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VP_{16-213} and Cyclophosphamide in Advanced Breast Cancer

A Phase II Study

J. Estapé[1], L. Cirera[2], A. Millá[1], and F. Doncel[2]

[1] Servicio de Coordinación Oncológica, Hospital Clínico y Provincial, Facultad de Medicina, C/Casanova 143, Barcelona 36
[2] Hospital Mutua de Terrassa, Terrassa (Barcelona), Spain

Summary. *Twenty-seven patients with histologically proved advanced breast cancer were given VP 16-213 and cyclophosphamide. Twenty-one had shown resistance to other chemotherapy schedules and six had experienced relapse during adjuvant chemotherapy.*

There were four complete responses (15%) and seven partial responses (26%). Median survival was 61 weeks and median duration of response was 31.4 weeks. All patients experienced gastrointestinal toxicity and 22 patients (81%) showed bone marrow toxicity.

This regimen is effective in advanced breast cancer resistant to other chemotherapy regimens.

Introduction

VP 16-3213 is a semi-synthetic derivative of podophyllotoxin, and is active in various solid tumors and malignant hemopathies [6]. At an experimental level it shows synergism with Ara C [11], cyclophosphamide and BCNU [5, 10], and cisplatinum [12]. Initial trials in breast cancer yielded a response rate of 5% [6]. Van Echo et al. [13] combined VP 16-213 and adriamycin in 15 cases of disseminated breast cancer; six presented objective responses of over 50% (2 CR and 4 PR).

Cyclophosphamide is the alkylating agent of choice for breast cancer therapy. Its efficacy as single-agent therapy is 35% [2].

The combination of VP 16-213 and cyclophosphamide has demonstrated synergism in lung cancer, especially in the oat cell variety [7, 8].

On the basis of these facts we have studied its possible efficacy in disseminated breast cancer.

Materials and Methods

Twenty-seven patients with histologically proved breast cancer and distant metastases were entered on study (Table 1). Twenty-one of them were entered because they had shown resistance to other chemotherapy schedules (vincristine + adriamycin, melfalan as single agent, or V-CMFP). The other six patients had presented multiple metastases during treatment with CMF adjuvant to primary surgery.

The regimen used was the following:

VP 16-213 120 mg/sq. m. day × 5 days, PO;

Cyclophosphamide 120 mg/sq. m. day × 5 days, IV.

The VP 16-213 capsules were administered on an outpatient basis, followed by immediate administration of cyclophosphamide IV. There was a therapeutic rest period of 7–10 days between every two courses.

Reprint requests should be addressed to J. Estapé, Esq.

Table 1. Patients' characteristics

Total no. of patients	27
Age range	40–70 years
Mean age	56.9 years
Hormonal status	
Premenopausal	2
Postmenopausal	25
Previous treatments	
Surgery	27
Radiotherapy	5
CMF	6
Other chemotherapy regimens	21
Performance status (ECOG)	
1	5
2	14
3	8
Metastases	
Bone	13
Skin	5
Liver	5
Lung	5
Pleura	4

After the fourth course, results were assessed according to the following criteria:

Complete Response (CR): Disappearance of all clinical evidence of disease for longer than 3 months;

Partial Response (PR): Decrease by > 50% of clinically detectable tumors;

Improvement (I): Tumor decrease by less than 50%;

Stable Disease (SD): No change;

No Response (NR): Increase of the tumor lesions.

Patients with CR or PR received the same therapeutic schedule in monthly courses while they maintained their initial response.

As a guide for administration of the cytostatics, the following parameters were used:

1. > 4,000 WBC/mm^3 and > 130,000 platelets/mm^3: 100% of the dose was given;

2. WBC between 2,000 and 3,999/mm^3; platelets between 70,000 and 129,999/mm^3: the dose was reduced to 50%;
3. With less than 2,000 WBC/mm^3 or 70,000 platelets/mm^3, therapy was discontinued long enough to allow the cytopenia to recover.

The actuarial survival curves were analyzed according to Kaplan and Meier [9]. The median response duration was only studied in patients achieving CR or PR.

Results

Eleven patients (41%) achieved an objective response of greater than 50% (4 CR and 7 PR); one patient showed improvement and another patient stable disease, while the other fourteen did not respond (Table 2). Some examples of

Table 2. Response evaluation

	No. of patients	% Patients
Complete response (CR)	4	15
Partial response (PR)	7	26
Improvement (I)	1	3.5
Stable disease (SD)	1	3.5
No response (NR)	14	52
Response in the metastases		
Liver	1/5	
Bone	5/13	
Skin	4/5	
Pleura	1/4	
Lung	2/5	

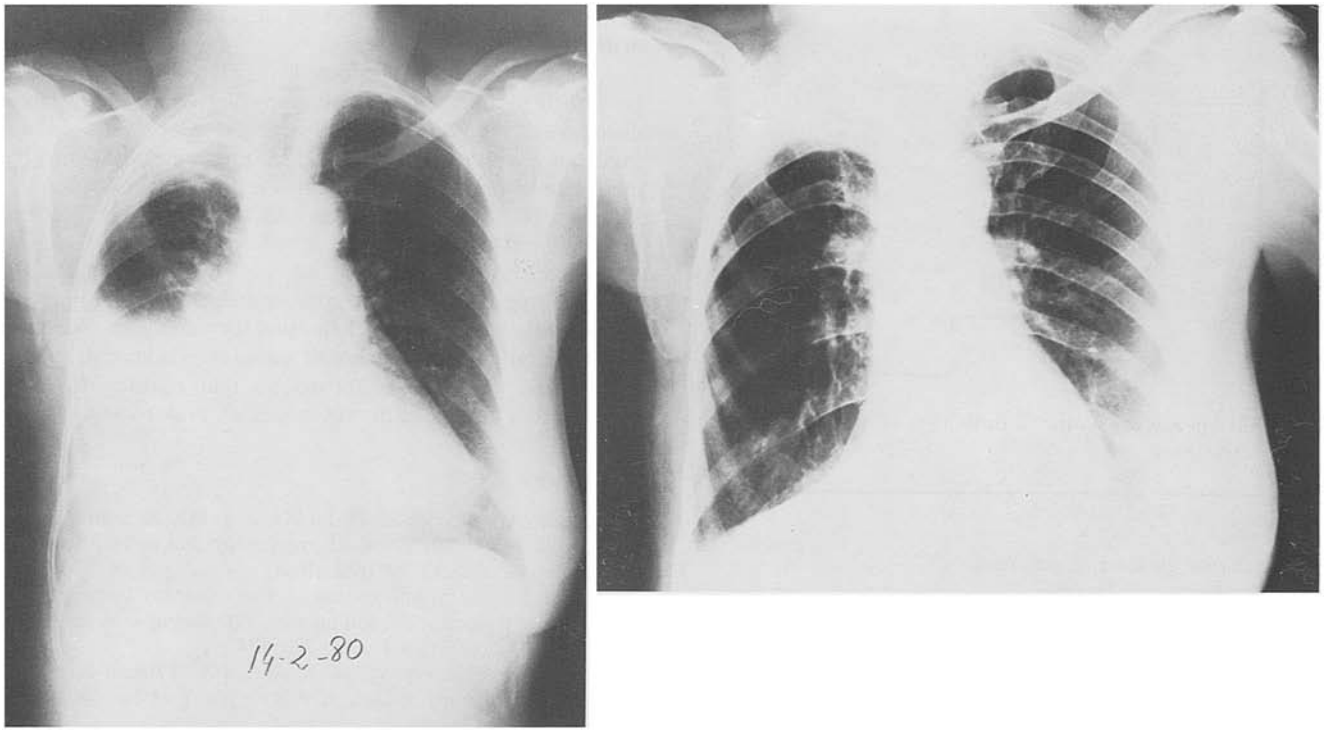

Fig. 1a and b. Example of complete remission. The right pleural effusion, axillary nodes and a subcutaneous tumor mass in the right scapular region (**a**) disappeared (**b**) after three courses of VP 16 plus cyclophosphamide. The patient is living and in complete remission 120 weeks later

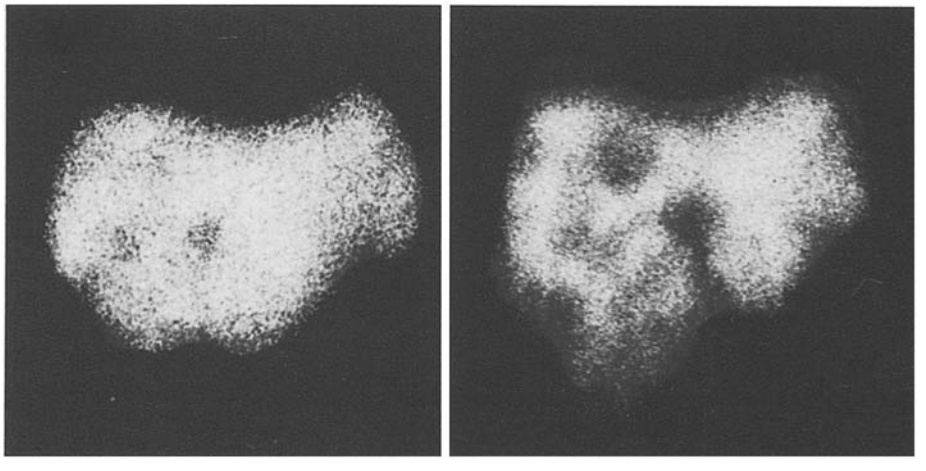

Fig. 2. a Liver scan showing multiple metastases. A partial remission (**b**) was obtained after four courses of chemotherapy

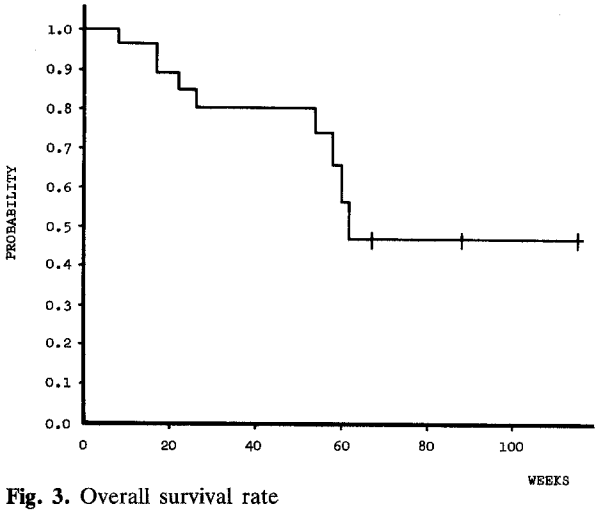

Fig. 3. Overall survival rate

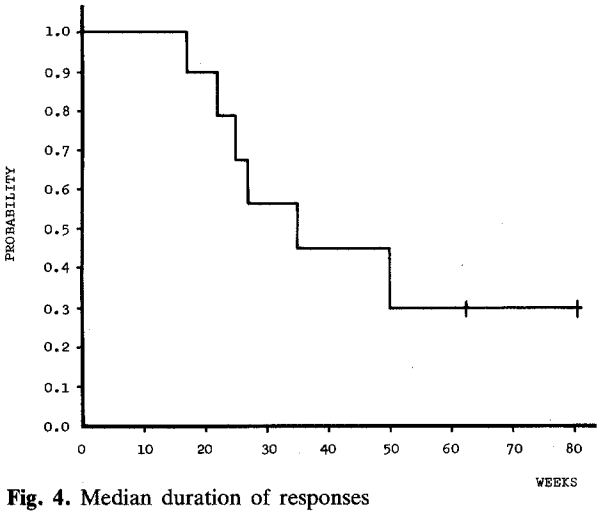

Fig. 4. Median duration of responses

Table 3. Toxicity

	No. of cases	% Cases
Nausea and vomiting	27	100
Alopecia	27	100
Leukopenia	22	81
Thrombocytopenia	2	7

these results are shown in Figs. 1 and 2. Seventeen patients showed an improvement over their initial performance status, including those who achieved an objective response.

The overall survival rate was 61 weeks, and the median duration of responses with maintenance therapy was 31.4 weeks (Figs. 3 and 4).

As to toxicity, alopecia and gastrointestinal dysfunction (nausea and vomiting) were seen in all patients. Leukopenia occurred in 22 patients (nadir 2,900/mm^3) and thrombocytopenia in two (100,000 and 95,000/mm^3, respectively) (Table 3). Neither infections nor hemorrhage related to myelosupression were noted, and no other toxicity related to the use of the two drugs was seen.

Discussion

The choice of this therapeutic regimen for trial in disseminated breast cancer was based in the following features:
1. Wide and positive initial experience in bronchogenic cancer (oat cell variety);
2. Experimental synergism of the two drugs;
3. Mild toxicity allowing treatment on an outpatient basis;
4. Absence of previous experience with this combination in breast cancer.

The 41% objective response rate achieved shows a similar efficacy to that of other polychemotherapy regimens [3]. The long median survival it yields and the median duration of response are greater than those obtained with Cooper's-type regimens and are only slightly lower than those achieved with adriamycin combinations [1, 4]. This should be noted because most of our patients (21/27) had received prior chemotherapy. Four of the six patients who failed on CMF achieved an objective response, so this therapy ought to be studied further in more cases.

Prior therapy also affected toxicity. The 21 patients previously treated with chemotherapy had leukopenia, so their doses were modified in some of the four courses. In our experience with previously untreated lung cancer patients, the incidence of leukopenia was less. Probably administration of less than 100% of the dose accounts for the lower efficacy of the regimen.

In conclusion, our results allow us to assert that the VP 16-213 + cyclophosphamide combination is effective in breast cancer resistant to other chemotherapy regimens. We must also point out the convenience of ambulatory administration in polytreated patients. To prove its real efficacy we shall continue the trial in different stages of breast cancer.

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