Management of Myeloma: Current and Future Approaches

Martin M. Oken, MD

New treatment interventions for multiple myeloma provide options for improving survival, safety, response, and response duration.

Background: The treatment of multiple myeloma, relatively stagnant for many years, appears to be entering a promising era for improvement. This paper reviews treatment interventions available for patients with multiple myeloma to indicate a standard approach and to evaluate the spectrum of current standard therapy.

Methods: The author reviews published literature on the treatment of multiple myeloma. Both journal articles and papers presented at national and international meetings are utilized.

Results: Intensive combination chemotherapy offers relatively modest improvement over standard melphalan plus prednisone, but the use of interferon for maintenance therapy lengthens response duration and possibly survival. High-dose chemotherapy with stem-cell transplantation is a relatively safe and effective treatment modality for patients under 70 years of age at first relapse. Studies in progress will determine its role in first response consolidation. Use of hematopoietic growth factors, prophylactic antibiotics, and bisphosphonate treatment of lytic bone disease has diminished disease morbidity.

Conclusions: While cure of multiple myeloma remains elusive and 10-year survival is still uncommon, newer treatment approaches offer better control of disease manifestations and perhaps a real opportunity to prolong functional life. Future treatments that will address minimal residual disease may improve long-term survival.

Introduction

Multiple myeloma is a relatively common hematologic malignancy with an annual incidence in the United States of approximately 13,000 patients and a risk of over 4 cases per 100,000 per year. It leads to progressive morbidity and eventual mortality by lowering resistance to infection and by causing bone pain and skeletal destruction, hypercalcemia, anemia, renal failure, and weight loss. In a minority of patients, multiple myeloma also causes neuropathy, hyperviscosity, and abnormalities in hemostasis. Although myeloma may be indolent or smoldering at the time of diagnosis in 5% of patients, virtually all patients with myeloma develop active symptomatic disease that requires treatment.

Goals and Strategy of Treatment

At present, cure is a realistic goal for only a small minority of patients with multiple myeloma. Cure is not presently attainable with standard chemotherapy, interferon, or high-dose chemotherapy followed by autologous transplantation regimens with bone marrow or peripheral blood stem cells. Cure or long-term disease-free survival is seen in less than 20% of patients under 55 years of age who have a related-donor match and receive an allogeneic graft, either from bone marrow or peripheral blood stem cells.1,2 Treatment-related mortality for patients treated with this approach still exceeds 50%.

For the vast majority of myeloma patients, the rational goals of treatment are meaningful prolongation of life with durable relief of pain and other disease symptoms, and protection of a normal performance status and quality of life for as long as possible. These are usually achieved through reduction of the myeloma tumor burden by establishing a plateau phase and delaying disease progression. The strategy, therefore, is to select a safe and well-tolerated treatment that can reliably produce objective response of long duration or can at least delay relapse or progression for many years. Treatment goals may be similar for a frail 75-year-old patient and a younger, more fit patient, but the means to deliver these goals may be quite different.

Choice of an Initial Treatment Regimen

For over three decades, a standard treatment for multiple myeloma has been the alkylating agent melphalan usually administered with prednisone (MP) as a moderate-dose, intermittent, oral outpatient regimen.3 Numerous prospective trials demonstrated that MP yields a 50% response rate based on the criteria of a 50% reduction in the concentration of myeloma protein, a remission duration of 18 months, and a median survival of 24 to 30 months.4,6 Complete responses are rarely obtained. Fifty percent of patients present with myeloma that is clinically resistant to MP. Even responders invariably develop resistance, usually within two years. By five years, more than 80% of patients treated with MP have died. Because of these unsatisfactory results, several multidrug regimens have been developed in an effort to improve treatment efficacy. To evaluate these in comparison to MP, it is necessary to focus on the treatment goals. Two-year survival is achieved in 55% to 65% of patients with virtually any active regimen. Similarly, 10-year survival is obtained in only 3% to 5% of patients, regardless of the regimen selected for initial treatment. A reasonable target for a patient with myeloma is to obtain good functional status and long-term relief from pain with survival that exceeds five years. This seemingly modest goal is actually ambitious, given that today’s treatments achieve five-year survival in fewer than 33% of patients.7

Multidrug regimens used for the treatment of myeloma are diverse with regard to drug selection, dose-intensity, and toxicity. The most extensively studied multidrug regimens as shown in Table 1 include VBMCP (vincristine, carmustine [BCNU], melphalan, cyclophosphamide, and prednisone, patterned closely after the M-2 regimen) and VMCP/VBAP (vincristine, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, prednisone). The original reports of the M-2 regimen indicated a 78% response rate and 38-month median survival. An Eastern Cooperative Oncology Group (ECOG) study comparing VBMCP to MP corroborated the superiority of VBMCP over MP in producing objective responses (72% vs 51%, P<0.001) and superior median response duration (24 vs 18 months, P=0.007) but showed no difference in median survival (30 vs 28 months).6 Elderly bedridden patients had worse survival on VBMCP; however, the remaining
85% of patients had a significantly improved survival on VBMCP. The five-year survival for patients treated with VBMCP was 26% compared with 19% for MP. Hazard analysis reveals that the hazard of death is reduced by 29% with VBMCP compared with MP from year 3 to 6 ($P=0.02$) after which the apparent advantage dissipates. This treatment effect is most prominent in patients with stage I-II disease. While the survival advantage with VBMCP is marginal, a superiority of VBMCP over MP in producing and maintaining objective responses is apparent. Over 90% of objective responses with either regimen were associated with documented symptomatic improvement. Therefore, the higher response rate with VBMCP reflected superior palliative treatment for most patients.

The Southwest Oncology Group (SWOG) found that the alternating cycle regimen VMCP/VBAP produced significantly more objective responses than MP and that the more intense regimen had a survival advantage as well. The median survival on a more recent VMCP/VBAP report is 30 months, similar to VBMCP. A study reported by the Medical Research Council (MRC) of a Great Britain trial comparing doxorubicin, BCNU, cyclophosphamide, and melphalan (ABCM) to MP (or melphalan alone) also showed significant survival advantage for the more intensive ABCM regimen. ABCM is essentially the VMCP/VBAP regimen with the vincristine and prednisone deleted.

These three multi-institutional controlled trials represent more than 1,300 patients randomized to either single-agent melphalan with or without prednisono or to a more intensive combination chemotherapy regimen. They demonstrate an improved response rate and duration for the more intensive regimen over MP and at least a modest survival benefit expressed as a consistently higher rate of long-term survival (Table 2).

### Table 1: Regimens for Initial Treatment of Multiple Myeloma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Drugs</th>
<th>Schedule</th>
<th>Cycle (days)</th>
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<tbody>
<tr>
<td>3, 4, 6</td>
<td>MP</td>
<td>M 8 mg/m² po d 1-4</td>
<td>28</td>
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<tr>
<td></td>
<td></td>
<td>P 75 mg po d 1-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6, 8</td>
<td>VBMCP</td>
<td>V 1.2 mg/m² iv d 1</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 20 mg/m² iv d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>M 8 mg/m² po d 1-4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>C 400 mg/m² iv d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P 40 mg/m² po d 1-7, then 20 mg/m² po d 8-14 (cy 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9, 10</td>
<td>VMCP/VBAP (alternating cycles)</td>
<td>V 1 mg/m² iv d 1</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VMCP</td>
<td>M 6 mg/m² po d 1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C 125 mg/m² po d 1-4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>P 60 mg/m² po d 1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>VBAP</td>
<td>V 1 mg/m² iv d 1</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 30 mg/m² iv d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A 30 mg/m² iv d 1</td>
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<tr>
<td></td>
<td></td>
<td>P 60 mg/m² po d 1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13, 14, 15</td>
<td>ABCM (alternating cycles)</td>
<td>A 30 mg/m² iv d 1</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B 30 mg/m² iv d 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C 100 mg/m² d 1-4</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>M 6 mg/m² d 1-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13, 14, 15</td>
<td>VAD*</td>
<td>V 0.4 mg iv d 1-4 (continuous infusion)</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A 10 mg/m² d 1-4 (continuous infusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>D 40 mg po d 1-4, 9-12</td>
<td></td>
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</table>

M = melphalan  
P = prednisone  
A = Adriamycin  
B = BCNU  
C = cyclophosphamide  
D = dexamethasone  
V = vincristine  
*Trimethoprim/sulfamethoxazole-DS recommended twice daily, d 10-20.

### Table 2: Combination Therapy vs M/MP: Three Major Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th>Combination</th>
<th>Control</th>
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These three multi-institutional controlled trials represent more than 1,300 patients randomized to either single-agent melphalan with or without prednisone or to a more intensive combination chemotherapy regimen. They demonstrate an improved response rate and duration for the more intensive regimen over MP and at least a modest survival benefit expressed as a consistently higher rate of long-term survival (Table 2).
Other trials, mostly smaller, failed to show a therapeutic advantage of various combination therapy regimens over MP. An attempt was made to resolve this issue through a meta-analysis based on 18 published trials composed of 3,814 patients comparing combination chemotherapy regimens to MP. Two-year survival was 55.5% with combination chemotherapy and 57.5% with MP. Based on this finding, the meta-analysis was interpreted as showing no overall difference in efficacy between combination chemotherapy and MP.

The meta-analysis was carefully performed, but two problems argue against using its findings to determine the relative merits of MP vs more intensive multi-agent chemotherapy. First, because of the variable follow-up available, the meta-analysis was entirely based on two-year survival. As already discussed, this is not the primary goal of treatment for myeloma. Comparison is more useful when based on endpoints that represent the central treatment goals. In this case, longer-term survival (eg, five years) would have been a better endpoint. Quality of life or durable control of disease manifestations would also be pertinent, but such data are not available in most clinical trial reports. The second problem pertains to the way in which the issue is framed. Combination chemotherapy includes a diverse group of treatment regimens. Many are more intensive than MP, but some are equal and a few may actually represent less intensive treatment than the MP to which they are compared. The published meta-analysis includes all published randomized trials that compared combination chemotherapy with MP. Selection of trials was not readily possible within the constraints of meta-analysis without risk of introducing bias. However, the clinically relevant issue is not whether combination chemotherapy is superior to melphalan or MP. Rather, it is to determine whether more intensive treatment regimens composed of combinations of drugs are a better treatment choice than standard MP or melphalan alone.

The problem of attempting a clinically relevant meta-analysis that compares the more intensive combination chemotherapy regimens to MP without introducing bias may not be soluble. At this time, available data suggest that for patients who can tolerate it, treatment with a moderately intensive combination chemotherapy regimen may offer the surest way to reach and maintain a plateau without undue toxicity and may offer a modest advantage in long-term survival.

The VAD regimen consisting of vincristine, doxorubicin, and dexamethasone (Table 1) has been reported to yield response rates comparable to other combination chemotherapy regimens in previously untreated patients. Two positive attributes of this regimen are its rapid onset of response and its tendency to cause less damage to bone marrow progenitors. Follow-up is still relatively short, and it is not yet proven whether VAD produces long-term results comparable or better than those of the other intensive combination regimens. Its tendency to spare marrow progenitors recommends VAD for patients in whom autologous bone marrow or stem-cell transplant is contemplated.

Interferon

The role of interferon (IFN) and high-dose therapy with bone marrow or peripheral blood stem-cell transplantation in myeloma is well reviewed elsewhere in this issue. I will briefly address their impact on current standard therapy. Most clinical trials in myeloma have utilized recombinant interferon(IFN)- . IFN is active as a single agent in patients with newly diagnosed myeloma and in patients with relapsed or refractory disease. However, the response rates are low -- inferior to those obtained with standard chemotherapy and the role of IFN as single-agent induction is limited to occasional patients with relapsed or refractory disease.

Although IFN is weak when used as a single-induction agent, it has been combined with VBMCP as alternating cycles to increase the rate of complete response (CR) and the response duration. Another study combining MP with IFN given simultaneously and mid-cycle showed a response benefit with IFN and an apparent survival increase in some patient subsets. Will the improved response duration and increased rate of CR with IFN induction regimens be confirmed, and are these benefits of sufficient magnitude to be worth the added toxicity and expense? A meta-analysis by the Myeloma Trialists and an ongoing phase III ECOG study address the issues of response duration, CR rate, and overall survival. The meta-analysis results will be presented at the American Society of Clinical Oncology meeting in May 1998. At present, it seems clear that IFN
does not have an established role in the standard induction therapy of multiple myeloma, but the possibility that it may be an effective way to induce many more CRs is promising lead for future treatment development.

Most trials in maintenance therapy indicate that IFN prolongs response duration. Some show significantly increased survival, others show a non-significant trend in that direction, and some show no difference. Few, if any, suggest a decreased survival with IFN. The recently reported meta-analysis demonstrated a significant benefit in the form of improved relapse-free survival and overall survival for patients treated with IFN, either in induction or maintenance-phase therapy. A reasonable approach would be to administer maintenance-phase IFN at 3 MU/m² for 24 months or until relapse.

**Duration of Therapy and Maintenance**

Maintenance chemotherapy increases response duration but not survival. Prolonged chemotherapy in myeloma carries a substantial risk on leukemia and myelodysplastic syndrome that could be related to cumulative exposure. Interferon maintenance appears to improve response duration and may prolong survival. Furthermore, there is no evidence that IFN maintenance is leukemogenic in contrast to prolonged administration of most chemotherapy regimens. Therefore, the choice of IFN maintenance seems to represent a reasonable option to consider for patients who can tolerate it without undue toxicity, particularly fatigue. Issues remain to be clarified regarding what types of myeloma are associated with the greatest IFN benefit and whether IFN responsiveness is related in any way to tumor burden. Ultimately, the decision regarding IFN maintenance will be based on whether the magnitude of benefit is worth the toxicity and expense to the individual patient.

**High-Dose Therapy With Autologous Stem-Cell Rescue in the Standard Treatment of Myeloma**

Theoretically, high-dose therapy with alkylating agents or alkylating agents plus total body irradiation might eradicate the myeloma clone or reduce it to levels that would allow a lengthy CR. Unfortunately, data available at this time suggest the possibility that no myeloma patients are cured with current autologous transplantation techniques. Data reported by the Intergroupe Francais du Myelome (IFM), recently updated, demonstrate improved CR rate, event-free survival, and overall survival with an autologous bone marrow transplant regimen vs conventional chemotherapy as initial induction treatment. Ongoing studies by another group in France and by the US Intergroup trial are both evaluating whether high-dose therapy with autologous stem-cell rescue is better when applied early in first remission or after first relapse. Overall, the median survival is close to five years in most reports with early high-dose therapy with autologous stem-cell rescue, including the IFM report. It is therefore interesting that when the Spanish Cooperative Group for the Study of Hematological Malignancies Treatment (PETHEMA) retrospectively examined their potential candidates for early high-dose therapy with stem-cell rescue who were treated with conventional chemotherapy, they also found a five-year median survival.

The role of high-dose therapy with stem-cell rescue early in first remission is not yet clear but might be resolved when the results of ongoing studies are available. With improvements in supportive care, the procedure is becoming safer at qualified centers. If the expense continues to decrease and the efficacy is established as superior to conventional chemotherapy, high-dose therapy might be a reasonable four- to six-week alternative induction of plateau phase that would provide more frequent complete responses, and it could prove to be easier and possibly safer than one to two years of conventional treatment.

The current lack of curative potential highlights the importance of studying the biology and treatment of the minimal residual disease (MRD) that remains after induction of CR. With high-dose therapy as an increasingly effective debulking mechanism, new approaches to more effective control of MRD will lead to prolonged objective response and CR, improved survival, and possibly cure.

**Relapsed or Refractory Disease**

Patients who undergo relapse six to 12 months after discontinuing therapy are usually successfully reinduced with the original regimen. The VAD regimen is also effective in this setting. However, second remissions of greater than 12 months are the exception. In patients who are suitable candidates, high-dose therapy with stem-cell rescue can be highly effective and is perhaps more likely to yield a response duration that exceeds one year. It should be strongly considered in young patients in first relapse and in patients under 70 years of age who have disease progression through their initial induction regimen. It is not likely to be effective in patients with late myeloma who have been exposed to extensive treatment with multiple regimens.

VAD is the treatment chosen for most patients with relapsed myeloma. VAD has been given as three- or four-week cycles. The dexamethasone may be limited to the first four days of each cycle, but it is frequently given in four-day courses beginning on day 1 and day 9 (and, in four-week cycles, on day 17). The number of dexamethasone courses per cycle should be diminished once response is reached. Some have recommended prophylactic antibiotics with VAD. Response rates to VAD after first relapse are approximately 40%. It is a good regimen to use to induce a second response if high-dose therapy with autologous stem-cell transplantation is planned.

High doses of alkylating agents or cortico-steroids have been used with some short-term success in patients with resistant myeloma. High-dose cyclophosphamide at 600 mg/m² daily on days 1 through 4 should be used with granulocyte colony-stimulating factor (G-CSF) support starting on day 5. This regimen is relatively platelet sparing and can be given as repeated in four- to five-week cycles. G-CSF could theoretically improve the efficacy of high-dose cyclophosphamide that, as originally reported, was given for only one or two cycles prior to the availability of growth factor support. For patients with marked bone marrow impairment, high-dose melphalan/prednisolone may provide good palliation. In this regimen, melphalan/prednisolone is administered at a dose of 2 g intravenously three times a week for eight weeks, then at 2 g weekly. The response rate in a small series of heavily pretreated patients was 35%. Interferon, either alone or in combination with corticosteroids, has also been effective in some patients with resistant disease. While current efforts are actively evaluating agents designed to overcome multidrug resistance, such agents are not yet part of standard treatment.

**Supportive Care**

Recent advances have emerged in three important areas of supportive care of myeloma patients: bone marrow failure, infection, and skeletal destruction.

Bone marrow failure, particularly in the form of anemia and later treatment- and disease-induced neutropenia, has a major deleterious impact on the well being of the patient and on the course of disease. Anemia occurs in most myeloma patients, and when severe, it markedly contributes to weakness, fatigue, and loss of function. Previously, many myeloma patients became dependent on transfusions. It is now possible to treat patients with severe anemia with recombinant human erythropoietin at a dose of 150 to 300 U/kg subcutaneously three times per week and achieve good responses in 50% or more. It is often possible to avoid the need for blood transfusions. Response rates are best in patients with low or suboptimally elevated levels of endogenous erythropoietin. Neutropenia, usually mild at diagnosis, frequently supervenes and becomes chronic as a result of treatment toxicity and progressive disease. It may severely limit the ability to deliver effective doses of chemotherapy. When this occurs, the prophylactic use of G-CSF may allow effective chemotherapy and can be crucial in allowing the patient to tolerate regimens such as VAD.
as high-dose cyclophosphamide.

Patients with multiple myeloma are at increased risk for infection. Clinically significant infections occur at an average rate of nearly 1.5 infections per year over the clinical course of myeloma. During the first two months of initial chemotherapy, the incidence is at least twofold higher. These early infections have a high mortality rate, and patients who recover often have severe disruption of their chemotherapy regimen that diminishes the likelihood of a good response. In a prospective, randomized study involving 57 patients, prophylactic administration of a double-strength tablets of trimethoprim-sulfamethoxazole every 12 hours for the first 60 days of initial chemotherapy decreased the bacterial infection rate by 88%. Studies are currently in progress to confirm this finding and to compare trimethoprim-sulfamethoxazole to ciprofloxacin or ofloxacin. Pending the results of these, it is reasonable to use prophylactic trimethoprim-sulfamethoxazole for the first two months of initial chemotherapy in patients who are not sulfa-allergic.

Skeletal destruction is a major cause of morbidity, functional loss, and mortality in multiple myeloma. In patients with lytic bone disease, treatment with 90 mg of intravenous pamidronate (four-hour infusion) administered monthly has been shown to reduce the incidence of skeletal events including pathologic fracture, as well as the need for radiotherapy or surgery to bone and spinal cord compression. The reduction in skeletal events is almost 50% and persists over the 21 months of observation to date. Pamidronate is also useful in the treatment of hypercalcemia. Further work in progress with newer, more powerful bisphosphonates promises continued improvement in the control of myeloma bone disease.

References


From the Virginia Piper Cancer Institute, Minneapolis, Minn.

Address reprint requests to Martin M. Oken, MD, Director, Virginia Piper Cancer Institute, Abbott Northwestern Hospital, 800 East 28th St, Minneapolis, MN 55407-3799.