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Short Report

Mitomycin-C, VP16-213 Combination as Third Line Chemotherapy in Advanced Breast Cancer

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Introduction

Chemotherapy is the treatment of choice in advanced and hormone-resistant breast carcinoma. There are muliple combinations for first and second line treatment [2, 3, 7, 11]. Despite the excellent responses from these combinations, only a few last long. New combinations or new drugs are necessary to increase survival.

Mitomycin-C is an effective drug in 38% of breast carcinomas [1]. VP16-213 is effective in 11% [5]. The combination of both mitomycin-C and VP16-213 does not appear to show crossresistance to CMF combinations (cyclophosphamide, methotrexate, and fluorouracil) and TVA (thiotepa, vinblastine, and adriamycin) normally used by us as first and second line treatment. For this reason, in 1980 we started a pilot study to evaluate the effectiveness of the combination mitomycin-C and VP16-213 administered as third line therapy in advanced breast carcinoma.

Table 1. Patient features

Number	15
Median age	47
Range	27–64
Menstrual status	
Still menstruating	2
Castrated	2
Post menopausal	11
Metastatic site	
Single	1
Multiple	14
Skin-nodes	13
Pleura-lung	10
Bone	8
Liver	4
Prior treatments	
Surgery	11
Irradiation	12
Hormonotherapy	4
Chemotherapy	15
Performance status	
≥ 60	2
60–40	13

Patients and Methods

Only patients with histologically proven breast carcinoma, under 65 years old, with performance status over 40% on the Karnofsky index and a minimum survival estimated as 3 months, resistant to the combinations CMF, CMFVP or to combinations with adriamycin type AV and TVA were selected. They were also resistant to hormonal treatment.

Patients with WBC counts under 5,000 per cu. mm and plattelet counts under 120,000 per cu. mm and hemoglobin under 12 g were excluded. Also excluded were patients with other malignant tumors or serious disease such as uncompensated diabetes, cirrhosis or other hepatic dysfunction or infections.

Only 15 patients were selected. Their clinical characteristics showing the degree of tumor progression appear in Table 1. Only one of the patients had metastasis in a single site. The rest had multiple metastases. The most frequent were skin and node and then lung and bone metastases.

All patients had been multitreated. Seventy-four percent had undergone surgery or radiotherapy. All had been treated with chemotherapy. All had received CMF. The median number of CMF courses previously administered was seven. Also all of them had received adriamycin. The median dose was 160 mg/m^2.

Treatment was given with mitomycin-C 10 mg/m^2 i.v. every 6 weeks and VP16-213 80/100 mg/m^2 either i.v. or p.o. daily for 5 days every 21 days.

The criteria for response were: Complete response (CR): disappearance of all lesions for at least 4 weeks. Partial response (PR): a decrease by > 50% or more in the product of the two largest diameters of the lesions or a decrease by 30% or more in the diameter of lesions that could only be measured in one plane. The duration of decrease had to be at last 4 weeks and without appearance of new lesions.

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Table 2. Response rate

CR	0 of 15
PR	2 of 15 (13%)
MR	1 of 15
SD	2 of 15
PD	10 of 15

Table 3. Response rate by site

	Skin-nodes	Pleura-lung	Bone	Liver
CR	0 of 13	0 of 10	0 of 8	0 of 4
PR	2 of 13	0 of 10	0 of 8	0 of 4
MR	1 of 13	0 of 10	0 of 8	0 of 4
SD	2 of 13	2 of 10	2 of 8	0 of 4
PD	8 of 13	8 of 10	6 of 8	0 of 4

Minor response (MR): a clear and measurable regression although smaller than a PR and greater than 25%.

No change or stable disease (SD): stability of lesions and/or decrease smaller than 25%.

Progression (PD): increase in the size of any lesion or occurrence of new lesions.

Results

Only two patients (13%) responded to treatment (Table 2). The responses occurred only in skin and node metastases (Table 3). There were no objective responses in visceral and bone metastases.

The duration of responses was 7 and 3 months.

The median survival has been 4 months. Of the two responding patients, one died after 6 months and the other is still alive after 14 months. Deaths occurred from progression of lesions present before the start of the treatment, but in two cases new brain metastases appeared.

Toxicity was easily controllable and only four patients showed hematologic toxicity. Gastrointestinal toxicity consisted of nausea and vomiting that occurred in 100% of the patients either in small or great intensity. In only three cases was intensity important enough to require parenteral hydration and nourishment.

Stomatitis appeared in 20% of the cases and alopecia in 67%.

Discussion

Mitomycin-C has been used in the treatment of breast carcinoma resistant to other cytostatics, as a single agent or in combination with other drugs. The results obtained were 60% [4], when used as a single agent in high doses and 27% [9], 31% [12], 45% [8], and 36% [6] when used in combination.

VP16-213 used as a single agent in resistant breast carcinoma yielded responses ranging between 16 and 18% [10] when administered as a bolus or continous i.v. infusion.

Our results are clearly inferior to those recorded with Mitomycin as a single agent or in combination and also to the results obtained with VP16-213 as a single agent. The explanation may be that mitomycin-C doses given by us are comparatively low when compared to the doses given by others [4]. All our patients hat been previously treated with adriamycin and this seems to be a reason for the poor responses to treatment achieved with VP16-213 as there seems to be a cross-resistance with both drugs [5].

The results obtained are also lower than those achieved with new drugs [14] or new therapeutic schedules [13].

The treatment was only effective in skin and node sites; it did not yield objective responses in visceral and bone metastases. The duration of responses was very short.

Conclusion

The combination of mitomycin-C and VP16 is not effective as third line treatment of advanced breast carcinoma.

Responses were achieved in skin and node metastases only.

Tolerance was acceptable but hematologic and gastrointestinal toxicity was notable.

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