Am J Clin Oncol (CCT) 12(5): 397–401, 1989.

120 Hours Simultaneous Infusion of Cisplatin and Fluorouracil in Metastatic Breast Cancer

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Thirty-six patients with metastatic breast cancer, 23 with documented progression of the disease after first-line chemotherapy (CAF or CMF) and 13 without prior chemotherapy, were treated with a simultaneous 120-h infusion of cisplatin (CDDP) and 5-fluorouracil (5-FU). Objective response was demonstrated in 19 patients (52.7%), stable disease in 7 patients (19.4%) and progression of the disease in 10 patients (27.7%). Similar response rate was observed according to tumor site (soft tissues, 50%; bone, 52%; lung, 63%; liver, 55%; and pleura and peritoneum, 42%) and previous treatment (previous chemotherapy, 48%; previously untreated, 61%). Median duration of response was 8 months. Toxicity was characterized by stomatitis and myelodepression and required dose adjustments in 30% of patients. CDDP and 5-FU infusion deserve further investigation because it appeared to have substantial activity in this preliminary study in metastatic breast cancer.

Key Words: Cisplatin–Fluorouracil—Chemotherapy—Breast cancer.

Cisplatin (CDDP) as a single agent had minor activity in heavily pretreated patients with metastatic breast cancer, but definitive antitumor effect was demonstrated in patients without prior chemotherapy (1). In selected patients, CDDP, as a first-line chemotherapy, indicated high activity with a response rate of 45–54% (2,3).

5-Fluorouracil (5-FU) is an agent usually used in initial chemotherapy programs in the treatment of breast cancer (i.e., CMF, CAF). In these programs 5-FU is administered as an intravenous bolus injection of 600 mg/m^2 weekly on 2 consecutive weeks. More recently, there is a renewed interest in this drug, owing to a better understanding of its mechanism of action and to the possibility of increasing the binding of 5-FU to its target enzyme, thymidilate synthetase, which is accomplished by exogenous folinic acid loading (4–6). Simultaneous administration of folinic acid and 5-FU demonstrated a response rate of 48–61% in untreated (7,8) and 16–19% in previously treated breast cancer patients (9,10).

Another approach taken to improve the efficacy of 5-FU is to administer the drug in prolonged infusion. Continuous intravenous infusion of 5-FU induces a plasma steady state with a greater drug–target interaction. Prolonged exposure in vitro to 5-FU is more effective than short-term treatment (11). More importantly, continuous infusion allows the delivery of a higher total 5-FU dose, thus representing a better schedule; although this has already been proven in metastatic colorectal cancer there are no data available for breast cancer (12). On the other hand, protracted-dose 5-FU in very prolonged continuous infusion, which indicated high activity in colorectal carcinoma (13), has recently demonstrated a 50% response rate in previously treated metastatic breast cancer in the series of Huan et al. (14).

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The combination of CDDP and 5-FU is another subject of recent studies. Experimental tumor models indicated synergism between CDDP and 5-FU (15,16). The basis of the synergism is not well understood. Scanlon et al. proposed that CDDP increased the 5,10 methylene tetrahydrofolate pool that would allow for a secondary increase in deoxythymidine monophosphate synthesis, which may also account for the increased sensitivity to fluoropyrimidines (17).

CDDP and 5-FU combination chemotherapy has indicated moderate activity in several solid tumors, such as epidermoid carcinoma of the head, neck, and the esophagus and adenocarcinoma of stomach, colorectum, and ovary (18–23).

Jacobs et al. reported for the first time the activity of CDDP–5-FU in previously treated patients with breast cancer, indicating the appearance of a partial response in five of 14 patients (35%) (24). Subsequent studies by different groups have confirmed this activity (25–28).

This report represents the final analysis of one of these Phase II trials (25).

MATERIALS AND METHODS

Eligibility criteria for the study included all of the following: pathology-proven metastatic breast cancer, presence of measurable metastases for the evaluation of response, documented progression to conventional chemotherapy (CAF or CMF), and serum creatinine < 1.3 mg/dl. To modify the dose for high-risk patients, reductions on the length of each chemotherapy cycle were planned for the following risk factors: elderly patients > 69 years of age, low performance status < 60 on the Karnofsky scale, prior extensive radiotherapy to the spine and/or pelvic bones, previous history of myelosuppression on chemotherapy, and poor liver or bone marrow function.

In a second series the study was enlarged, including patients without prior chemotherapy for metastatic disease, keeping the same protocol eligibility and dose-reduction criteria.

Baseline data included medical history, physical examination with measurement of lesions, evaluation of the performance status, complete blood cell count, serum biochemistry (hepatic and renal function tests), chest x-ray, and skeletal survey. Liver CT scan was performed when hepatic metastases were suspected. Tumor measurements were repeated before each treatment.

Treatment program consisted in 15 mg/m^2 CDDP in 1,000 ml of 5% D/WS containing mannitol 50 mg, given in 24-h infusion daily for 5 days, and a simultaneous infusion of 1,000 mg/m^2 5-FU in 2,000 ml of 5% D/WS containing methochlopramide 2 mg/kg, given in 24-h infusion daily for 5 days every 4 weeks. Dose reductions, according to the stated criteria, provided an initial 4-day infusion of CDDP–5-FU for patients with one risk factor present and an initial 3-day infusion of CDDP–5-FU in case two or more risk factors were present.

Dose reductions were planned for toxic cycles, which were defined as grade 1 or higher mucositis and grade 2 or higher bone marrow aplasia. When this occurred the dose was reduced by omitting one treatment day: i.e., from 5 days to 4 days of infusion. Further episodes of toxicity indicated a subsequent dose reduction: i.e., from 4 days to 3 days of infusion. Further dose reductions below 3-day CDDP–5-FU infusion were not allowed in the protocol. Toxicity was recorded as the most severe seen.

Specific reductions of CDDP were planned for patients with increasing creatinine levels between 1.2 and 1.6 mg/dl or severe paresthesia. In such cases, CDDP was reduced by 50% in the total dose without a reduction in the length of treatment. Higher creatinine levels, >1.6 mg/dl, indicated a discontinuation of CDDP treatment.

When WBC count at the time of the treatment was <3,000/mm^3, platelet count was <100,000/mm^3, and/or serum creatinine was >1.1 mg%, therapy was delayed to allow hematologic and renal recovery.

The criteria for definition of response and grade of toxicity were that of Miller et al. (29).

Complete response (CR) was defined as the disappearance of all known disease, determined by two observations not <4 weeks apart. Partial response (PR) was a decrease by ≥50% in the tumor volume, as measured by the product of the largest perpendicular diameters determined by two observations not <4 weeks apart. No change (NC) was assessed when a 50% decrease in total tumor size could not be established or a 25% increase in the size of one or more measurable lesions had not been demonstrated. Progressive disease (PD) was a >25% increase in the size of one or more measurable lesions or the appearance of new lesions. In bone metastases, CR was a complete disappearance of all lesions on x-ray or bone scintigraphy for at least 4 weeks; PR was a partial decrease in the size of lytic lesions, a recalcification of lytic lesions, or a decreased density of blastic lesions for at least 4 weeks; and the designation of NC in bone metastases was not applied until at least 8 weeks had passed from the start of therapy. Treatment was continued until the progression of disease was documented. Duration of response was measured from the date in which response criteria were met until the date of progression of the disease. Overall response lasted from the first day of treatment to the date PD was first observed.

TABLE 1. *Patient characteristics*

Characteristics	Patients
Total	36
Age	
Range (30–73)	
Median 51	
Menopausal status	
Premenopausal	3
Postmenopausal	33
Performance status	
40–50%	4
60–70%	21
80–90%	11
No. of tumor sites	
1	14
2	17
≥3	5
Site of metastasis	
Soft tissue	10
Bone	23
Lung	11
Liver	9
Ascites or pleural effusion	7
Dominant site of disease	
Viscera	12
Bone	16
Soft tissue	8
Previous treatment	
Hormonotherapy	26
Chemotherapy	23
Radiotherapy	10
None	10

RESULTS

Thirty-six patients with metastatic breast cancer were treated with CDDP–5-FU infusion. All patients were evaluable for response and toxicity.

Two patients were excluded from the analysis of the duration of response: one was lost to follow-up after an objective response, and another underwent a non-protocol change of treatment when the disease was stable.

Patient characteristics are reported in Table 1. The majority of patients were postmenopausal, with a good performance status and metastatic disease localized in bone (63%) or viscera (50%). Failure of previous hormone therapy was documented in 26 patients, and 23 patients (67%) had been refractory to previous chemotherapy combinations: CAF in 16 cases and CMF in another 7 patients. Ten patients had undergone previous palliative radiation therapy to one or several bony areas (e.g., pelvis, spine).

Table 2 shows the results of treatment according to the site of metastases, and Table 3 demonstrates the results of treatment according to previous chemotherapy. The majority of the patients had relief of bone pain during therapy, but this was not recorded as a response.

There were 11 objective responses to CDDP–5-FU infusion among the 23 patients refractory to CMF and/or CAF. Responses were observed among patients who had a previous response (5 of 8), as well as patients who had progression of disease (2 of 6). As CMF and/or CAF were given in other centers, in four patients it was not possible to learn the previous response to chemotherapy; this particular group presented responses to CDDP–5-FU infusion as well (3 of 4) (Table 4). Median duration of response was 8 months.

The time to disease progression ranged from 2 to 19 months, with a median of 4.5 months for the whole group of patients.

Median survival was 12.5 months for patients responding to CDDP–5-FU infusion and 8 months for patients exhibiting no changes or progression to CDDP–5-FU infusion.

TABLE 3. *Response according to previous treatment*

Previous chemotherapy	Patients	PR (%)	NC (%)	PD (%)	MDR
No	13	8 (61)	3 (23)	2 (15)	8
Yes	23	11 (48)	4 (17)	8 (34)	8
Overall	36	19 (52)	7 (19)	10 (28)	

PR, partial response; NC, no change; PD, progressive disease; MDR, median duration of response in months.

TABLE 2. *Response according to site of disease*

Site of disease	Patients	CR	PR	NC	PD	CR + PR (%)
Soft tissue	10	1	4	2	3	50
Bone	23		12	7	4	52
Lung	11		7	2	2	63
Liver	9		5	1	3	55
Pleural effusion and ascites	7	1	2	1	3	42

CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

TABLE 4. *Response according to the previous treatment response*

Response to previous chemotherapy		Response to CDDP–5-FU infusion		
		PR	NC	Progression
PR	8	5	1	2
NC	5	1	2	2
Progression	6	2	1	3
Unknown	4	3		1

PR, partial response; NC, no change.

A total of 198 cycles of treatment were given (median 4, range 1–15). The initial dose as designed in the protocol was not modified in 53% of patients: 11 patients received 5-day treatment, 5 patients received 4-day treatment, and 3 patients received 3-day treatment from the beginning of the study. In the rest of the patients the length of the infusion was modified according to toxicity, which was mild to moderate. Seventeen patients required a 1-day decrease in the length of CDDP–5-FU infusion and 11 of these patients required a second dosage reduction, that is, a 2-day decrease in the length of infusion. Main toxicities are shown in Table 5. Only 3% of the hematological toxic episodes were severe (6 of 198). In two patients, CDDP was discontinued because of raising creatinine values up to 1.8 and 1.6 mg/dl after 15 and 12 cycles of treatment, respectively. Another patient had CDDP discontinued as well because of peripheral neuropathy after 6 cycles. Complete alopecia was seen only in three patients. Nausea and vomiting (grades 1–2) were present in the majority of patients, and was easily managed using conventional antiemetic drugs. Mucositis (grade 1–3) occurred in 30% (11 of 36) of patients, and it represented the main reason for dose reduction.

DISCUSSION

In this trial the response rate observed in 23 patients refractory to conventional chemotherapy (48%; 95% confidence intervals 27.4% and 68.2%) was subsequently confirmed in 13 previously untreated patients (response rate 61%; 95% confidence intervals 35% and 87.9%). The median duration of response was similar in both groups (8 months). This level of activity was unexpectedly high, better than has been reported for other drug combinations in resistant metastatic breast cancer, and certainly similar to the best initial regimens, which do contain doxorubicin. In addition, toxicity was mild and transient: there were very few episodes of bone marrow depression and alopecia occurred infrequently.

TABLE 5. *Toxicity*

Toxicity	Grading			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematological				
Anemia	14	6	4	1
Leukopenia	13	4	3	2
Thrombocytopenia	5	4	1	1
Nephrotoxicity	4	0	0	0
Gastrointestinal (mucositis)	4	5	2	0

These results might be attributable to the administration of 5-FU as a continuous 3–5-day infusion because this schedule can be a more effective way of administering the drug. Unfortunately, there is not enough data available for this particular schedule of administration and the data supporting this approach come from studies in colorectal cancer.

The results of different studies of CDDP–5-FU in colorectal cancer do suggest that activity might be related to the schedule of 5-FU administration. In fact, although this is not the place to make a meta-analysis of the trials of CDDP–5-FU in colorectal cancer, a brief look to the published results indicates that response rates are higher for the CDDP–5-FU prolonged infusion (overall 74 of 199, 37%; range 25–63%) (30–33) than for the CDDP–5-FU bolus injection (overall 21 of 100, 21%; range 19–33%) in eight published reports (34–36).

Other trials have indicated activity for CDDP–5-FU in metastatic breast cancer. Jacobs et al. administered 100 mg/m^2 CDDP in 24 h, followed by 1 g/m^2/day 5-FU for 4 days in 14 patients who had received doxorubicin, 5-FU bolus i.v. and other agents, and found objective response in 5 patients (35%) (24).

Piccart et al. (26) and Amoroso et al. (27) have communicated the preliminary results of ongoing studies in which activity was as well detected.

Finally, Strauss et al. (28) recently reported the initial results of a study comparing 20 mg/m^2 CDDP weekly and 300 mg/m^2 5-FU daily for 6 weeks, with 5-FU at the same dose and schedule as a single agent in previously treated patients. Responses were observed in 10 of 21 patients, 3 of 11 with 5-FU as a single agent and 7 of 10 with CDDP–5-FU combination therapy.

This data needs further confirmation in large multicentre trials. In the event that this high response rate is confirmed, it might represent the basis of a combination chemotherapy to build up a more effective treatment program, since other drugs such as anthracycline derivatives or alkylating agents could be easily added without predictable serious toxicity. ₡

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