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Treatment of Melphalan-resistant Multiple Myeloma with Vincristine, BCNU, Doxorubicin, and High-dose Dexamethasone (VBAD)

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A total of 65 patients (35 male/30 female) with multiple myeloma primarily (33) or secondarily (32) resistant to melphalan and prednisone were treated with vincristine, carmustine (BCNU), doxorubicin, and high-dose dexamethasone (VBAD) at 4-week intervals. Among 60 evaluable patients the overall response was 36.6% (21.6% objective response plus 15% improvements). The response rate was significantly higher in primarily resistant patients than in those becoming resistant after a prior response (48.4 vs. 24.1%, $P < 0.05$). The median duration of response was 17.5 months. When survival of responders and non-responders were compared by the conventional method, a highly significant difference was observed ($P < 0.001$). However, using the Mantel and Byar procedure and the landmark method, only a trend for longer survival in the responders was registered. These results indicate that although VBAD is effective in at least one third of patients with advanced multiple myeloma resistant to melphalan, its impact on survival is limited.
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INTRODUCTION

PATIENTS WITH multiple myeloma (MM) who either fail to respond or become refractory to initial alkylating treatment usually have a low response rate to subsequent chemotherapy and a short survival [1–3]. Based on the observations that carmustine (BCNU) and doxorubicin seem to have a synergistic effect in myeloma [4], and that the addition of vincristine and prednisone also appear to have a positive effect on response rate and/or survival [5, 6], the Southwest Oncology Study Group, in a large cooperative study, employed a combination of vincristine, BCNU, doxorubicin and prednisone (VBAP) in refractory myeloma with encouraging results [7]. In this regard, we obtained similar results in a series of 33 patients from a single institution with myeloma resistant to alkylating agents [8]. On the other hand, high-dose glucocorticoids, particularly dexamethasone, seem to have higher antitumour activity in refractory myeloma than prednisone at standard doses [9, 10]. Taking into account these facts, we designed a regimen combining vincristine, BCNU, doxorubicin and high-dose dexamethasone (VBAD). We report the results obtained in 65 patients with melphalan-resistant MM treated with such a regimen by the Spanish Cooperative Group PETHEMA (Program for the Study and Therapy of Haematological Malignancies, Spanish Society of Haematology).

PATIENTS AND METHODS

Patients' characteristics

From January 1985 to March 1991, 65 patients with MM refractory to melphalan from 16 institutions from PETHEMA were entered into the study. The diagnosis of MM was established according to the criteria of the Chronic Leukaemia Myeloma Task Force [11]. Previous treatment consisted of intermittent courses of oral melphalan 9 mg/m^2 and prednisone 60 mg/m^2 orally or intramuscularly for 4 days, repeated at 4-week intervals [12]. Resistance to initial treatment was defined as any of the following: (a) progressive disease after at least 4 courses; (b) lack of response after 8 courses of adequate therapy (primary resistance) or (c) progression of myeloma during therapy following an initial response (secondary resistance). 33 patients showed primary resistance, whereas the remaining 32 became resistant after having achieved a response with melphalan prednisone (MP) therapy. Patients with symptomatic cardiopathy, severe arrhythmia or gastroduodenal ulcus were excluded. Table 1 summarises the patients' characteristics imediately before the start of VBAD therapy.

Treatment schedule

A cycle of treatment consisted of vincristine 1 mg intravenously, BCNU and doxorubicin 30 mg/m^2 each intravenously on day 1, and dexamethasone 25 mg/m^2 on days 1–4, 9–12, and 17–20 in the first course and on days 1–4 in subsequent courses. Cycles were repeated at 4-week intervals. Responding patients continued to receive treatment until disease progression was observed. When an accumulative dose of doxorubicin of 540 mg/m^2 was reached, this drug was discontinued and therapy was restricted to vincristine, BCNU and dexamethasone. The mean number of VBAD or VBD cycles per patient was nine (range: 1–30). All patients received antacid treatment with cimetidine or ranitidine and antibiotic prophylaxis with trimethroprim-sulphametoxazole at least for the first 5 weeks of therapy, when higher doses of dexamethasone were administered.

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Table 1. Patients characteristics immediately before VBAD therapy

No. of patients	65
Males/females	35/30
Age [mean (SD)] years	63.9 (7.04)
Myeloma protein type	
IgG	37
IgA	18
Light chain only	9
Non-secretory	1
Clinical stage	
IA	3
IIA	13
IIIA	40
IIIB	9
LDH > 500 U/l	20% (10/50)
B_2-microglobulin > 6 mg/l	29% (9/31)
Response to MP	
Good (with secondary resistance)	32
Primary resistant	33
Duration of MP chemotherapy [Mean (SD)] months	16.2 (10.9)
No. of MP courses [mean (SD)]	11.8 (7.04)

LDH = Lactate dehydrogenase; MP = melphalan/prednisone.

Criteria of response

An objective response was defined as a reduction of 50% or more of the M-component, improvement in performance status by at least two grades, and a decrease of more than 50% in measured cross-sectional area of plasmocytomas [11]. Furthermore, the size and number of lytic bone lesions must not have increased and also there must have been correction of hypercalcaemia (< 11.5 mg/dl), anaemia (> 9 g/dl) and hypoalbuminaemia (> 3 g/dl). In those patients fulfilling the above criteria but with a reduction in M-component of less than 50%, a partial response (or improvement) was considered. When the criteria for objective or partial response were not found, the case was considered a failure. Finally, patients who died within 2 months from start of therapy were considered as early deaths.

Statistical methods

The Fisher's exact test was used to assess the statistical significance of comparison of response rates. Survival times were estimated from the start of the VBAD therapy to the date of death or last follow-up. Survival curves were plotted according to the method of Kaplan and Meier [13] and statistically compared by means of the log–rank test [14]. Finally, the influence of response on survival was analysed by the Mantel and Byar procedure and the landmark method [15, 16].

RESULTS

Among the 65 patients entered into the study, 60 were evaluable for response. 5 patients were considered non-evaluable for the following reasons: major protocol violation (3 cases), early death (1 patient) and lost to follow-up (1 patient).

Response to treatment

The overall favourable response rate was 36.6% (22 out of 60 patients; 13 objective responses and 9 improvements), whereas 38 patients showed no response. Table 2 shows the correlation between response to initial MP treatment and response to VBAD. As it can be observed, the response rate was 24.1% (7/29) in patients with secondary resistance to MP and 48.4% (15/31) among patients who were primarily resistant ($P = 0.045$). The median duration of response was 17.5 months (Fig. 1).

Table 2. Response to VBAD according to the prior response to MP (60 patients)

	Response to VBAD		
Prior response to MP	Objective	Partial	Failure
Primarily resistant ($n = 31$)	8	7	16
Secondarily resistant ($n = 29$)	5	2	22

$P = 0.045$

Toxicity

The treatment was generally administered on an outpatient basis and was clinically well tolerated. Side-effects of VBAD were graded according to the WHO scale [17]. Although grade 2 or more myelotoxicity was recorded in 26 patients (40%), severe granulocytopenia ($< 5 \times 10^9$/l) and thrombocytopenia ($< 25 \times 10^9$/l) were only observed in 4 and 1 patients, respectively. There were nine episodes of severe infection requiring hospitalisation during VBAD therapy. 5 patients developed heart failure after receiving a total doxorubicin dose ranging from 120 to 450 mg/m^2. In all of them doxorubicin was discontinued. 4 patients had grade 2 peripheral neuropathy attributed to vincristine. In one patient who developed an steroid psycosis, dexamethasone was discontinued. No treatment-related deaths were observed.

Survival

The overall median survival of the series was 13 months, with 47 patients having died at the time of this analysis. The median survival for the reponders was 30 months vs. 9.8 months for

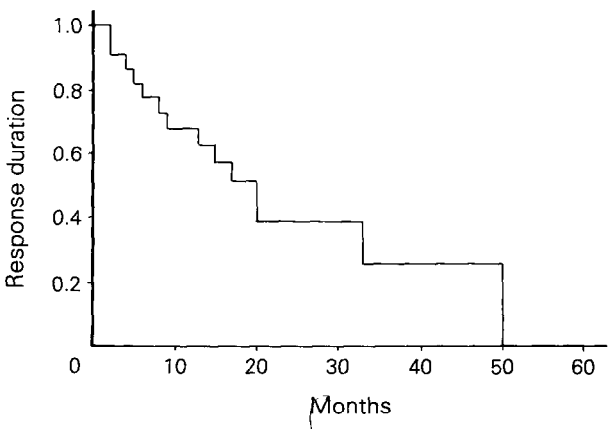

Fig. 1. Response duration in 22 responding patients.

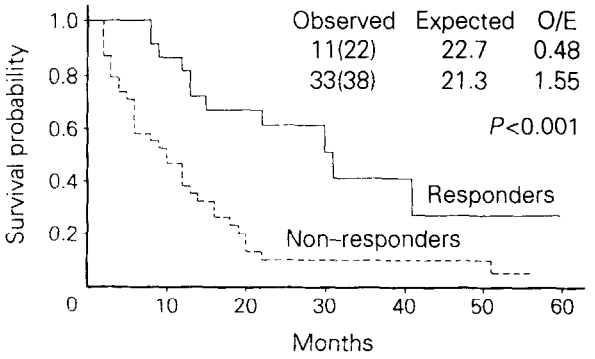

Fig. 2. Survival of responders (thick line) and non-responders (thin line) to VBAD therapy ($P < 0.001$).

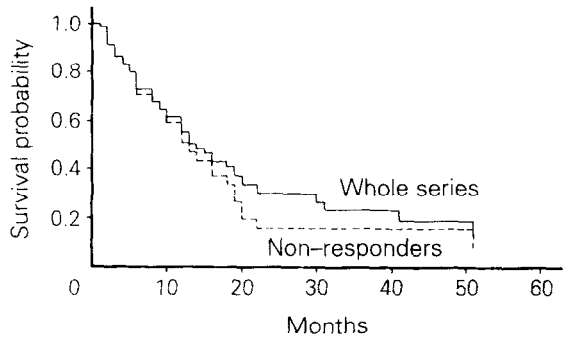

Fig. 3. Survival of the overall series (thick line) as compared with that of non-responding patients (thin line) by the Mantel and Byar test (χ^2: 2.85, $P = 0.091$).

non-responders (Fig. 2). This difference was highly significant when analysed by means of the standard method, considering the response as an initial variable ($P < 0.001$). However, when the Mantel and Byar procedure [15] (Fig. 3) and the landmark method [16] (Fig. 4) were applied, only a trend in favour of responders was observed. Disease progression and infection were the main causes of death.

DISCUSSION

The combination of melphalan and prednisone constitutes the standard treatment for most patients with MM. However, about 40% of patients do not respond to MP and, moreover, all patients initially responding eventually become resistant. The use of other alkylating agents is precluded by cross-resistance [18]. On the other hand, although selected patients can benefit from high-dose therapy with haematopoietic stem cell grafting or haematopoietic growth factors [19, 20], this approaches can be applied to a minority of patients only. Second line treatments for refractory multiple myeloma produce disappointing results due to both the low response rate to salvage therapy and the short duration of clinical response [1–3]. With the combination of vincristine, BCNU, doxorubicin and prednisone (VBAP), response rates of about 25%, as well as survival prolongation for responding patients, have been reported [7, 8]. In addition, high-dose corticosteroids, particularly dexamethasone, have clearly shown antitumour activity in refractory myeloma. Thus, Alexanian *et al.* [10] reported a response rate of 27 and 21% in primary refractory and relapsing patients, respectively, with dexamethasone alone. Furthermore, according to Buzaid and Durie [2], the expected response to high-dose glucocorticoids in resistant myeloma is about 25%. With this background, we employed the VBAP regimen with high-dose dexamethasone instead of prednisone. However, taking into account both the considerable toxicity of high-dose glucocorticoids in pretreated myeloma patients and that response to dexamethasone-containing regimens usually occurs rapidly [21–23], dexamethasone was given for 4-day courses, beginning on days 1, 9 and 17 in the first cycle and only for days 1 to 4 in subsequent cycles in our study, in order to prevent severe steroid toxicity.

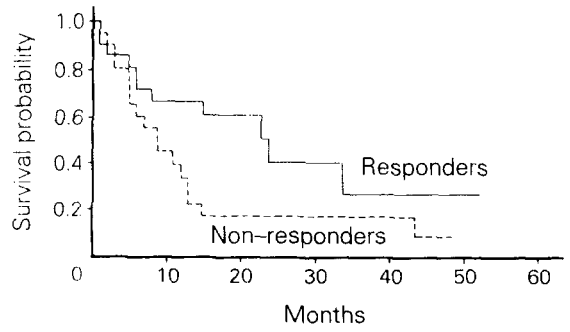

Fig. 4. Survival of responders vs. non-responders by the landmark method with landmark at 8 months after starting VBAD (χ^2: 3.57, $P = 0.057$).

As VBAD regimen constituted the rescue therapy of the MP arm in a cooperative randomised study of the PETHEMA group [12], all of our patients had been homogeneously treated and more than one third of them responded to VBAD. It is of note that the response rate was significantly higher in primary than in secondary resistant patients (48.4 vs. 24.2%, $P < 0.05$). This fact may be due to the emergence of chemotherapy-resistant clones in patients heavily pretreated with melphalan. An alternative explanation would be the usefulness of dexamethasone in patients unresponsive to initial therapy [2, 10]. In fact, in previous studies [7, 8] the response rate of primary resistant myeloma to VBAP was only 25 and 7%. The median duration of response to salvage regimens, including VAD and high-dose melphalan, usually ranges between 6 and 9 months in refractory MM [3, 10, 21–25]. In the present series, the median duration of response is longer than in the above reports. This might be explained in part by the fact that our patients had received only MP as previous therapy.

As in the previous series with VBAP [7, 8], VBAD was well tolerated. There were no treatment-related deaths, the most frequent toxicity being moderate myelosuppresssion due to BCNU and doxorubicin. In contrast with other studies in which dexamethasone was employed at higher doses [21–23], in the present series no excessive dexamethasone toxicity was registered. Indeed, some studies have reported a decrease in severe dexamethasone-related toxicity with reductions in the initial doses [21, 23].

The method more frequently used to analyse the impact of response on survival consists of separating patients into two groups according to whether or not they have achieved a response [13], the survival curves being compared by different statistical methods, such as the log-rank test [14]. In our series, this comparison showed a highly significant difference between responders and non-responders. However, this method is misleading, since it introduces a bias in favour of responders (i.e. the time from the start of treatment necessary to detect the response, that in myeloma usually varies over a wide range). In addition, responders may survive longer than non-responders for other reasons than the treatment itself (i.e. prognostic

factors), [16, 26, 27]. To reliably assess the impact of treatment results on survival, the Mantel and Byar procedure and the landmark method are currently recommended [15, 16]. Using these methods, no significant differences between responders and non-responders were observed in our series, although both methods showed a trend in favour of responders. In this sense, a lack of correlation between response and survival has recently been reported in previously untreated myeloma patients [28, 29]. Because of the poor correlation between response and survival in myeloma, it has been suggested that the magnitude of response, as currently defined, may not adequately assess the efficacy of current therapy [28–30].

In conclusion, VBAD is a well-tolerated and effective salvage regimen for at least one-third of patients with refractory myeloma, particularly those primarily resistant to melphalan. This regimen can be useful in alkylating-resistant patients who are not candidates for experimental treatments, such as high-dose therapy followed by bone marrow stem cell grafting and/or haematopoietic growth factors [19, 20].

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