



## THE ASSOCIATION OF CYCLOPHOSPHAMIDE AND DEXAMETHASONE IN ADVANCED REFRACTORY MULTIPLE MYELOMA PATIENTS

LIDIA CELESTI, MARINO CLAVIO, ALESSIA POGGI,\* SALVATORE CASCIARO,\* EMANUELA VALLEBELLA, MARCO GOBBI

Chair of Hematology, Department of Internal Medicine, University of Genoa; \*II Division of Internal Medicine, S. Martino Hospital, Genoa, Italy

### ABSTRACT

VAD is the most active regimen in refractory myeloma patients; however, the role of vincristine and doxorubicin remains unclear. Relatively high doses of cyclophosphamide (3.6 g/sqm) increased the response rate and survival in resistant MM. Cyclophosphamide and dexamethasone were administered to 28 patients with advanced refractory myeloma. Thirteen patients received cyclophosphamide 1.2 g/sqm on days 1 and 3 and dexamethasone 40 mg/day from day 1 to day 4, every 4 weeks for 6 cycles (schedule A); 15 patients were treated with cyclophosphamide 0.5 g/sqm on days 1 and 3 and dexamethasone 40 mg/day from day 1 to day 4, every two weeks for 12 cycles (schedule B). Overall, 21 patients (75%) responded

and 10 achieved an objective response (36%), while 11 reached a partial response. Twenty patients died (68%), most of them of disease progression, and 8 are still alive (32%). Median length of response and survival is 6 and 8 months, respectively. Therapy was easily applied and well tolerated. The overall response rate (75%) compares favorably with the best published results in this setting. The two schedules proved to be equally effective but patients treated with schedule B had more infections, which may have been related to the higher dosage of steroids.

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Key words: cyclophosphamide, dexamethasone, refractory myeloma

About 40% of patients with multiple myeloma (MM) are refractory either to alkylating agents and prednisone or to more complex cytotoxic drug combinations.<sup>1</sup> Furthermore, virtually all patients who initially respond develop resistance after variable periods of time, usually not exceeding 36-40 months. The most active regimen in refractory patients is VAD, which includes vincristine, doxorubicin administered in continuous infusion, and high-dose dexamethasone.<sup>2</sup> However, the role of vincristine and doxorubicin remains unclear since it has been shown that comparable results can be obtained in this setting with dexamethasone alone.<sup>3</sup> Moreover, VAD increases multidrug resistance gene expression in neoplastic plasma cells, thus worsening the drug resistance phenomenon.<sup>4</sup> As a matter of fact, these patients benefit for a very short period and their survival does not usually exceed 6 months. Recently, relatively high doses of cyclophosphamide (3.6 g/sqm) followed by G-CSF support increased response rate and survival in patients with resistant MM.<sup>5</sup>

Here we report on 28 patients with advanced refractory disease who received a combination of cyclophosphamide and dexamethasone (CY-DEX), given with two different schedules.

### Patients and Methods

From January 1992 to June 1996, CY-DEX were administered to patients with advanced, alkylating refractory multiple myeloma as salvage therapy. Refractory status implied disease progression during first-line therapy or lack of response after at least 3 courses of alkylating agent-containing therapy given for relapse. The main treatments employed before CY-DEX were MP (n = 12), VAD-VND (n = 6), VMCP (n = 6) and VCAP (n = 3). Patients over 75 years of age or with severe heart, lung or liver impairment were excluded. Two different institutions (Chair of Hematology DIMI and II Division of Internal Medicine, S. Martino Hospital, Genoa) enrolled patients. Clinical and hematological data are reported in Table 1. CY-DEX were administered according to two different schedules (Table 2). Thirteen patients received cyclophosphamide 1.2 g/sqm on days 1 and 3 and dexamethasone 40 mg/day from day 1 to day 4, every 4 weeks for 6 cycles (schedule A); 15 patients were treated with cyclophosphamide 0.5 g/sqm on days 1 and 3 and dexamethasone 40 mg/day from day 1 to day 4, every two weeks for 12 cycles (schedule B). Allocation of patients to either schedule A or B was not random, but was made on the basis of the therapeutic policy of the participating institutions; however, the two patient groups were similar as far as age, stage and performance status were concerned. Responding patients did not receive any maintenance treatment. Response criteria have already been published.<sup>6</sup> Patients receiving at least 3 (schedule A) or 6 (schedule B) courses of therapy were evaluated for response. The duration of response was calculated from the end of therapy to the time the M-protein began to rise again. Survival was calculated from the start of treatment to the date of death or to December 1996.

Correspondence: Prof. Marco Gobbi, Chair of Hematology DIMI, University of Genoa, viale Benedetto XV 6, 16132 Genoa, Italy. Tel. ☎ Fax. international +39.10.3538953.

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Table 1. Characteristics of the patients.

	All patients	Schedule A	Schedule B
Number	28	13	15
M/F	15/13	7/6	8/7
Median age	63 (44-74)	69 (44-74)	61 (54-73)
Stage IA	1 (3.5%)	-	1 (7%)
IIA	5 (18%)	4 (31%)	1 (7%)
IIB	1 (3.5%)	-	1 (7%)
IIIA	19 (68%)	8 (62%)	11 (72%)
IIIB	2 (7%)	1 (7%)	1 (7%)
Previous therapy (number of lines):			
1	11 (40%)	8 (60%)	3 (20%)
2	5 (18%)	1 (8%)	4 (27%)
3	8 (28%)	3 (24%)	5 (33%)
4	3 (10%)	1 (8%)	2 (13%)
5	1 (4%)	-	1 (7%)
MC: IgG	18 (64%)	7	11
IgA	8 (28%)	5	3
IgD	1 (3.6%)	-	1
BJ	1 (3.6%)	1	-
Bone disease	27 (96%)	13 (100%)	14 (93%)
WHO pretreatment performance status			
1	5	1	4
2	10	6	4
3	13	6	7

Table 2. Response and toxicity.

	All patients	Schedule A	Schedule B
Objective response	10 (36%)	5 (38%)	5 (34%)
Partial response	11 (39%)	4 (31%)	7 (46%)
Progression	3 (11%)	3 (23%)	-
Stable disease	4 (14%)	1 (8%)	3 (20%)
Median duration of:			
-response (months)	6.3	7.6	5.2
-OR	8	8.6	7
-PR	5	6.5	4
Toxicity (WHO max):			
0	12 (43%)	4 (31%)	8 (53%)
1	8 (28%)	4 (31%)	4 (27%)
2	7 (25%)	4 (31%)	3 (20%)
3	1 (4%)	1 (7%)	-
Infections:			
sepsis	2	-	2
bpn	2	-	2
fuo	3	2	1
other infections	2	2	-
Alive/dead	8 / 20	4 / 9	4 / 11
Causes of death:			
MM	20	9	11
Median survival (months)	7.8	9.4	6.3
surv. responders	8.2	10.5	6.5
surv. non responders	6.2	7	5.3

## Results

Therapeutic response was assessed in all 28 patients. Overall, 21 (75%) responded and 10 achieved an objective response (36%); 11 reached a partial response (39%), while 7 patients showed stable or progressive disease (25%). Reduction of the M component was always associated with a marked improvement of the performance status; responsive patients experienced a relevant decrease in bone pain.

The two schedules were well tolerated, as can be seen by the low myelotoxicity score and produced comparable therapeutic results (Table 2). The maximum grade 2-3 myelotoxicity score, on neutrophils was slightly higher in patients treated with schedule A than in those receiving schedule B (37% vs. 20%, respectively), but infectious complications (mainly sepsis and bronchopneumonia) were more frequent in patients belonging to the latter treatment group. Therapy-related myelotoxicity did not increase the need for transfusional support.

As of December 1996, 20 patients have died (68%), almost all of them of disease progression, and 8 are still alive (32%). Median length of response and survival is 6 and 8 months, respectively.

## Comment

Although the overall response rate in our series (75%) compared favorably with the best published results in this setting, its duration was short and there was no difference in survival between responders and nonresponders (8 and 6 months, respectively).

These results are in line with previously published data<sup>3,4</sup> on salvage treatment in MM. The reason for this short time is mainly related to the poor prognosis of these patients, as already mentioned. However, it should be emphasized that a marked reduction in bone pain as well as an improvement in the performance status were achieved in all responding patients. Both treatments were easily applied and well tolerated, and patients were mostly followed on an outpatient basis.

The greater number of infections observed in patients treated with schedule B may have been due to the severe immunosuppression related to the higher dosage of glucocorticoids administered with this schedule. The higher incidence of sepsis and bronchopneumonia may also explain the shorter median survival in this same cohort of patients.

Although cyclophosphamide<sup>7</sup> and dexamethasone as single drugs have been widely employed as salvage therapy, their association has not yet been reported.

Leoni *et al.*<sup>8</sup> reached an overall response rate of 73% in advanced refractory myeloma using teniposide, dexamethasone and cyclophosphamide. Their

survival was also comparable to that obtained in our study, but this complex drug combination required at least 7 days of hospitalization every month.

The higher dosage of cyclophosphamide administered by Palumbo *et al.* (3.6 g/sqm in 2 doses) in association with prednisone (2 mg/kg  $\times$  4 days) produced a lower response rate and more severe myelotoxicity.<sup>5</sup>

In conclusion, the combination of intermediate doses of cyclophosphamide and dexamethasone would appear to be a feasible and effective salvage treatment for resistant MM patients, and seems to be more effective than highly complex and toxic regimen. They should therefore be included within the current therapeutic options for multiple myeloma.<sup>9</sup> Extension of survival is still an unresolved issue but recent advances in our knowledge of myelomagenesis<sup>10</sup> will hopefully be translated into new therapeutic means.

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