Eur J Cancer Clin Oncol, Vol. 22, No. 7, pp. 761–764, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Platinum and Etoposide in Chemotherapy Refractory Metastatic Breast Cancer. A Phase II Trial of the Italian Oncology Group for Clinical Research (G.O.I.R.C.)

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Abstract—*Twenty-four evaluable extensively pretreated advanced breast cancer patients received a combination of platinum and etoposide. Platinum was given i.v. at the dose of* 80 mg/mq *at day* 1. *Etoposide was given at the dose of* 120 mg/mq i.v. *at day* 1, *and* p.o. *at the dose of* 200 mg/mq *at day* 3 *and* 5. *Treatment was repeated every* 3 weeks.

CR was never obtained. PR was observed in four patients (17%), *MR in two, NC in seven and PD in* 11 *patients. PR plus MR occurred in six patients* (25%). *Considering the extensive pretreatment of patients, the results seem to indicate that this combination is active and can be included among the possible options in treating chemotherapy refractory advanced breast cancer. Moreover, it deserves further evaluation in an earlier phase of the disease.*

INTRODUCTION

THERE IS A relative lack of effective chemotherapy combinations in metastatic breast cancer after failure of the most common first and second-line regimens, mostly cyclophosphamide, methotrexate, 5-florouracil followed by adriamycin or adriamycin containing combinations. Only a few agents have been found to possess significant antitumor activity in chemotherapy resistant disease.

Platinum showed a low order of responsiveness in the earliest studies [1–5]. Recently, however, a 21% response rate in previously treated [6] and a striking 54% response rate in previously untreated patients have been reported [7]. Etoposide has not been adequately studied. However, a 9% response rate in heavily pretreated cases and a 17% in a more favorable group of patients have been reported [8, 9].

Accepted 16 September 1985.
Supported by Bristol Myers Pharmaceutical Research and Development.
Supported in part by the CNR Finalyzed Project "Oncologia": contract no. 84.00521.44
Medical Oncology Service of Piacenza (Rodolfo Canaletti, Carmelina Rodino') contributed with some cases to the patients' accrual.
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These heterogeneous clinical results, with either platinum and etoposide used as single agents, and their synergistic activity when used together, which has been shown in animal models [10–14], have prompted us to evaluate the antitumor effectiveness of their combination in advanced breast cancer, after failure of standard chemotherapy and hormonal treatments.

MATERIALS AND METHODS

Thirty patients with histologically confirmed metastatic breast cancer were considered eligible for the study. All patients had measurable disease, a history of prior treatment for advanced disease, no prior therapy with platinum or podophyllotoxin derivatives, wbc count > 4000/mm, platelet count > 130,000/mm, normal renal function (creatinine < 1.5 mg%), and a performance status > 50 (Karnofsky scale).

The regimen used was the following: *cis*-platinum, 80 mg/mq i.v. day 1, etoposide, 120 mg/mq i.v. day 1 and 200 mg/mq p.o. day 3,5. *Cis*-platinum was given with pre and posthydration and with mannitol-induced diuresis. Treatment was repeated every 3 weeks. Patients were considered evaluable for response if they had received at least two courses of therapy. Therapy was continued until progression or relapse of the disease

occurred. Therapeutic response was defined by UICC criteria [15]. Duration of response, time to progression and survival were calculated from day 1 of the first course, using the Kaplan–Meier method.

RESULTS

Characteristics of the 24 evaluable patients are detailed in Table 1. Six patients were considered non-evaluable for response assessment because of refusal of treatment after the first course (three cases), or because of rapidly progressive disease (two cases) and appearance of brain metastases during the first course (one case). All patients had previously been treated multiple cytotoxic agents, ranging in number from two to six drugs. Patients received an average of 3.7 courses, ranging from 2 to 8.

Table 2 reports response to treatment. Four of 24 patients (17%) achieved PR, two patients showed MR and seven NC, while the other 11 did not respond. Responses by site in the four responding patients were: PR in skin and CR in nodes (patient 1), CR in skin and PR in nodes and pleura (patient 2), PR in breast and CR in skin and nodes (patients 3), PR in liver and CR in nodes (patients 4).

Table 1. Characteristics of patients

Characteristics		No. of patients
No. of evaluable patients		24
Median age (yr—range)	56 (34–70)	
Median performance status* (range)	80 (50–100)	
Median disease-free interval (months—range)	14 (0–66)	
Menopause		
from <5 yr		9
from >5 yr		15
Dominant disease site		
soft tissue		5
bone		4
viscera		15
Prior treatment		
with chemotherapy		24
with combined chemo and endocrine therapy		8
with endocrine therapy		17
average no. of cytotoxic agents	4.2	
average no. of hormone manipulations	1.5	

* Karnofsky criteria.

Table 2. Response to treatment

	No. of patients
Total evaluable patients	24
Objective regression	
Complete Remission (CR)	–
Partial Remission (PR)	4
Minor Remission (MR)	2
CR + PR	4 (17%)
CR + PR + MR	6 (25%)
No change	7
Progressive disease	11

Table 3 shows the objective responses at sites of involvement in all patients. Responses were frequently observed in soft tissue.

One of two patients with pleural and one of seven with liver involvement achieved PR.

Median duration of objective remission was 17 weeks, ranging from 15+ to 24. Median duration of MR and of NC was 14 weeks, ranging from 10 to 39+ weeks. Considering all patients, median time to treatment failure was 14 weeks, ranging from 6 to 39. Median duration of survival was 33 weeks, ranging from 7 to 77.

As far as toxic effects are concerned, nausea and vomiting occurred in 90% of patients. Three of the above mentioned non-evaluable patients refused continuation of treatment because of severity of nausea, vomiting and asthenia. In one case a transient mild increase of creatinine was observed. Ototoxicity, in the form of tinnitus, was observed in one case. Hematological toxicity is reported in Table 4.

DISCUSSION

The principal aim of this study was to make available a third-line chemotherapy combination in advanced breast cancer when the two previously mentioned most common conventional regimens have failed. The platinum and VP16 combination was selected on the basis of some activity reported when each drug is used as a single agent [1–9] and because it has been found to be very active in some chemoresistant tumors such as non-small cell lung cancer [16]. The combination was also chosen in consideration of its synergistic activity in some experimental system [10–14] and, finally, because of its totally innovative character in breast cancer. Oral administration of VP16 on days 3 and 5 was decided either because a satisfactory plasma availability using this route of administration has been demonstrated [17] or because it was desirable to limit to 1 day every 3 weeks the admittance of patients to the out-patient clinic.

Results of this study indicate a rather low 17% objective remission rate. However, some CR in skin and nodes at disease sites and some PR in pleura and liver metastases must be carefully considered. Furthermore, patients admitted to this study had been heavily pretreated in multiple endocrine and chemotherapy trials, and in their existing condition few if any different drugs or combinations could have given the same or better results.

*Table 3. Objective responses at sites of involvement**

Sites	Complete remission	Partial remission	CR+PR	Other types of response
Breast	–	1/2	1/2	1/2
Skin	2/15	2/15	4/15 (27%)	11/15
Nodes	1/9	3/9	4/9 (44%)	5/9
Bone	–	–	–	6/6
Pleura	–	1/2	1/2	1/2
Lung	–	–	–	7/7
Liver	–	1/7	1/7 (14%)	6/7
Peritoneum	–	–	–	1/1

* Numerator = No. of responses at stated site; denominator = No. of patients with stated site evaluable for response and involved from the beginning of treatment.

Table 4. Hematological toxicity

	No. of patients	(%)
White blood cell count (1000/mm^3)		
grade 1 3.0–3.9	4	17
grade 2 2.0–2.9	8	33
grade 3 1.0–1.9	8	33
grade 4 < 1.0	1	4
Platelet count (1000/mm^3)		
grade 1 75–99	8	33
grade 2 50–74	3	13

As far as toxic effects are concerned, nausea and vomiting were common. Hematologic toxicity was rather frequent but toxic deaths, infections or hemorrhages never occurred.

Only a limited number of drugs or combinations can be usefully administered as salvage regimens in chemotherapy–refractory advanced breast cancer. A 17 and 23% response rate have been reported using mitomycin [18, 19]. With a continuous infusion of vinblastine, response rates of 40, 36 and 21% [20, 21] have been found, together with totally negative results [22]. Vindesine as single agent has shown some activity, with a response rate of 19% [23].

Considering the combinations of multiple drugs, mitomycin C and vinblastine have been reported as being remarkably active, with response rates of 40 and 36% [24, 25]. In refractory breast cancer, however, it is difficult to attribute an absolute value to these high response rates, as selection of patients can significantly influence results. The combination of platinum and vindesine has been tried by the EORTC Breast Cancer Cooperative Group and the 20% reported response rate is considered as an indication of a valuable therapeutic alternative in pretreated cases [26].

We think that the combination of platinum and VP16 should be considered among the new options in treating refractory advanced breast cancer. Moreover, this combination deserves further evaluation in an earlier phase of the disease.

Acknowledgements—The authors thank Dr. P. Hilgard for his advice in designing this study, Mrs. Katherine Tonato for help in translating the manuscript and Mrs. Cesarina Dalco' for secretarial assistance.

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