RAPID COMMUNICATION

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 DEX accounted for most of the plasma cell reduction achieved with VAD. Serious complications occurred in 27% of patients treated with VAD, but in only 4% of those who received DEX.

In view of a similar outcome with fewer serious complications, DEX provided a simple, effective, and safe primary treatment for a large fraction of patients with MM. Patients who appear most likely to benefit include those with hypercalcemia or pancytopenia, or who require simultaneous radiotherapy for a pathologic fracture.

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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. 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).

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three patients responded
mass. Between 1986 and 1989, VAD was
mg/m² orally each morning for 4 days; three patients
of vincristine 0.8 mg/m², doxorubicin
limited to the 62 consecutive patients with high or intermediate tumor
with aIFN. Five of ten patients with evaluable data re-
standard program of intermittent melphalan-prednisonex;
two patients responded. Seven patients died before a secondary treatment could be
start of chemotherapy. None of our previous patients who
DEX have relapsed to date despite maintenance treatment
vos~ion. This
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
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 compli-
cations 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 × 10⁹ U three times weekly, and the dose was
reduced to 1 × 10⁹ 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. However,
primary VAD in newly diagnosed patients did not improve
either response rate or survival time in comparison with
previous experiences. 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 previ-
ously with primary melphalan-prednisone. Resistance to
DEX was usually associated with resistance to other stan-
dard therapies, a finding also consistent with the similar re-
dose 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, perhaps
because of our longer rest periods and provision for early
to treat patients with the DEX regimen for which they 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.

Among patients with comparable tumor mass, the pro-
jected survival times for patients treated with DEX were
similar to those of patients treated with VAD (Fig 1).
Preclinical 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/µL between days 10 and 16 after the start of chemother-
apy. Central venous catheters were usually retained for

**Table 1. Clinical Features of Patients**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>112</td>
<td>177</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60 (30-85)</td>
<td>61 (22-81)</td>
</tr>
<tr>
<td>Frequency of complications (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;8.5 g/dL</td>
<td>10</td>
<td>28</td>
</tr>
<tr>
<td>Calcium &gt;2.0 mg/dL</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>β2 microglobulin &gt;6.0 mg/L</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>Tumor mass (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>Intermediate</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Low</td>
<td>42</td>
<td>25</td>
</tr>
</tbody>
</table>

*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.

**Table 2. Response Rates in Previously Untreated Patients With MM**

<table>
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<th>Tumor Mass</th>
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<th>DEX</th>
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<td>Low</td>
<td>69%</td>
<td>51%</td>
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<td>High or Intermediate</td>
<td>50%</td>
<td>37%</td>
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**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 cyclo-
phosphamide 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-prednisone⁶; 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 aIFN. Five of ten patients with evaluable data re-
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.⁵,⁶

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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.

REFERENCES


Primary dexamethasone treatment of multiple myeloma

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