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Dibromodulcitol, Mitomycin C and Vinblastine (DMV) Chemotherapy in Advanced Breast Cancer

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Abstract—*A combination of dibromodulcitol* 500 mg *orally, mitomycin C* 10 mg *i.v. and vinblastine* 10 mg *i.v. all given on day* 1 *and repeated every* 4 weeks *was given to* 40 *patients with advanced breast cancer. All but one had received previous endocrine therapy. The response rate (CR + PR) in* 24 *previously untreated patients was* 66% *and was* 37% *in* 16 *previously treated patients. The survival of responders was significantly longer than non-responders. Thirty-two per cent of patients experienced nausea and vomiting. There was little myelosuppression or thrombocytopenia on the day of starting a new course of therapy but the haemoglobin dropped by* 2 g/dl *in* 32% *of patients during therapy. Thus DMV is a relatively non-toxic active regimen for patients with advanced breast cancer.*

INTRODUCTION

ALTHOUGH over 50% of patients with advanced breast cancer respond to treatment with combination chemotherapy, they will almost invariably progress at a later date. There continues to be a need for effective second-line chemotherapy. In addition, most of the first-line regimens are associated with significant toxicity; over the past few years the remission rate and duration for first-line treatment has not been improved. A drug combination which is relatively non-toxic but as active as conventional regimens would therefore be of benefit. We have assessed the value of a combination of dibromodulcitol (DBM), mitomycin C (MMC) and vinblastine (Vb) in previously treated patients with advanced breast cancer. Encouraged by the relative lack of toxicity, we also assessed the regimen in previously untreated patients.

As single agents, the reported response rates to DBM, MMC and Vb are 28% [1–5], 30% [3, 6–8, 9] and 20% [3, 10, 11] respectively. Thus these are three relatively effective agents which might be expected to be more active in combination. Judged by their activity as single agents in previously treated patients, they are non-cross resistant with many of the commonly used agents [4]. Additional positive features are the ability of DBM to cross the blood-brain barrier [4] and the reported synergism between MMC and Vb [12].

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MATERIALS AND METHODS

Dibromodulcitol was given at a dosage of 500 mg orally stat, mitomycin C 10 mg i.v. stat and vinblastine 10 mg i.v. stat. All drugs were given on day 1 and repeated at intervals of 4 weeks. There was no dosage adjustment for surface area. Treatment was delayed for 1 week if the white count was less than 3.5 × 10/l and the platelet count less than 100 × 10/l. Patients were treated until relapse or until toxicity precluded further treatment.

Patients

Forty evaluable patients were treated. The mean age was 62 yr and the median 61 yr (Table 1). Sixteen patients had been previously treated with chemotherapy; in five of these chemotherapy was given as an adjuvant to surgery (melphalan, 2; vincristine, cyclophosphamide and methotrexate, 1; and cyclophosphamide, methotrexate, fluorouracil, adriamycin and vincristine, 2) and in ten chemotherapy was given for advanced disease (AC, 4; CMFP, 2; vincristine, adriamycin, prednisolone and cyclophosphamide, 2; CMFAV, 1; cyclophosphamide, 1). Including the latter patients, six were given 2 chemotherapy regimens before DMV was administered and ten 1 chemotherapy regimen. All but one patient had

one or more trials of hormone therapy before chemotherapy was given.

The dominant site of metastasis was bone in 45% of patients, but most of these (16/18) had additional soft tissue disease, which was the major marker for response (Table 1). In the previously treated patients there was a preponderance of patients with three or more metastatic sites involved and in those not previously treated there was a preponderance of patients with liver metastases.

The mean number of courses of DMV given was 5.75 for all patients and 6.5 for responders.

All patients were evaluated according to UICC criteria [13]. The duration of remission was measured from the start of chemotherapy. The survival was analysed by the log-rank method [14].

RESULTS

Therapeutic effect

The overall response rate to DMV was 58% (Table 2). Sixteen of 24 (66%) patients who had received no previous chemotherapy responded and 6 of 16 (37%) who were previously treated had an objective regression. Eight patients had a period of no change in their disease status (median, 214 days). The median duration of remission was 219 days (previous chemotherapy, 239 days; no previous chemotherapy, 217 days). The median duration of survival was 313 days (previous chemotherapy, 280 days; no previous chemotherapy, 324 days). Responders lived significantly longer than non-responders (CR + PR vs NC + PD, $P<0.02$; CR + PR + NC vs PD, $P<0.002$; Fig. 1). Remissions were observed in the following disease sites; soft tissue 10, bone 1, bone and soft tissue 4, liver 3 and lung 4.

Toxicity

The toxicity of DMV is summarised in Table 3. Less than one-third of the patients (32%) had nausea or vomiting for one or more courses of treatment (Table 3). Alopecia was seen in 11 patients, two of whom required a wig. The major toxic effect was haematological; a drop in

Table 1. Patient characteristics

	All patients ($n=40$)	Previous chemotherapy ($n=16$)	No previous chemotherapy ($n=24$)
Mean age (yr)	62 (range, 33–76)	59	64
Pre-menopausal	6 (15)*	4 (25)	2 (8)
Post-menopausal	34 (85)	12 (75)	22 (92)
Mean disease-free interval (months)	34	39	30
Mean time from first relapse until DMV treatment	29	24	32
Dominant site of disease			
Soft tissue	8 (20)	3 (19)	5 (21)
Lung	8 (20)	2 (12)	6 (25)
Liver	6 (15)	6 (37)	0 (0)
Bone	18 (45) 16†	5 (32) 4	13 (54) 12
No. of metastatic sites			
1	10 (25)	4 (25)	6 (25)
2	23 (57)	7 (44)	17 (71)
3	7 (18)	5 (31)	1 (4)

*(%).
†No. of patients with additional soft tissue disease.

Table 2. Response rate and duration of response

	All patients	Previous chemotherapy	No previous chemotherapy
CR	2 (15)*	1 (6)	1 (4)
PR	20 (50)	5 (31)	15 (62)
NC	8 (20)	3 (19)	5 (21)
PD	10 (25)	7 (44)	3 (13)
Median duration of remission (days)	219	239	217
Median duration of survival (days)			
All patients	313	280	324

*(%).

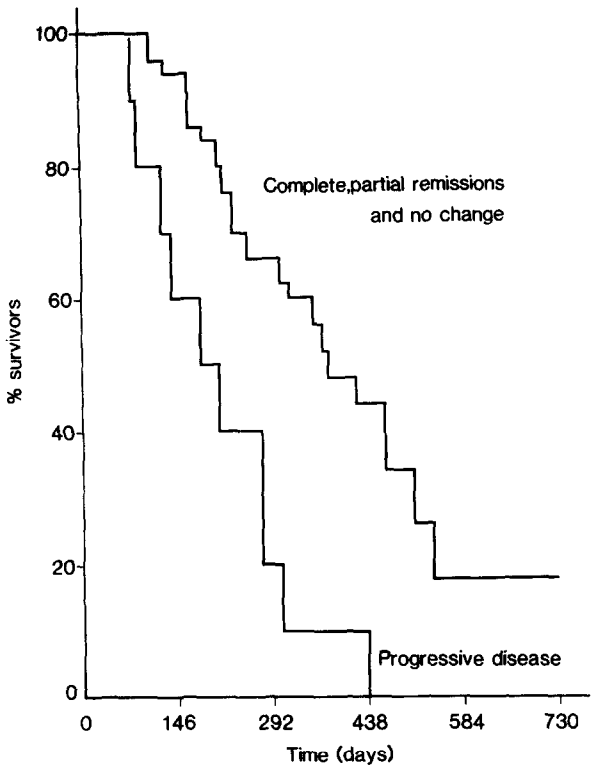

Fig. 1. Effect of DMV treatment on survival.

Table 3. Toxicity of treatment

Toxicity	No. of patients affected	%
Nausea and vomiting	13	32
Alopecia	11	28
Lassitude	5	13
Wt loss (>10% body wt)	4	10
Diarrhoea	1	3
Bleeding gums	1	3
Rash	1	3
Anaemia (>2 g/dl drop in HB during treatment)	13	32
WBC:		
$<3.5 \times 10^9$/l	2	5
$<2.5 \times 10^9$/l	1	3
Platelets $<100 \times 10^9$/l	1	3
MCV:		
>95 μm^3	6	15
>100 μm^3	3	15
>105 μm^3	4	10

haemoglobin of more than 2 g/dl was seen in 13 patients and a rise of the mean corpuscular volume above the upper limit of normal was seen in 16 patients. In four the value was greater than 105 μm and in these mitomycin C was stopped while patients continued on dibromodulcitol and vinblastine. Nadir white cell and platelet counts were not estimated. Values taken immediately before the next course of chemotherapy were usually within the normal range.

The treatment of 15 patients was stopped because of progressive disease. Among the causes of cessation of treatment before progression were nausea and vomiting (3), lethargy (2) and anaemia (3).

DISCUSSION

The response rate (66%) using DMV in previously untreated patients was similar to other first-line combination chemotherapy regimens, although the median duration of remission was relatively short (217 days). Tormey *et al.* [15] compared a DBM-containing regimen (DAV—DBM, adriamycin and vincristine) with CAF (cyclophosphamide, adriamycin and fluorouracil). The response to DAV was 52% after the first three cycles of treatment; patients were then crossed over to CMF and the final overall response was 77%. It was concluded that the DBM-containing regimen was at least as effective as CAF in untreated patients with metastatic breast cancer.

In this study the response rate of 37% in previously treated patients indicates that DMV is a reasonably active regimen for this group. It is difficult to compare other second-line regimens because of differences in previous treatments, patient characteristics and agents used. However, there are several other studies where either DBM or MMC or both have been used in combination.

DBM has been used mainly with adriamycin with and without additional agents. Di Stefano *et al.* [16] used adriamycin, DBM and MMC. The response rate was 43% and the median duration was 7 months. A combination of adriamycin, vincristine and DBM gave a response rate of 23%, with a duration ranging between 4.1 and 4.6 months [17]. Twenty-three of 50 patients (46%) responded to a combination of adriamycin and DBM, with a median duration of 5.1 months [18]. However, Ingle *et al.* [19] compared adriamycin alone with adriamycin plus DBM; the remission rates were 22 and 25% respectively. In our study the median response duration (239 days) was similar to the study of Di Stefano *et al.*, and thus there may be some advantage in using three rather than two agents in terms of response duration.

In a study using MMC with vinblastine the response rate was 40%, with a median duration of 127 days [20]. Mattsson *et al.* [21] treated 35 patients with MMC and fluorouracil, with a response rate of 51% and a duration of more than 8 months. A combination of MMC and adriamycin gave a response rate of 48% [22]. Thus, as in our study, combinations containing MMC appear active as second-line regimens, with response rates higher than MMC when used alone.

The toxicity associated with DMV is less in our experience than with the more commonly used first-line regimens such as CMF or adriamycin and cyclophosphamide. Less than one-third of

patients had nausea or vomiting, which when present was usually mild. The major toxicity was a drop in haemoglobin of more than 2 g/dl, seen in one-third of the patients, associated with a marked rise in MCV in 10%. There were no serious infections or bleeding episodes.

Thus DMV is a well-tolerated, active regimen for advanced breast cancer for both previously treated and previously untreated patients.

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