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Cisplatin plus Vindesine in Advanced Breast Cancer: a Phase II Trial of the EORTC Breast Cancer Cooperative Group

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Abstract—*This phase II clinical trial was conducted in a series of patients with advanced breast cancer, refractory to conventional chemotherapy. The therapeutic regimen consisted of a combination of cisplatin* 100 mg/m², *given as a* 24-*hr infusion on day* 1 *and vindesine (VDS)* 2 mg/m², *i.v. bolus on days* 1 *and* 8. *VDS injection was omitted on day* 8 *in patients with poor bone marrow reserves (prior extensive irradiation). Courses were repeated at* 4-*week intervals until documented disease progression. Among* 46 *evaluable patients, there were two complete and seven partial remissions for an overall response rate of* 20%. *These responses lasted for a median of* 21 weeks (*range* 8-89 weeks). *Remission rates according to the predominant metastatic site were as follows: soft tissue,* 3/8 (38%); *bone,* 0/6 (0%); *viscera,* 6/32 (19%). *Transient myelosuppression and gastrointestinal intolerance were almost universal. Renal function impairment and neurologic manifestations were frequently encountered but these adverse reactions were generally mild. Significant antineoplastic activity in far-advanced and heavily pretreated patients warrants further evaluation of this regimen at an earlier stage of the disease.*

INTRODUCTION

VINDESINE (VDS) and cisplatin (DDP) are widely used in clinical practice for the treatment of various neoplasms [1, 2]. In advanced breast cancer, VDS (3 mg/m² weekly) was found effective even in heavily pretreated patients [3-5]. Under similar conditions the single-agent activity of DDP was rather disappointing [6-8]. Better results were obtained with 120 mg/m² than with 60 mg/m² q 3 weeks, with response rates of 4/19 and 0/18 respectively, suggesting that the therapeutic efficacy of DDP might be dose-related [8]. Provocative results were recently reported on its single-agent activity in patients with no prior chemotherapy [9].

According to *in vitro* and animal experiments, additive or synergistic effects are observed when DDP is used with a number of other antineoplastic compounds [10, 11]. These findings, as well as the relatively low myelotoxicity of DDP, prompted its incorporation into combination chemotherapy regimens for various indications. Two-drug programs with DDP and VDS yielded encouraging results in lung carcinoma [12, 13], whereas data were somewhat inconclusive in malignant melanoma [14]. A pilot study of a similar combination in seven far-advanced breast cancer patients was also conducted at the Institut Jules Bordet [15]. The initial protocol used DDP 100 mg/m² on day 1 and VDS 3 mg/m² on days 1, 8 and 15. The dosage of VDS was subsequently reduced as heavily pretreated patients exhibited severe and prolonged leukopenia. In this small pilot series, 2/5 evaluable patients had substantial regression of liver metastases. Interest in the development of new non-cross-resistant combinations led the EORTC Breast Cancer Cooperative Group to conduct this phase II trial.

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MATERIALS AND METHODS

Patients

Progressive, locally advanced or metastatic breast carcinoma, proven by histology, was

required. The disease was considered no longer suitable for surgery or radiation therapy and refractory to conventional systemic treatments, with hormonal manipulations and chemotherapy. All patients had measurable or evaluable lesions assessable by physical and/or radiological examination. Lymphoedema, hilar enlargement, pleural or peritoneal effusion, bone marrow infiltration or osteoblastic metastases were considered to be non-evaluable. All prior antineoplastic drugs had been withdrawn for at least 4 weeks before the initiation of the present protocol. Patients with neuromeningeal metastases or with a second malignancy were systematically excluded. Other required eligibility criteria included age below 70 yr, WHO performance status of 3 or less, leucocytes 4000/mm^3 or more, platelets 100,000/mm^3 or more, and normal hepatic and renal functions, i.e. bilirubin below 1.5 mg/dl and creatinine below 1.2 mg/dl.

Treatment schedule

All patients were prehydrated with 1 l of a 5% dextrose 0.5 N saline solution (DNS) administered intravenously for 4 hr; a continuous infusion of DDP 100 mg/m^2 diluted in 4 l DNS was then delivered over the next 24 hr. Dilution of DDP was prepared immediately prior to drug administration and perfusions were supplemented with 1.5 g KCl and 12 g mannitol added to each liter. Diuresis and emesis were measured every 6 hr during the first 2 days of treatment. Furosemide 20–40 mg was given i.v. if diuresis fell below 600 ml/6 hr. During day 2, another 3 l of the same fluid (DNS) were given over 24 hr. VDS 2 mg/m^2 was administered as an i.v. bolus on day 1 prior to DDP. VDS administration was repeated on day 8 unless there was extensive prior radiation therapy. In the other patients the dose of VDS on day 8 was reduced by 50% if the WBC were between 2000 and 3000/mm^3 or if the platelets were between 50,000 and 75,000/mm^3. The drug was withheld with lower values.

Treatment duration and response evaluation

Courses were repeated at 4-week intervals but, when needed, treatment was postponed by 1 or 2 weeks in order to allow a full haematologic recovery (WBC $\geqslant$ 4000, platelets $\geqslant$ 100,000). All patients had to receive a minimum of two courses of therapy unless there was evidence of earlier disease progression. The response to treatment was assessed according to the standard UICC criteria [16]. Briefly, a complete remission was defined as the resolution of all signs and symptoms and the complete disappearance of all evaluable disease; a partial remission was defined as a decrease by 50% or greater in the sum of the products of the two longest perpendicular diameters of all measurable lesions and/or recalcification of osteolytic lesions lasting at least 30 days; patients were classified as having stable disease when a decrease of less than 50% or an increase of less than 25% over the original measurements was recorded; an increase of more than 25% and/or the occurrence of new lesions and/or the extension of osteolytic lesions indicated a progression of the disease.

All patients regularly underwent a physical examination, performed at monthly intervals, and during which superficial lesions were measured and therapy side-effects were recorded. The performance status was evaluated by standard criteria, where score 0 represents no symptoms, score 1 represents symptoms with the patient remaining fully ambulatory, scores 2 and 3 apply to patients spending part of the day in bed, i.e. less or more than 50% of their waking time, respectively, and score 4 represents totally bedridden patients. Haematology, liver and renal function tests were obtained at least prior to each course. All baseline investigations including chest X-rays, bone scintigraphy or skeletal survey were repeated after 2 months for initial evaluation and at 4-month intervals thereafter. The treatment was pursued until progression of the disease was documented.

RESULTS

Five European institutions contributed to this study by including a total of 56 eligible cases meeting the selection criteria defined above. All case report forms were reviewed by the study coordinator (R.P.). In every case deemed to have responded favourably to the treatment, the medical record was audited by an external reviewer. Ten cases were excluded because of treatment refusal (three cases), major protocol violation (three cases), inadequate documentation (three cases) or loss to follow-up (one case). Thus 46 patients were fully evaluable for response and toxicity. Their characteristics are summarized in Table 1. Most of them were considered to bear life-threatening lesions, as indicated by the high proportion of patients (70%) with visceral metastases. Thirty-nine patients (85%) had undergone radiation therapy on one or more fields. Owing to the large extent of bone marrow previously irradiated, mainly for painful bone metastases, 14 cases were considered not suitable for VDS retreatment on day 8 of each course. The vast majority of patients had undergone multiple endocrine manipulations. All had experienced disease progression under appropriate therapy with various chemotherapy regimens combining the most active agents against breast cancer, i.e.

Table 1. Pretreatment characteristics of the evaluable patients

Total No.	46
Median age in yr (range)	53 (30-65)
Median WHO performance index (range)	1 (0-3)
Predominant metastatic site:	
soft tissue	8 (17%)
bone	6 (13%)
viscera	32 (70%)
Prior surgery, No. of patients (%)	43 (93%)
Prior irradiation	39 (85%)
extensive	14 (30%)
Prior endocrine therapy	42 (91%)
median No. of treatments/patient (range)	2 (1-3)
Prior chemotherapy	46 (100%)
median No. of drugs/patient (range)	4 (3-9)
No. of patients treated with:	
cyclophosphamide	46 (100%)
5-fluorouracil	46 (100%)
doxorubicin	44 (96%)
methotrexate	41 (89%)
VDS analogues	16 (35%)

cyclophosphamide, 5-fluorouracil, doxorubicin and methotrexate. Sixteen cases had even been previously treated with one analogue of vindesine, i.e. vincristine or vinblastine.

A total of 143 courses of therapy were administered, with a median number of 2.5 cycles per patient. Among those patients who achieved objective remission or disease stabilization, the median number of courses per patient was 5 (range 3-9), whereas in the case of treatment failure the corresponding number was 2 (range 1-5). The details of responses to treatment are given in Table 2. Nine patients presented an objective remission, giving an overall response rate of 20%. These remissions lasted from 8 to 89 weeks, their median duration being 21 weeks. Worthy of note, the remission was complete in two cases: a total healing of liver metastases, documented by laparotomy, lasted for 89 weeks in one patient and clearing of extensive skin lymphangitis and pleural effusion was observed during 11 weeks in the other. Disease stabilization for at least 2 months was seen in four patients. Survival was very short, with a median of 23.5 weeks for the entire group of patients. This median reached 38 weeks among the responders.

A number of pretreatment patients' characteristics might affect remission rates. With the relatively small sample sizes in our series, none of the factors analyzed in Table 3 exerted a sufficient prognostic influence to identify risk categories with statistically significant differences. It should be stressed, however, that patients with only soft-tissue metastases and those with a good general condition had about twice as many remissions as those with other metastatic sites involved and those with a poor performance status. A similar trend was also observed for patients without prior extensive irradiation and for those who had responded favourably to previous chemotherapy. In contrast, responses appeared independant of prior treatment with vinca alkaloids.

Every patient experienced at least one of the toxic effects listed in Table 4. Nausea and vomiting occurred in almost all patients and were found to be severe in about one-half of the cases. These gastrointestinal disturbances generally lasted 24-48 hr and were considerably alleviated by the proper use of antiemetic drugs (mainly high doses of metoclopramide, with or without benzodiazepine derivative). Myelosuppression was always reversible and generally acceptable, with leucocyte and platelet count nadirs (not systematically recorded) occurring by the end of the second week of the cycles (i.e. the median leucocyte nadir of 2300/mm^3 occurred on day 15 and the median platelet nadir of 78,000/mm^3 occurred on day 11). No case of severe treatment-related infection was recorded. Several patients complained of leg muscle cramps which were generally tolerable and did not preclude further therapy. Worthy of note, two patients had epileptic seizures within 48 hr of the cisplatin infusion. Investigation of the brain with computed tomography demonstrated the presence of previously undiagnosed metastases in both cases. Mild nephrotoxicity occurred in 27% of the

Table 2. Response to treatment in 46 evaluable patients

Type of response	No. of patients (%)	Duration in weeks Median	(Range)
Complete	2 (4)	-	(11-89)
Partial	7 (15)	21	(8-63+)
Stable disease	4 (9)	31	(20-74)
Failure	33 (72)	-	-

Table 3. Response according to prognostic factors

Prognostic factor	No. of patients	CP+PR (%)	SD (%)	PD (%)
Predominant metastatic site:				
soft tissue	8	3 (38)	1 (12)	4 (50)
bone	6	0 (0)	1 (17)	5 (83)
viscera	32	6 (19)	2 (6)	24 (75)
Performance status (WHO):				
0-1 (good condition)	29	7 (24)	4 (14)	18 (62)
2-3 (debilitated)	17	2 (12)	0 (0)	15 (88)
Prior irradiation:				
none or minimal	32	7 (22)	4 (13)	21 (65)
extensive	14	2 (14)	0 (0)	12 (86)
Response to prior chemotherapy:*				
yes	14	4 (29)	1 (7)	9 (64)
no	30	5 (17)	3 (10)	22 (73)
Prior vinca alkaloids:				
yes	16	3 (19)	3 (19)	10 (62)
no	30	6 (20)	1 (3)	23 (77)

*Inevaluable in two cases.

Table 4. Toxic effects

Type	Toxic patients (%)	WHO grade 3 toxicity (%)
Nausea + vomiting	95	58
Alopecia	76	40*
Myelosuppression	76	20
Peripheral neuropathy	36	2
Nephrotoxicity	27	6
Diarrhoea	20	0
Infection	14	0

*Severe alopecia was already present in most patients at entry.

patients, consisting of a slight reversible rise in the serum creatinine levels for several days following DDP infusion.

DISCUSSION

The present clinical trial demonstrates that the combination of DDP and VDS displays significant antineoplastic activity in advanced breast cancer. The population of patients selected for this study indeed had a very poor prognosis, as indicated by the poor survival (median 23.5 weeks) of the whole group. The overall 20% remission rate achieved in these heavily pretreated cases seems to be higher than one could have reasonably expected in a comparable population of patients treated either with DDP alone [7] or with low doses of VDS [5]. In the vast majority of the patients there was intrinsic or acquired resistance to the four best presently available cytotoxic drugs for breast cancer: doxorubicin, cyclophosphamide, methotrexate and 5-fluorouracil. Several of them had even received vinca alkaloid analogues (i.e. vincristine or vinblastine) as part of a previous multidrug programme. This factor, however, did not appear to influence the response rate to the DDP + VDS association.

Careful analysis of features which might affect the therapeutic response to chemotherapy yields interesting information. Remissions were rare among patients in bad general condition. Poor results were also achieved in the cases of previous extensive irradiation, possibly because of more widespread disease and/or reduced doses of VDS. These observations corroborate earlier ones in breast cancer as well as in other tumour types. They clearly indicate that the results of phase II trials could be considerably improved by properly selecting patient populations with particular attention to performance status and bone marrow reserve.

The most prominent side-effects of therapy were cisplatin-induced nausea and vomiting. These manifestations were generally limited in time (24-48 hr) and were adequately alleviated in most cases with high doses of metoclopramide. Further improvement in this respect could be obtained with corticoids [17] or other newer antiemetic measures. No unexpected toxicity was recorded and tolerance to this regimen was generally acceptable, keeping in mind the poor population of patients selected. Thus, in view of

the present results, we conclude that the DDP + VDS combination represents a valuable second- or third-line therapeutic alternative for patients with advanced breast cancer. Further evaluation of this new regimen at an earlier stage of the disease deserves consideration.

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