

Primary Dexamethasone Treatment of Multiple Myeloma

By Raymond Alexanian, Meletios A. Dimopoulos, Kay Delasalle, and Bart Barlogie

Intermittent courses of dexamethasone (DEX) were administered to 112 consecutive, previously untreated patients with multiple myeloma (MM). Using criteria based on a 75% or greater reduction of calculated tumor mass, the overall response rate was 43%. Among comparable patients, response rates were approximately 15% less than those observed previously with vincristine-doxorubicin by continuous infusion with intermittent DEX (VAD) and similar to those with melphalan-prednisone. The projected survival times with VAD or DEX were similar. Results indicated that

DURING THE PAST 10 years, several treatments have been found useful for patients with multiple myeloma (MM). The combination of vincristine-doxorubicin by continuous infusion with intermittent dexamethasone (VAD) has reduced tumor mass markedly in about 25% of patients resistant to standard regimens and in about 45% of patients with relapsing disease.^{1,2} Yet, this program did not improve the frequency of response or the survival time of newly diagnosed patients.³ Dexamethasone alone (DEX) was effective in about one-fourth of myeloma patients with resistant disease, and appeared to account for most of the responses to VAD, but has not been studied in previously untreated patients.² These observations prompted the current study of high-dose DEX in previously untreated patients. Results indicated that this glucocorticoid provided a simple, effective, and safe treatment for many patients with MM.

MATERIALS AND METHODS

Patients and drug regimens. Between August 1989 and December 1991, DEX was administered to 112 consecutive patients with symptomatic MM. Their clinical features are summarized in Table 1. The DEX dose regimen was 20 mg/m² each morning for 4 days beginning on days 1, 9, and 17. After a 14-day rest, the treatment was repeated with downward dose adjustments for side effects; the dose was reduced by 20% in seven patients and by 40% in three patients because of uncomfortable hiccoughs, severe hyperglycemia, moderate irritability and insomnia, or oral candidiasis. No more than three cycles of DEX were required to confirm a response. All responding patients were maintained on α interferon (IFN) 2×10^6 U/m² subcutaneously every Monday, Wednesday, and Friday. This treatment was conducted after approval by our Institutional Review Board and in accord with an assurance filed with, and approved by, the Department of Health and Human Services.

Staging and clinical response. The diagnosis of MM was based on standard criteria; all showed bone marrow plasmacytosis of more than 15%, all but 4% showed a monoclonal globulin on serum or urine electrophoresis, and more than 70% had lytic bone lesions. Plasma cell tumor mass was defined in each patient as high, intermediate, or low. High tumor mass was defined by either serum calcium greater than 11.5 mg/dL or hemoglobin less than 8.5 g/dL. Low tumor mass required normal serum calcium, hemoglobin greater than 10.5 g/dL, and serum myeloma protein less than 4.5 g/dL. All other patients were classified as intermediate tumor mass.^{4,5} Clinical response was defined as a 75% reduction of serum myeloma protein production, disappearance of Bence Jones protein, and reduction of marrow plasmacytosis to less than 5%.⁶ Only two patients died during the first 4 weeks; they were considered

unresponsive. Response and survival data were compared with those of a VAD regimen studied immediately before the DEX program in 177 previously untreated patients.³

Statistical analyses. Patients treated with DEX had less extensive disease than patients treated previously with VAD (Table 1). Consequently, response rates and survival times were assessed in comparable subgroups of patients with similar tumor mass grades. After preliminary analyses showed similar results for patients with either high or intermediate tumor mass, patients in both groups were combined into one category. Survival curves were calculated from the start of treatment by the Kaplan-Meier method, and compared by the Wilcoxon test.⁷

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RESULTS

Frequency of response. The overall response rate was 43% with DEX and 55% with previous VAD. Among patients with comparable tumor mass, the frequencies of remission with DEX were approximately 15% less than those achieved with VAD (Table 2). Four of the 10 patients in whom the dose was reduced because of side effects achieved a response, a frequency similar to that of all other patients.

The rapidity of response was assessed from serial changes in IgG or IgA myeloma protein production.⁶ The tumor mass halving times for patients responding to DEX were identical to those of patients responding previously to VAD (median, 0.5 months). All patients responding to VAD or DEX showed a tumor halving time of 3.2 months or less, and a remission was confirmed in 80% of patients within 2 months. Serum myeloma protein disappeared on immunofixation studies in 3% of patients treated with DEX alone, and in 8% of patients treated with VAD ($P = .13$).

From the University of Texas M.D. Anderson Cancer Center, Houston, TX.

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Address reprint requests to Raymond Alexanian, MD, Box 1, 1515 Holcombe Blvd, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030.

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Table 1. Clinical Features of Patients

	DEX (1989-1991)	VAD (1983-1989)*
No. of patients	112	177
Median age (range)	60 (30-85)	61 (22-81)
Frequency of complications (%)		
Hemoglobin < 8.5 g/dL	10	28
Calcium > 12.0 mg/dL	6	23
Creatinine > 2.0 mg/dL	12	25
β_2 microglobulin > 6.0 mg/L	21	45
Tumor mass (%)		
High	15	39
Intermediate	43	36
Low	42	25

*Between 1983 and 1986, VAD was administered to 115 consecutive patients with all tumor mass grades. Between 1986 and 1989, VAD was limited to the 62 consecutive patients with high or intermediate tumor mass.

Treatment of nonresponders. A CVAD combination was administered to the first 31 unresponsive patients consisting of vincristine 0.8 mg/m², doxorubicin 35 mg/m², and cyclophosphamide 400 mg/m² intravenously (IV) with DEX 20 mg/m² orally each morning for 4 days; three patients responded (10%). Twelve subsequent patients received a standard program of intermittent melphalan-prednisone⁸; three patients responded (25%). Four patients without medical contraindications received an intensive program of etoposide and cyclophosphamide⁹; two patients responded. Seven patients died before a secondary treatment could be offered and there was insufficient data in nine patients treated elsewhere.

Remission and survival. Twelve patients responsive to DEX have relapsed to date despite maintenance treatment with α IFN. Five of ten patients with evaluable data responded to their first exposure to melphalan-prednisone; all five patients remain in remission 3 to 12 months after the start of chemotherapy. None of our previous patients who relapsed to VAD responded to standard therapy, and only those few who received intensive therapy achieved a second remission.^{9,10}

Among patients with comparable tumor mass, the projected survival times for patients treated with DEX were similar to those of patients treated with VAD (Fig 1). Preliminary analyses also showed similar remission times for responding patients treated with each program.

Toxicity. Among the 177 patients treated with VAD-based regimens, hospitalization was required in 27% for septic complications due to neutropenia or a central venous catheter. The median nadir level of granulocytes was 800/ μ L between days 10 and 16 after the start of chemotherapy. Central venous catheters were usually retained for

longer than 6 months, but premature removal was required in 16% of patients because of thrombosis or infection. Virtually all had symptoms of mild vincristine neuropathy, alopecia, and mild Cushingoid features. Most patients treated with DEX also showed Cushingoid features and/or insomnia, but there was no myelosuppression; other complications attributed to DEX, such as oral candidiasis, herpes lesions, aggravation of diabetes, peptic ulcer, hiccoughs, or quadriceps weakness, each occurred in less than 5% of patients. Hospitalization was required in four patients treated with DEX, two with a perforated diverticulum, one with pancreatitis, and one with pneumonia. There was no significant toxicity with IFN that was adjusted in dose to maintain a normal quality of life. Mild fever, achiness, and fatigue were the most frequent side effects. Patients older than 70 years of age were usually unable to tolerate a dose higher than 2×10^6 U three times weekly, and the dose was reduced to 1×10^6 U three times weekly in four older patients.

DISCUSSION

Among patients with MM resistant to intermittent courses of melphalan-prednisone, either VAD or DEX achieved remissions in about one-fourth of the patients.² However, primary VAD in newly diagnosed patients did not improve either response rate or survival time in comparison with previous experiences.³ In this report, we confirm a response rate with DEX that was only about 15% less than that with VAD, suggesting that this steroid accounted for most of the plasma cell reduction achieved with VAD. Results with primary DEX were also similar to those observed previously with primary melphalan-prednisone.⁸ Resistance to DEX was usually associated with resistance to other standard therapies, a finding also consistent with the similar response rates with DEX, VAD, and melphalan-prednisone.

Serious toxicity with DEX was rare in contrast to a trial by others in patients with resistant myeloma,¹¹ perhaps because of our longer rest periods and provision for early dose reduction. The reasonably high response rate with minimal side effects supports the value of DEX alone for many patients, and especially those with hypercalcemia or pancytopenia, or those who require simultaneous radiotherapy for a pathologic fracture. However, among those unlikely to respond to DEX or other standard regimens, more intensive primary chemotherapy should be considered. Based on recent prognostic factor studies,¹² such patients include those with high serum lactate dehydrogenase, hypodiploidy, or plasma cell leukemia, who represented 24% of our patients and among whom only 21% responded to DEX- or VAD-based regimens.

When patients who responded to DEX relapsed despite IFN maintenance, the myeloma responded again to standard chemotherapy in about one-half of the patients. Such preservation of sensitivity differed from previous trials in patients maintained on VAD when more intensive treatments were necessary to induce a remission.^{10,13} This difference is due to the universal resistance to standard chemotherapy of myeloma that progresses despite VAD, in comparison with the frequent sensitivity of myeloma that relapses despite IFN. Thus, the capacity to reduce and

Table 2. Response Rates in Previously Untreated Patients With MM

	No.	Tumor Mass	
		Low	High or Intermediate
VAD	177	69%	50%
DEX	112	51%	37%

$P = .08$ (between VAD and DEX for Low tumor mass)
 $P = .08$ (between VAD and DEX for High or Intermediate tumor mass)

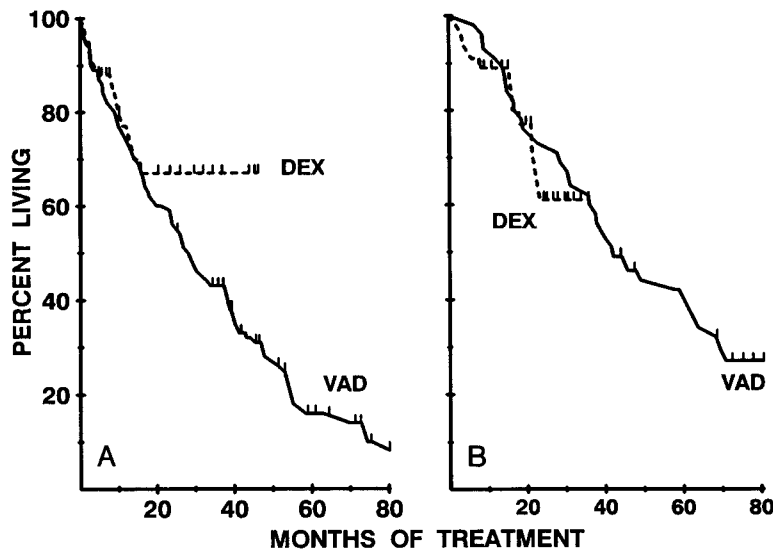


Fig 1. Survival from treatment with DEX (- - -) or VAD (—) of comparable patients with either high or intermediate tumor mass (A) or with low tumor mass (B).

stabilize the myeloma with a sequence of high-dose glucocorticoid and IFN provided an opportunity to observe later responses to the patient's first exposure to an alkylating agent. For those patients at high risk for early relapse and who qualify for a myeloablative treatment, autologous bone marrow or blood stem cells should be collected during remission. Such planning seems essential in view of the reduced mobilization and collection of blood progenitor cells with repeated myelosuppressive therapy.¹⁴

The mechanism of myeloma control with glucocorticoids remains unclear. Some have observed a correlation between steroid receptor levels and plasma cell reduction with DEX.¹⁵ Others have concluded that the quantity and affinity of glucocorticoid receptors were not predictive of response, and that unknown postreceptor mechanisms accounted for the sensitivity to steroids.¹⁶ Dexamethasone inhibits the messenger RNA expression of interleukin-6 (IL-6) in myeloma cells, a growth factor considered to be a major mediator of plasma cell proliferation.¹⁷ In view of the probably dominant role of bone marrow stromal cells in the

production of IL-6,¹⁸ DEX may induce a plasma cell apoptosis by blocking the IL-6 support network.

Regardless of the mechanism, intermittent high-dose DEX provided a simple, effective, and safe primary treatment for nearly one-half of newly diagnosed patients with MM. Responses were rapid in onset, a feature useful in the prompt reversal of complications such as hypercalcemia and renal failure. In contrast to alkylating agents, glucocorticoid treatment has not been associated with secondary leukemia and is more likely to preserve bone marrow function for either high-dose alkylating agent therapy,¹³ or for autologous marrow harvest and an intensive transplant-supported therapy in those who qualify for this procedure.¹⁰ Our results also indicate that high-dose DEX is the most effective single agent for MM, with a response rate higher than those observed previously with either intermittent melphalan or IFN.^{8,19} This experience justifies further trials of melphalan with repeated DEX in those newly diagnosed patients who are not candidates for intensive therapies.

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