 5, 12, 17, 19]. Very recent trials have also shown this cytostatic drug to posses marked antitumorigenic activity in primary and metastatic brain tumors [13–16]. In these trials, an obvious antitumorigenic effect of *cis*-DDP was also observed at other (extracerebral) metastatic sites, especially in patients with untreated breast cancer [14, 15].

Thus far breast cancer has not been studied in sufficient detail as far as the antitumorigenic effect of *cis*-DDP is concerned. Few reports discuss phase II *Cis* platinum trials in other than previously heavily treated breast cancer patients [3, 6, 18, 20, 27]. In as much as previously untreated patients were not included in these trials, such meager reports have supported the current view that breast cancer is not chemosensitive to *cis*-DDP, which is rather unexpected in view of its very broad spectrum of antitumorigenic activity and of the chemosensitivity of breast cancer.

This, along with the absence of phase II clinical trials of *cis*-DDP in nontreated metastatic breast cancer, is the rationale underlying the present trial.

Patients and Methods

The trial was conducted in a consecutive series of pre- and postmenopausal patients with metastatic breast cancer, who were up to 75 years old and previously untreated with cytostatic drugs. In all cases the diagnosis was confirmed pathohistologically. Patients who had undergone previous irradiation or hormone therapy were not excluded. The interval since the latest radiotherapy treatment had to be at least 4 weeks. Normal bone marrow, liver, and kidney function was required for the trial. Patients with serum creatinine levels of > 1.5 mg/100 ml serum and a performance status (Karnofsky score) of < 40 were not entered on the trial. The disease was measurable in all cases. Only patients with an expected survival of at least 6 weeks were included.

Prior to therapy all patients had a complete staging workup to document the extent of the disease, which included a clinical examination, blood count, chest and skeletal X-rays, liver and bone scans, and biochemical blood tests.

Thirty-eight patients meeting the foregoing criteria were entered on the trial consecutively. Patient characteristics are shown in Table 1. Predominating metastatic sites included soft tissues (19 patients), visceral organs (12), and bones (7). Patients with brain metastases were excluded from the trial because they were covered by a separate clinical trial.

cis-DDP was administered IV at a daily dose of 30 mg/m² body surface in the form of a slow 4-h 500-ml glucose-saline drip. This dose was administered on each of 4 consecutive days, giving a total of 120 mg/m² of *cis*-DDP per cycle. Hyperhydration was carried out in the form of 500 ml 5%

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glucose prior to *cis*-DDP infusion, and 500 ml 10% mannitol after infusion. A single antiemetic 250 mg methylprednisolone dose was injected 2 h before *cis*-DDP administration. The rest periods between cycles were 3–4 weeks.

All toxic side-effects, in particular the blood count, serum creatinine, ototoxicity, and neurotoxicity, were monitored regularly. Only patients who received at least two *cis*-DDP cycles were evaluated. *cis*-DDP administration was continued in the case of a favorable effect (complete or partial response), while one of the established chemotherapy protocols (FAC/CMF) was administered in the event of stable disease or disease progression. If bone marrow or nephrotoxicity was observed the next cycle was postponed until blood count and creatinine serum level, respectively, returned to normal. Criteria recommended by the UICC/WHO Committee (complete response, partial response, stable disease, progression) were applied in the evaluation of treatment results [24].

Table 1. Patient characteristics[a]

Patients entered on study	38
Evaluable patients	35
Age	32–74 years (mean 50)
Premenopausal patients	15
Postmenopausal patients	23
Previous radiotherapy	23
Previous hormone treatment	11
Performance status	
40– 70	11
80–100	27
Predominant metastatic site	
Soft tissue	19
Visceral organs	12
Bones	7

[a] Patients with brain metastases were excluded from the study

Results

Of the 38 patients entered on trial, 35 were evaluable. Three patients received only one course of chemotherapy and have not been evaluated because of violation of the protocol and inadequate follow-up. The patients evaluated received two (minimum) to nine (maximum) *cis*-DDP cycles (average 5 cycles). The administration of *cis*-DDP produced a response in 19 of the 35 cases (54%). Complete response was observed in 13 patients (37%), and partial response in six (17%). In eight patients the disease was stable (response 0–50%), and in eight others the disease progressed. The average duration of remission was 4.6 months; it was as high as 6.8 months in the complete responders.

Analysis of the response rate with regard to localization and number of metastatically affected organs (Table 2) showed most complete and partial remission to have occurred in soft tissues (15/22; 68%). Such a high rate of regression was found in metastases in the skin, subcutaneous tissue, and lymph nodes; cutaneous lymphangiosis appeared to respond particularly well. So far as metastases in visceral organs are concerned, three regressions (two complete, one partial) were observed in eight cases of lung metastases. Liver metastases regressed only partially (2/7). Bone metastases also presented a lower response rate to *cis*-DDP. Of eight cases, only one complete remission, with recalcification of the lesion (2 × 2 cm) on the pelvis (left supra-acetabular position), and 1 partial regression were observed. Three patients experienced relief of bone pain following the administration of *cis*-DDP, but there was no objective regression of bone alterations.

Response to therapy was also monitored with regard to menopausal status, previous treatment, performance status, and predominant metastatic sites (Table 3). Thus, no essential differences – in terms of response to therapy – were found between premenopausal (7/14; 50%) and postmenopausal

Table 2. Response rate with regard to localization and number of metastatic organs

Localization of metastases	Complete response	Partial response	Stable disease	Progression	Response rate
Skin, subcutaneous tissue, primary tumor	4	2	2	1	6/9
Lymph nodes	4	1	2	1	5/8 } 15/22 (68%)
Cutaneous lymphangiosis	4	–	1	–	4/5
Lung	2	1	2	3	3/8
Liver	–	2	3	2	2/7
Bones	1	1	1	5	2/8

Table 3. Response rate with regard to menopausal status, previous treatment, performance status, and predominant metastatic site

	No. of patients	Complete response	Partial response	Stable disease	Progression	Response rate
Premenopausal patients	14	4	3	3	4	7/14 (50%)
Postmenopausal patients	21	9	3	5	4	12/21 (57%)
Previous irradiation	21	6	4	4	7	10/21 (46%)
No previous irradiation	14	7	2	3	2	9/14 (64%)
Previous hormone treatment	11	3	2	3	3	5/11 (46%)
No previous hormone treatment	24	10	4	5	5	14/24 (58%)
Performance status						
40– 70	11	3	1	3	4	4/11 (36%)
80–100	24	10	5	5	4	15/24 (63%)
Soft tissue	19	10	3	4	2	13/19 (68%)
Visceral organs	10	2	2	2	4	4/10 (40%)
Bones	6	1	1	2	2	2/ 6 (33%)

patients (12/21; 57%; $P > 0.05$). The effect of *cis*-DDP was lower in previously irradiated patients (10/21; 46%) than in nonirradiated ones (9/14; 64%; $P > 0.05$). Previous hormone therapy appeared to have no influence on the response rate (46% vs 58%; $P > 0.05$). On the other hand, the performance status was of essential significance for response to therapy. Thus, only four of 11 (36%) patients with performance status 40–70, as against 15 of 24 (63%) in the 80–100 group, responded to *cis*-DDP therapy. The difference was statistically significant ($P < 0.05$). As far as the relation between response to therapy and the predominating metastatic site is concerned, the best response was observed in patients with metastases in soft tissues (13/19; response rate 68%). In the case of visceral metastases the response rate was moderate (4/10 or 40%), and it was lowest in bone metastases (2/6; 33%).

Toxic side-effects (Table 4) involved primarily gastrointestinal upsets in the form of persistent vomiting, which was observed in 51% of cases. The antiemetic given, methylprednisolone, is believed to have reduced this unpleasant side-effect, which usually occurs in almost all cased treated with *cis*-DDP. Leukopenia was observed in 26% of cases, and was of a fairly low grade according to UICC/WHO toxicity criteria (I, II); thrombocytopenia was observed in two patients (6%; grade II). Transient episodes of elevated creatinine, which normalized spontaneously in rest period between cycles, occurred in four patients. Very unpleasant polyneuropathies, in the form of pronounced paresthesiae in the legs, were observed in two patients. In both cases *cis*-DDP had to be discontinued in spite of the good response achieved after four and five cycles, respectively. A single case of palmar fibrosis on both hands was seen following one course of therapy. The clinical picture was very similar to that of Dupuytren's contracture. Two months after the fifth *cis*-DDP cycle (discontinuation of administration) the fibrous changes disappeared spontaneously. The frequency of toxic side-effects was higher in patients with a lower performance status (40–70). In this group an average of 1.8 toxic incidents per patient was observed, as against only 0.7 in the 80–100 group.

Discussion

Our phase II clinical trial was focused on the effect of *cis*-DDP in metastatic breast cancer of patients previously untreated with cytostatic drugs. In the 35 patients evaluable in this trial *cis*-DDP has given an overall response rate of 54% (19/35); more importantly, however, it has given a very high complete response rate of 13/35 (36%). Soft-tissue metastases proved to be particularly sensitive, with a response rate of 13/19 (68%) and a high percentage of complete remissions (10/19). Remissions developed very rapidly, usually after only two cycles, and a particularly good response was observed in metastases in the skin, subcutaneous tissue, and lymph nodes. Primary inoperable breast tumors and cutaneous lympangiosis also responded to therapy very rapidly and obviously. Where visceral organs are concerned, lung metastases appeared to be more sensitive to therapy than metastases in the liver. Bone metastases were the most resistant to therapy.

The therapeutic effects appeared to be independent of menopausal status and response to prior hormone therapy. There was a reduced response rate in patients who had received prior radiotherapy and those with a performance status < 80. The high response rate observed in our trial could also be attributed to the supportive antitumorigenic activity of corticosteroids administered as an antiemetic. Corticosteroids are known to have an effect, albeit very mild, on breast cancer. It is not of great importance, however, because numerous past trials and results achieved with combination chemotherapy have shown that combinations of cytostatic agents and corticosteroids do not produce better results than combination of cytostatic agents alone [2].

Insofar as the toxic side-effects of our *cis*-DDP protocol are concerned, a single methylprednisolone dose succesfully counteracted the otherwise very persistent and unpleasant vomiting in about 50% of our cases. Bone marrow and nephrotoxicity were moderate, and in the majority of cases did not require discontinuation of therapy. Therapy had to be discontinued in two cases involving neurotoxicity (severe paresthesiae in the form of tingling, anesthesia, and marginal pain). Moreover, toxic side-effects were more marked in patients with a compromised physical condition (performance status 40–70).

In a way, our results are interesting because so far *cis*-DDP has not been thought to be particularly active in breast cancer. In the analysis of past *cis*-DDP trials in breast cancer (Table 5), however, few reports (phase II trial in disease-oriented organ) of trials involving heavily pretreated patients were found to have been published. This is also of relevance for our results, because the response of previously treated and exhausted patients to a cytostatic drug may be expected to be very low. Thus, Samal et al. [20] and Yap et al. [27] reported a very low, almost nonexistent antitumorigenic effect of *cis*-DDP in previously treated breast cancer cases. Bull's report, however, on the same patient category, is somewhat more encouraging [3]. Bull observed a partial response in 13% of cases, and a stable disease condition in as many as 81% (13/16). Due mention should also be made of the results obtained by the groups of Ostrow, Hakes and Forastiere, who achieved a response rate of 21%–29%, even in previously heavily pretreated patients, mainly with higher *cis*-DDP doses (100–120 mg/m^2 per cycle) [6, 8, 18]. According to these data, the results of *cis*-DDP treatment in an untreated group of patients could be expected to be better. However, this information does not seem to have motivated and initiated any trials focused on evaluating the actual worth of *cis*-DDP in previously untreated patients. Thus the drug has so far hardly been used in breast cancer chemotherapy. On the other

Table 4. Toxic side-effects with regard to performance status

Performance status	Vomiting (> 2×)	Leukopenia	Thrombocytopenia	Increased serum creatinine	Polyneuropathy	Palmar fibrosis
40– 70	8/11 (73%)	5 11 (46%)	1/11 (9%)	147, 152, 160, 3/11 (27%)	2/11 (18%)	1/11 (9%)
80–100	10/24 (42%)	4/24 (17%)	1/24 (4%)	146, 1/24 (4%)	0/24	0/24
Total	18/35 (51%)	9/35 (26%)	2/35 (6%)	4/35 (11%)	2/35 (6%)	1/35 (3%)

Table 5. cis-Platinum response rate in previous trials (breast cancer)

Author	No. of patients	Schedule	Response Rate (> 50%) tumor regression	Response rate (< 50%) tumor regression	Remarks
Hayes et al. [9]	3	3 mg/kg Day 1	0/3	–	Patients heavily pretreated
Catane et al. [4]	3	100 mg/m^2 Day 1	1/3	–	Patients heavily pretreated
Yap et al. [27]	14	100 mg/m^2 Day 1	1/26 (4%)	–	Patients heavily pretreated
	12	20 mg/m^2 Day 1, 2, 3, 4, 5			
Samal [20]	15	15 mg/m^2 Day 1, 2, 3, 4, 5	0/23	–	Patients heavily pretreated
	8	120 mg/m^2 Day 1			
Bull et al. [3]	16	70 mg/m^2 Day 1	2/16 (13%)	13/16 (81%)	Patients heavily pretreated
Ostrow [18]	9	100 mg/m^2 Day 1	2/9 (22%)	–	Patients heavily pretreated
Hakes et al. [8]	16	60 mg/m^2 Day 1	0/16	–	Patients heavily pretreated
	17	120 mg/m^2 Day 1	5/17 (29%)	–	Patients heavily pretreated
Forastiere et al. [6]	19	120 mg/m^2 Day 1	4/19 (21%)	–	Patients heavily pretreated
	18	60 mg/m^2 Day 1	0/18	–	Patients heavily pretreated

hand,our trial has shown *cis*-DDP to be an extremely active cytostatic drug in untreated breast cancer cases, particularly for metastatic processes in soft tissues and the lungs. It is our belief that the action of the drug should be re-evaluated in untreated breast cancer cases. Following the results obtained in the present trial, we have already incorporated *cis*-DDP into combination breast cancer chemotherapy, and a phase III controlled clinical trial is already under way.

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Received November 22, 1982/Accepted May 13, 1983