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Short Report

Adriamycin and VP16-213 Combination Treatment for Breast Cancer Previously Treated by the CMF Regimen

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Introduction

Adriamycin is the most effective drug in the treatment of breast carcinoma [10]. Even in patients previously treated with other cytostatic agents, adriamycin can be very effective.

At present many patients with breast carcinoma are treated with CMF adjuvant chemotherapy. Adriamycin as a single agent or in combination is effective in patients who fail on CMF.

VP16-213 is an effective agent in 11% of breast carcinoma [3]. It is able to cross the blood brain barrier and in our group it was effective in 47% of patients with brain metastases from breast cancer [2].

In 1980 we started a pilot study to evaluate the efficacy of the combination adriamycin and VP16-213 in the treatment of breast carcinomas resistant to CMF or CMFVP treatment and also to evaluate its efficacy in preventing the development of brain metastases. The study is still in progress.

Patients and Methods

Eleven patients with advanced breast carcinoma previously treated with adjuvant or therapeutic CMF or CMFVP chemotherapy were treated in this pilot study.

Criteria for exclusion were: No histology, no measurable lesions, less than three months expectation of life or a performance status inferior to 40% on the Karnofsky scale.

Patients were also excluded if they had heart disease incompatible with treatment with adriamycin, WBC and/or platelet counts inferior to 5,000 per cu mm and/or 120,000 per cu mm and less than 12 g of hemoglobin or more than twice the normal plasma value of transaminase and/or bilirubin.

Patients were also excluded if they were older than 65, if they had other tumors or a serious disease unrelated to tumor. Those whose homes were far from hospital or those who for different reasons could not follow the treatment and be adequately followed up were also excluded.

Characteristics of the patients are shown in Table 1. Most of them had multiple metastatic lesions and all of them had been multitreated.

Treatment was adriamycin 45 mg/m^2 day 1 of each course and repeated every 21 days. VP16-213 was administered days 1–5 of each course and repeated every 21 days. The doses administered were 80 or 100 mg/m^2 depending on the administration being either i.v. or p.o. Nine patients were treated this way. In two, the treatment was modified to VP16-213 150 mg/m^2 weekly intravenously.

Criteria for response were: Complete response (CR) disappearance of all lesions at least for 4 weeks. Partial response (PR) was a decrease by 50% of more in the product of the longest and shortest diameter of the lesions that could only be measured in one dimension. Duration of response had to be 4 weeks or longer. New

Table 1. Patient features

Number	11
Median age	44
Range	39–64
Menstrual status	
Still menstruating	2
Castrated	2
Post menopausal	7
Performance status	
≥–60	4
60–40	7
Metastatic site	
Single	1
Multiple	10
Skin-nodes	7
Pleura-lung	3
Bone	3
Liver	2
Prior treatments	
Surgery	6
Irradiation	4
Hormonotherapy	4
Chemotherapy	11

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Table 2. Response rate

CR	0 of 9
PR	3 of 9
MR	1 of 9
SD	1 of 9
PD	4 of 9

Table 3. Response rate by site

	Skin-nodes	Pleural-lung	Bone	Liver
CR	0 of 7	0 of 3	0 of 3	0 of 2
PR	3 of 7	0 of 3	0 of 3	0 of 2
MR	1 of 7	0 of 3	0 of 3	0 of 2
SD	1 of 7	1 of 3	1 of 3	0 of 2
PD	2 of 7	2 of 3	2 of 3	2 of 2

lesions or progression of any of the existing lesions could not occur.

Minor response (MR) was defined as similar to partial response but with a decrease less than 50% or greater than 25%.

Stable disease (SD) was a stability of lesions or a decrease inferior to 25% without occurrence of new lesions and no progression of the existing lesions.

Progression (PD) was occurrence of new lesions or increase in the existing lesions.

Results

No patient achieved a complete response (Table 2) but there were five responses superior to 50%. Of these responses two were obtained with the modified treatment. Of the nine patients treated with the initial schedule, responses were achieved in three patients which represents 33% of objective responses.

Only skin nodules (Table 3) responded. There were no objective responses in visceral and bone sites.

The median duration of response was 5 months. The median survival for patients with no response was 4 months and for the five patients with response median survival is 6 months.

No patient has developed a brain metastasis.

Hematologic toxicity was important. Eight of eleven patients showed severe hematologic toxicity. Vomiting and nausea accurred in 100% of the patients and two of them needed hospitalization and hydration and parenteral nourishment. Stomatitis occurred in 2 of the 11 patients and alopecia in all of them. No patient exhibited cardiac toxicity, probably due to the low total dose of adriamycin, the median being 170 mg/m^2.

Discussion

Adriamycin is the most effective drug in the treatment of breast carcinoma. The response rates obtained with adriamycin average about 37% although in some studies response rates reach 50% [1]. Multiple combinations of adriamycin with other drugs have also proven effective. The responses obtained with them range between 40% and 80% [5, 8].

VP16-213 is a less effective drug in breast cancer. Response rates vary between 5 and 11% [3, 4].

VP16-213 in the treatment of breast carcinoma resistant to other cytostatics has yielded a response rate of 16%; when administered as an i.v. infusion the response rate was 18% [7]. The combination of both adriamycin and VP16-213 has yielded responses ranging from 40% [9] to 13% [6].

Our results, regardless of the two patients treated with a modification of the original schedule, are inferior to those obtained with adriamycin as a single agent or with any of the polichemotherapy regimes that contain adriamycin. However the results are superior to those obtained with VP16-213 as a single agent and to the results obtained with the combination of adriamycin and VP16-213 by other authors [6].

The daily administration of VP16-213 for 5 days seems to be more effective than its administration over 2 or 3 days [6, 9].

The two responses obtained in the two patients treated with a weekly administration of VP16-213 encourage us to continue this therapy in a larger number of cases in order to establish its real effectiveness.

The study of Egan [3] suggests that there is a cross-resistance between adriamycin and VP16-213. Our results and the ones obtained by other authors [6] suggest that there is no synergism in the combination.

Conclusions

The combination of adriamycin and VP16-213 has some effect in breast carcinoma resistant to CMF treatment.

The response rates were lower than those obtained with other combinations of adriamycin and other cytostatics and even lower than some responses reported for adriamycin as a single agent.

The best results are apparently obtained when VP16-213 is administered for 5 days.

Tolerance is acceptable although hematologic and gastrointestinal toxicities are important.

We do not recommend this combination for the treatment of breast cancer.

References

1. Ahmann DL, Bisel HP, Eagan RT, Edmonson JH, Hahn RG (1974) Controlled evaluation of adriamycin (NSC-123127) in patients with diseminated breast cancer. Cancer Chemo Ther Rep 58: 877–882
2. Baena LF, Perez R, Madrigal LP, Perez G, Vicente J, Montero JM (1977) Resultados preliminares en el tratamiento de las metastasis intracraneales (SNC) por cancer de mama con VP 16213. Oncologia 80: 104–111
3. Eagan RT (1978) Clinical investigation of podophyllotoxin derivatives at the Mayo Clinic. Chemother. Foundation Symposium III, October 27–28, Plaza Hotel, New York, NY, p 41
4. Issel BF, Crooke ST (1979) Etoposide (VP 16-213). Cancer Treat Rev 6: 107–124
5. Jones SE, Durie BGM, Salmon SD (1975) Combination chemotherapy with Adriamycin and Cyclophosphamide for advanced breast cancer. Cancer 36: 90–97
6. Rubin J, Decker DA, Ahmann DL, Eagan RT, Ingle JN, Hahn RG (1980) An evaluation of two schedules of VP16-213 and adriamycin in patients with advanced breast cancer. Oncology 37: 149–151
7. Scell FC, Yap HY, Hortobacyi GN, Buzdar AU, Blumenschein GR, Issel B, Esparza L (1981) Phase II study of VP16-213 (Etoposide) in refractary metastatic breast cancer. Proc Am Soc Clin Oncol 22: 357
8. Tranum B, Hoogstraten B (1976) Adriamycin in combination for treatment of breast cancer. Proc Am Soc Clin Oncol 17: 242
9. Van Echo DA, Aisner J, Wiernik PH, Morris D, Serpick A (1979) Combination chemotherapy of advanced breast cancer with Adriamycin and VP16-213. Proc Am Assoc Cancer Res 20: 228
10. Wasserman TH, Comis RL, Goldsmith M, Handelsman H, Penta JS, Slavik M, Soper WT, Carter SK (1975) Tabular analysis of the clinical chemotherapy of solid tumors. Cancer Chemother Rep 6: 399–419

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