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Treatment of Alkylating Resistant Multiple Myeloma with Vincristine, BCNU, Doxorubicin and Prednisone (VBAP)

JOAN BLADÉ, CIRIL ROZMAN, EMILI MONTSERRAT, FRANCISCO CERVANTES, EVARIST FELIU, ALBERT GRAÑENA, PEDRO MARÍN and BENET NOMDEDEU

Postgraduate School of Haematology 'Farreras Valentí', Hospital Clínic i Provincial, University of Barcelona

Abstract—*A total of* 33 *evaluable patients with multiple myeloma refractory to alkylating agents were treated with the regimen vincristine, BCNU, doxorubicin, and prednisone (VBAP) at* 3-week *intervals in a single institution for a* 5-yr *period. An overall response rate of* 21.2% *was achieved* (9% *objective plus* 12.2% *improvement). Treatment was well tolerated. The overall median survival was* 7.5 months. *However, responding patients attained a median survival of* 27.4 months *vs.* 5 months *for similarly treated nonresponding subjects* (P = 0.051). *These results indicate that VBAP is an effective treatment for a proportion of patients with advanced refractory multiple myeloma.*

INTRODUCTION

PATIENTS with multiple myeloma (MM) who either fail to respond or become refractory to initial alkylating treatment show a very low response rate to subsequent chemotherapy. Thus, besides the known cross-resistance between the two major alkylating agents (i.e., melphalan and cyclophosphamide) given at standard doses [1–4], new drugs effective in multiple myeloma have not yet been obtained. Furthermore, few combination regimens have proved of real value in refractory MM [5–12].

Based on the observations that BCNU and doxorubicin seem to have a synergistic effect in myeloma [5], and that the addition of vincristine and prednisone also appears to have a positive effect on response rate and/or survival of MM patients [13, 14], in a large cooperative study Bonnet *et al.* [10] employed a combination of vincristine, BCNU, doxorubicin, and prednisone (VBAP) in the treatment of refractory myeloma, with encouraging results. We report here the results obtained with the use of VBAP in a series of 33 evaluable patients with alkylating-resistant MM treated in a single institution for the last 5 yr.

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Address all correspondence to: Joan Bladé, Postgraduate School of Haematology, Hospital Clínic i Provincial, University of Barcelona, Villarroel, 170, Barcelona 08036, Spain.

MATERIAL AND METHODS

From January 1980 to December 1984, 36 patients with MM diagnosed according to the Criteria of the Chronic Leukemia Myeloma Task Force [15] who were resistant to alkylating therapy, either initially or after a response, were entered into the study. Previous treatment consisted of: intermittent courses of melphalan and prednisone (6 pts), cyclophosphamide, melphalan, and prednisone (23 pts), M-2 protocol [14] (1 pt), and continuous melphalan, cyclophosphamide and prednisone (1 pt). Resistance to prior treatment was defined as a lack of objective response or improvement after at least 4 months of adequate therapy or progression of myeloma after an initial response while under treatment. All patients had symptomatic myeloma. Thirty of them had progressive disease, whereas the remaining six had symptomatic, but stable disease non-responding to alkylating therapy. Patients with symptomatic cardiopathy or severe arrythmia were excluded. Table 1 summarizes the patients' characteristics immediately before the start of VBAP therapy.

Treatment schedules

A course of treatment consisted of vincristine 1 mg i.v., BCNU and doxorubicin (30 mg/m^2 each) i.v. on day 1, and prednisone (60 mg/m^2) i.v. or i.m. for days 1–4. Courses of therapy were repeated at 3-week intervals. In four patients with

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Table 1. Characteristics of patients immediately before the start of therapy

No. patients	36
Males/females	24/12
Age (mean + S.D., range) yr	64.4 + 11.2 (42–84)
Myeloma protein-type	
IgG	17
IgA	16
Bence-Jones only	1
NS*	1
Biclonal (IgG + IgD)	1
Response to prior chemotherapy	
Good (with further relapse)	18
Failure	18
Duration of prior chemotherapy (mean + S.D., range) months	19.3 + 18.9 (4–81)
Number of initial courses (mean + S.D., range)	12.1 + 10.1 (4–51)
Clinical stage	
IA	1
IIA	14
IIIA	17
IIIB	4

*NS = non-secretor.

renal failure, the doses of both BCNU and doxorubicin were reduced to 20 mg/m^2. 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 prednisone at the same doses. In seven patients with unresponsive progressive disease other treatments were tried: cycles of vindesine, CCNU, and prednisone (three patients), melphalan and prednisone (two patients) and vincristine, BCNU, doxorubicin and high-dose dexamethasone (two patients).

Statistical methods

Survival curves were plotted according to the method of Kaplan and Meier [16] and statistically compared by means of the log-rank test [17].

Criteria of response

Evaluation of the response was made following the guidelines of the Chronic Leukemia Myeloma Task Force [15]. According to these criteria, an objective response requires a change in at least one of the following direct manifestations of the plasma cell tumor: (1) a decrease in serum M-protein concentration or urine M-protein excretion to less than 50% of the pretreatment value; (2) a reduction of 50% or more in the product of the two largest diameters of palpable (or X-ray visualized) plasmacytomas or (3) definite radiographic evidence of skeletal healing. According to the Task Force improvement was defined as: (a) an increase in haemoglobin concentration $\geq$ 2 g/dl persisting for at least 1 month without blood transfusion in patients whose initial haemoglobin concentration was $\leq$ 9 g/dl and (b) improvement in performance status by at least 2 grades (0 = patient's activities normal, 1 = patient mildly symptomatic but ambulatory; 2 = patient with moderately severe symptoms but in bed < 50% of waking time; 3 = patient with severe symptoms and in bed > 50% of waking time; and 4 = patient completely bedridden). Improvement did not require an M-peak reduction. Patients were considered evaluable for response after two or more cycles of chemotherapy or after one cycle if there was obvious progression of disease.

RESULTS

Among the 36 patients entered into the study 33 were evaluable for response. Two patients died from pneumonia 8 and 22 days after the start of VBAP therapy. None of these two patients had granulocytopenia at the time of infection. Another patient died from unknown cause at his home 3 weeks after the start of treatment.

Response to treatment

The overall favorable response rate was 21.2% (7 out of 33 patients, three objective and four improvement). Twenty-six patients showed no response (seven remained clinically stable with no change in the amount of M-component, while 19 had clear disease progression under VBAP therapy). Table 2 shows the correlation between response to prior treatment and response to VBAP. The response rate was 17.6% (3/17) in patients who relapsed after initial response and 25% (4/16) among patients not responding to initial alkylating therapy. The response rate of patients with symptomatic progressive myeloma was 22.2% (6/27). On the other hand, only one of the six patients who had stable disease under alkylating therapy achieved a response with VBAP, but progression of disease was not observed in the remaining five patients. Among the four patients with renal

Table 2. Response to VBAP therapy according to response to initial treatment

Prior response	*Response to VBAP* OR	IMP	SD	PD
Objective (12)	1	1	1	9
Improvement (5)	–	1	–	4
Stable disease (6)	–	1	5	–
Progressive disease (10)	2	1	1	6

OR = objective response, IMP = improvement, SD = stable disease, PD = progressive disease.

failure, two showed an objective response, one patient showed no response, and the other died at 8 days of start of therapy and was subsequently excluded from evaluation. The mean number of VBAP or VBP cycles per patient was 9.7 (range 1–43). Seven patients with progressive disease received additional treatments (see Material and Methods) but no response was achieved.

Toxicity

The treatment was generally administered on an outpatient basis and was clinically well tolerated. Myelotoxicity was observed in 15 out of 33 evaluable patients (45.5%). Thrombocytopenia ($<100 \times 10^9/l$) was recorded in 12 patients (36.4%), but only three had platelet counts below $25 \times 10^9/l$. Furthermore, it must be remarked that two of them were severely thrombocytopenic ($< 10 \times 10^9/l$) at the start of therapy. Seven patients (21.2%) had granulocyte counts below $1.8 \times 10^9/l$, but severe granulocytopenia ($< 0.5 \times 10^9/l$) was only observed in a patient who initially showed a granulocyte count lower than $0.5 \times 10^9/l$. This patient had an aggressive plasma cell leukemia and died 10 days after the start of treatment from sepsis and progressive disease. No treatment-related deaths were observed.

In one responding patient who developed peripheral neuropathy attributed to vincristine subsequent dosages of this drug were reduced to one half. One patient developed myocardiopathy with heart failure after receiving a total doxorubicin dose of 540 mg/m^2. Two other patients with progressive disease had, respectively, supraventricular extrasystolia and atrial fibrillation after a total doxorubicin dose of 120 mg/m^2. Doxorubicin was discontinued in the latter three patients.

Survival

The overall median survival of the 33 evaluable patients was 7.5 months with 26 patients dead at the time of this analysis (Fig. 1). The median survival for the responders was 27.4 months vs. 5 months for nonresponders (Fig. 2, $P = 0.051$).

DISCUSSION

In multiple myeloma melphalan and cyclophosphamide are the more effective agents in producing tumor regression and prolonging survival. However, about 40% of patients with MM do not respond initially to alkylating agents. In addition, the disease usually becomes resistant to these drugs in those patients who respond initially. On the other hand, cross-resistance between alkylating agents generally exists in MM [1–4]. Therefore, many workers have developed efforts to find an effective second line therapy [5–12].

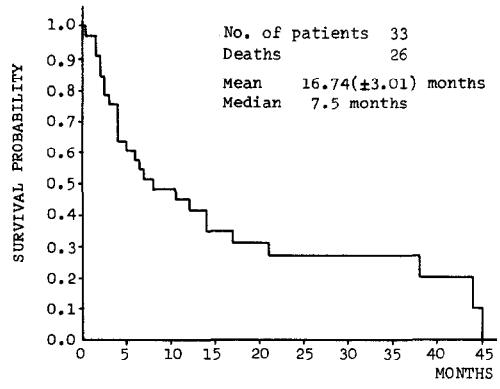

Fig. 1. Survival of 33 evaluable patients from the start of VBAP therapy.

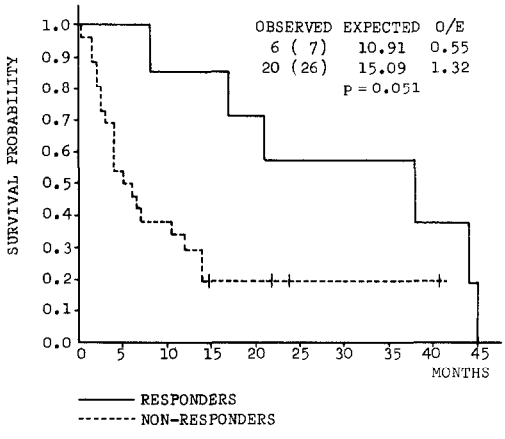

Fig. 2. Survival of responding (solid line) and non-responding (dash line) patients to VBAP therapy.

Chemotherapy combinations including Adriamycin (doxorubicin) and BCNU appear to be useful in some patients with MM refractory to alkylating agents [5, 6, 8, 10]. The South West Oncology Study Group (SWOG) carried out a large cooperative study using a combination of vincristine, BCNU, doxorubicin, and prednisone (VABP) [10]. With this regimen an objective response rate of 25% (39/151) and a significant survival prolongation for responding patients were achieved (78 vs. 33 weeks). With the same VBAP regimen we observed an overall response rate of 21.2% (9% objective plus 12.2% improvement). In addition, our responding patients attained a median survival of 27.4 months vs. 5 months for similarly treated nonresponding subjects ($P = 0.051$). This study confirms the efficacy of VBAP in a proportion of patients with MM resistant to alkylating agents. Also, in contrast with the results of Bonnet *et al.* [10] who reported only 7% (2/28) of responses among patients initially resistant to therapy, 4 out of 16 (25%) of our initially resistant patients responded to VBAP. Thus, in our opinion this therapy can be useful in patients who do not respond initially to alkylating agents. Other studies have also showed objective

response rates ranging from 22 to 54% employing regimens containing BCNU and doxorubicin, with significant survival prolongation for responding patients [5, 6, 8]. It is of interest to note the survival plateau of 20% observed in our non-responding patients. Indeed, the four non-responders who survive in the range of 15–41 months are patients in whom the disease remained stable either under alkylating and VBAP therapy, in spite of being symptomatic. As pointed out by other authors [18], it is possible that a proportion of patients normally classified as 'non-responders' may in fact have a prolonged survival because of 'non-progressing disease'. In view of the present results, a 'wait and see' approach would seem justified in those patients in whom the disease remains stable after six courses of alkylating therapy. Such approach requires a close follow-up and appropriate management of the disease's complications (for instance, hyperviscosity or infections), reserving the chemotherapy for patients with clearly progressive disease.

As in the original report from Bonnet *et al.* [10], VBAP was well tolerated. There was no treatment-related deaths, the most frequent toxicity being BCNU-related thrombocytopenia.

Two recent reports strongly suggest that both pulse prednisone therapy [19] and high-dose dexamethasone [20] have antitumor activity in refractory myeloma, leading to significant increases in response rate when employed along with vincristine and doxorubicin. Since standard doses of VBAP are well tolerated and effective in at least 20% of refractory MM patients, it is possible that a therapeutic approach including higher doses of BCNU and doxorubicin together with pulse prednisone or high-dose dexamethasone would increase the response rate, the duration of response and the survival of patients with advanced refractory multiple myeloma.

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