

1183

## Management of Multiple Myeloma Today

Kenneth C. Anderson, Terry J. Hamblin, and Ann Traynor

Multiple myeloma is almost invariably fatal despite a wide variety of chemotherapeutic and supportive treatment options. There are several unresolved problems with existing approaches, including the specific indications for treatment; the optimal combination of agents and doses; and the type, frequency, and timing of high-dose therapy and stem-cell transplantation. High-dose chemotherapy followed by stem-cell transplantation produces higher remission rates, but patients rarely, if ever, are cured by a single regimen. Allogeneic hematopoietic stem-cell transplantations offer a potential graft-versus-myeloma (GVM) effect. Researchers are focusing efforts on improving the safety of transplant procedures, increasing response rates to ablative therapy, and testing novel posttransplant options to improve outcomes. The newly devised National Comprehensive Cancer Network (NCCN) guidelines for treating multiple myeloma are also discussed.

*Semin Hematol* 36(suppl 3):3-8. Copyright © 1999 by W.B. Saunders Company.

**M**ULTIPLE MYELOMA IS A DISEASE in which malignant plasma cells derived from a single plasma cell clone accumulate in the bone marrow. It affects four of every 100,000 persons in the United States.<sup>1</sup> The disease is more common in African Americans than in Caucasians, and the male to female ratio is 3:2. The median age at diagnosis is 65 years.<sup>2</sup> The cause of multiple myeloma is unknown; however, radiation, exposure to environmental toxins, and a genetic component are considered possibilities.<sup>3</sup>

Currently available treatments often produce temporary remissions, but multiple myeloma consistently follows a progressive, ultimately fatal course (Fig 1). Approximately 25% of patients survive 5 years or longer, but fewer than 5% live more than 10 years.<sup>3</sup> For decades, the standard treatment for overt symptomatic disease has been chemotherapy. The standard regimen was melphalan and prednisone (MP), which induced an objective response in up to 60% of patients. Remissions typically lasted 2 years and were followed by a relapse. In an attempt to improve efficacy, various combination regimens, including vinca alkaloids, nitrosoureas, and anthracyclines (Table 1), have been tested.<sup>2</sup> However, there has been considerable controversy about whether any of the newer regimens is more effective than MP.

More recently, the treatment approach has been modified to include high-dose chemotherapy accompanied by hematopoietic stem-cell support via

autologous or allogeneic transplant. Although they frequently provide excellent remissions, these procedures carry a significant risk of morbidity and mortality in themselves. A variety of strategies for improving the results while minimizing the risks of these procedures are currently being investigated. Interferon- $\alpha$  (IFN- $\alpha$ ) has been administered after both standard- and high-dose chemotherapy, but there is some debate about its benefits.<sup>2</sup>

Improved understanding of the immunoregulatory mechanisms that contribute to the development of multiple myeloma, particularly the role of cytokines and dendritic cells, has led to alternate treatment approaches. Researchers are currently testing the efficacy of adoptive immunotherapy, monoclonal antibody serotherapy, and idiotypic and DNA vaccines.

### CURRENT ISSUES IN TREATMENT OF MULTIPLE MYELOMA

#### *Conventional Versus Combination Chemotherapy*

Dr Terry Hamblin, of Southampton, UK, reviewed outstanding issues in the treatment of multiple myeloma. Questions about the benefits of traditional MP chemotherapy were raised in a 1992 Medical Research Council (MRC) study, which reported that ABCM (doxorubicin, carmustine, cyclophosphamide, and melphalan) had significant survival advantages over melphalan alone.<sup>10</sup> However, those findings are at odds with the results of other studies comparing melphalan with combination chemotherapy. The absence of corticosteroids from the British regimen probably explains the discrepancy. A meta-analysis of studies of 4,000 patients (not including the MRC trial) found no difference between MP and various multiple chemotherapy regimens.<sup>11</sup> The VAD regimen (vincristine, doxorubicin, and dexamethasone) is generally used in the United Kingdom in patients under age

From the Dana Farber Cancer Institute, Boston, MA; Department of Haematology and Oncology, Royal Bournemouth Hospital, Bournemouth, UK; and Northwestern University, Chicago, IL.

Address reprint requests to Kenneth Anderson, MD, Dana Farber Cancer Institute, 44 Binney St, Room DL189, Boston, MA 02115.

Copyright © 1999 by W.B. Saunders Company  
0037-1963/99/3601-3002\$10.00/0



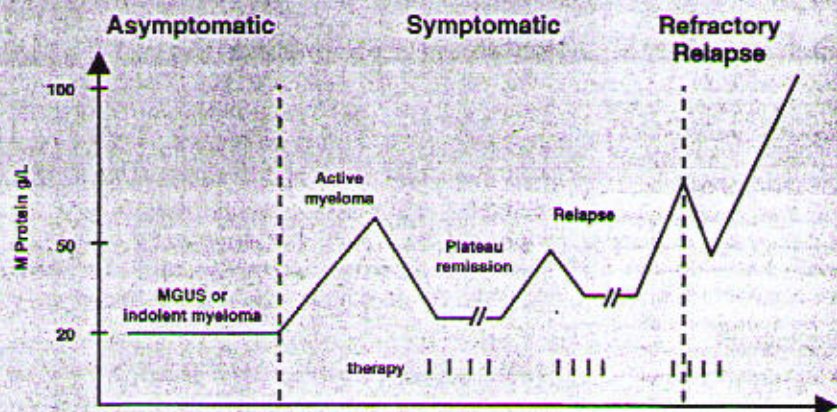


Fig 1. Schematic representation of the disease course of multiple myeloma over time. In most cases, the disease originates as monoclonal gammopathy of unknown significance (MGUS) or indolent myeloma, and the patient is asymptomatic. As the disease progresses, the M-protein level increases, and characteristic symptoms such as bone pain develop. Initially, the disease usually responds to chemotherapy. Over time, however, the disease recurs and chemotherapy is no longer effective. Adapted with permission.<sup>25</sup>

70 for a rapid response, although the likelihood of early relapse is recognized.<sup>12</sup>

#### Conventional Versus High-Dose Chemotherapy

The introduction of high-dose (140 mg/m<sup>2</sup>) melphalan by Selby et al produced a higher rate of remissions than had been experienced previously.<sup>13</sup> However, in patients achieving complete responses, the paraprotein could still be detected by immunofixation, and patients began relapsing by 18 months. At present, 20% to 30% of patients may have a complete response with high-dose chemotherapy.<sup>2</sup> The use of autologous bone marrow transplant (ABMT) and peripheral blood stem-cell transplantation (PBSCT) following high-dose chemotherapy has facilitated the use of more ablative regimens safely and may serve to improve survival rates and allow dose escalation, which may improve remission rates.

A nationwide, randomized trial in France of 200 multiple myeloma patients who received two courses of VMCP (vincristine, melphalan, cyclophosphamide, and prednisone) alternating with VBAP (vincristine, carmustine, doxorubicin, and prednisone) and then were randomized to receive either conventional chemotherapy (eight additional courses of VMCP/VBAP) or high-dose therapy (melphalan and total-body irradiation) followed by ABMT reported a significantly better remission rate and survival in the latter group.<sup>14</sup> With further follow-up evaluation, however, the difference between the two groups diminished. Although this study is encouraging, it is unlikely that patients will be cured after a single high-dose and stem-cell autografting regimen. An essential question is which patients should undergo this treatment approach.

The current MRC-7 trial compares, in patients

under 65 years, ABCM plus IFN- $\alpha$  maintenance with C-VAMP (cyclophosphamide, vincristine, doxorubicin, and methylprednisolone) to maximal response (at least three cycles) followed by high-dose melphalan (200 mg/m<sup>2</sup> plus methylprednisolone 1.5 g/d  $\times$  4) with ABMT or PBSCT followed by IFN- $\alpha$  maintenance.

#### Allogeneic Versus Autologous Transplantation

Allogeneic stem-cell transplantation dramatically reduces tumor mass, with complete response rates of approximately 40%.<sup>3</sup> However, even in human leukocyte antigen-identical siblings, the risk of significant complications and death is at least 20%; and, in some populations, the transplant-related mortality may be 40%. To reduce the risk of graft-versus-host disease, researchers at Dana Farber Cancer Institute are using CD6-depleted allografts obtained from histocompatible sibling donors. Initial results show a 29% complete response and a 55% partial response rate, with a mortality rate of 8%.<sup>15</sup>

Autologous transplantation has a relapse pattern similar to that seen with conventional chemotherapy. Attempts to deplete tumor cells from the autografts prior to transplantation include selection of normal hematopoietic progenitor cells by virtue of CD34 expression or multiparameter cell sorting.<sup>3</sup> At the Dana Farber Cancer Institute, high-dose chemotherapy and autologous hematopoietic stem-cell transplant (including monoclonal antibody-purged bone marrow or CD34<sup>+</sup> PBSCT, either of which depletes 3 logs of tumor cells) were performed in 105 patients. The results showed 30% of patients with complete response, 63% with partial response, 3% with no response, and one transplant-related death. Recent studies suggest



Table 1. Protocols in the Treatment of Multiple Myeloma

Drugs	Cycle	Dose
MP	4-6 weeks	Melphalan 8 mg/m <sup>2</sup> PO days 1-4 Prednisone 50-60 mg/m <sup>2</sup> PO days 1-4
VAD	4 weeks	Vincristine 0.4 mg/d IV day 1 Doxorubicin 9 mg/m <sup>2</sup> /d days 1-4 Dexamethasone 20 mg/m <sup>2</sup> /d PO days 1-4; days 9-12; days 17-20
VAMP	4 weeks	Vincristine 0.4 mg/d IV days 1-4 Doxorubicin 9 mg/m <sup>2</sup> IV days 1-4 Methylprednisolone 1 g/m <sup>2</sup> IV or PO daily
VBMCP	5 weeks	Vincristine 1.2 mg/m <sup>2</sup> IV day 1 BCNU (carmustine) 20 mg/m <sup>2</sup> IV day 1 Melphalan 8 mg/m <sup>2</sup> PO days 1-4 Cyclophosphamide 400 mg/m <sup>2</sup> IV day 1 Prednisone 20 mg/m <sup>2</sup> PO days 1-14
VMCP	3 weeks	Vincristine 1 mg/m <sup>2</sup> IV day 1 Melphalan 6 mg/m <sup>2</sup> PO days 1-4 Cyclophosphamide 125 mg/m <sup>2</sup> PO days 1-4 Prednisone 60 mg/m <sup>2</sup> PO days 1-4
VBAP	3 weeks	Vincristine 1 mg/m <sup>2</sup> IV day 1 BCNU 30 mg/m <sup>2</sup> IV day 1 Doxorubicin 30 mg/m <sup>2</sup> IV day 1 Prednisone 60 mg/m <sup>2</sup> PO days 1-4
ABCM	6 weeks	Doxorubicin 30 mg/m <sup>2</sup> IV day 1 BCNU 30 mg/m <sup>2</sup> IV day 1 Cyclophosphamide 100 mg/m <sup>2</sup> PO days 21-24 Melphalan 6 mg/m <sup>2</sup> PO days 21-24
PCAB	4 weeks	Prednisone 60 mg/m <sup>2</sup> PO days 1-5 Cyclophosphamide 600 mg/m <sup>2</sup> IV day 1 Doxorubicin 30 mg/m <sup>2</sup> IV day 1 BCNU 30 mg/m <sup>2</sup> IV day 1
HDM	1 cycle	High-dose melphalan 140-200 mg/m <sup>2</sup>

NOTE. This table does not represent an all-inclusive list of protocols available to treat multiple myeloma. Drug doses and cycle times may vary.

Abbreviations: PO, orally; IV, intravenously.

Data from Joshua and Gibson,<sup>4</sup> Oken,<sup>5</sup> Oken et al,<sup>6</sup> Balmer and Valley,<sup>7</sup> Weaver et al,<sup>8</sup> and Raju et al.<sup>9</sup>

that depletion of greater than 6 logs multiple myeloma cells may be achieved using selective adenoviral vectors to transfect the thymidine kinase (TK) gene followed by ganciclovir treatment.

#### Tandem Transplant and Posttransplant Treatments

Single autografts do not produce a plateau in survival curves, and tandem autografts have been

proposed as a means to improve outcome.<sup>16</sup> Preliminary reports from the French group indicate no greater benefit of two autografts over one.<sup>17</sup> Designs of two-versus-one trials are proceeding in the United Kingdom.

To improve outcome, one posttransplant strategy is to enhance autoimmunity against multiple myeloma cells. Researchers from the Dana Farber Cancer Institute have fused myeloma cells with dendritic cells (MM-DC). This fusion product preserves the function of dendritic cells and presents the antigenic profile of the myeloma cell when used in vaccination studies. They have demonstrated that MM-DCs can inhibit the induction of multiple myeloma in syngeneic mouse models and prolong survival in animals with multiple myeloma. Trials are under way to test the safety and efficacy of MM-DC vaccinations in humans.

To improve outcome of allogeneic stem-cell transplantation, researchers from the Dana Farber Cancer Institute and other centers are testing post-transplant strategies to enhance a potential graft-versus-myeloma (GVM) effect. The observation of a T-cell expansion concurrent with GVM was the rationale for using a CD8<sup>+</sup>-depleted donor lymphocyte infusion as a posttransplant treatment. Although the data are preliminary, they are currently characterizing T-cell clones mediating GVM, with the potential for ex vivo expansion and adoptive therapy.

#### Interferon- $\alpha$

Whether IFN- $\alpha$  therapy benefits patients with multiple myeloma is not yet known definitively. The cytokine IFN- $\alpha$  interferes with plasma cell growth and has been studied as maintenance therapy. Prolonged remissions were obtained with IFN- $\alpha$  in an Italian trial,<sup>18</sup> but subsequent studies gave conflicting results. In the MRC trial, IFN- $\alpha$  2b given during the plateau phase after ABCM chemotherapy did not prolong survival, and the trend toward a longer plateau phase was not significant.<sup>19</sup> Despite the modest benefits that IFN- $\alpha$  may offer, it is associated with significant side effects, such as fatigue, flu-like syndrome, and thrombocytopenia. An overview of 1,614 patients entered into 10 trials is under way, and this may clarify the therapeutic role of IFN- $\alpha$ .

#### Bisphosphonates

Multiple myeloma is characterized by destruction of bone. This can lead to spinal cord compres-







sonable practice and suggest areas where peer-reviewed trials are necessary to improve practice.

For example, in drawing up guidelines for the treatment of multiple myeloma (Fig 2), the NCCN myeloma committee acknowledged several recent publications applicable to supportive care in myeloma. Therefore, bisphosphonate therapy is listed as a standard supportive care for multiple myeloma with radiographic evidence of skeletal disease (Table 2). There is no set duration indicated for bisphosphonate therapy, because no decline in the benefit of bisphosphonate therapy has been shown. Bisphosphonate therapy is also listed in the guidelines for smoldering, or stage I, myeloma as an appropriate investigational therapy. This acknowledges that this class of agents could delay the development of active disease and that this has not yet been established in a prospective randomized study. The guidelines, therefore, state that stage I myeloma should be treated with a bisphosphonate within the context of a clinical trial.

The panel considered both conventional- and high-dose therapy approaches to myeloma. Based on a prospective, randomized trial that suggested a significant survival advantage to high-dose versus conventional therapy, the NCCN guidelines consider this appropriate practice.

Adjuvant therapy, following remission induction or stem-cell transplantation, remains a key focus of clinical research in the treatment of myeloma and other neoplasias. The NCCN guidelines for myeloma management acknowledge this by emphasizing clinical trials that evaluate adjuvant therapy after every established intervention. Likewise, the standard of care for relapsed, refractory myeloma should be

Table 2. NCCN Supportive Care Practice Guidelines for Multiple Myeloma

- Bone disease
  - Bisphosphonates
    - Patients with documented bone disease including osteopenia
      - Protocol use of bisphosphonates in earliest stage disease
      - Bone survey yearly
      - Bone densitometry or metabolic studies reserved for protocol
  - Radiation therapy
    - Low-dose radiation therapy as palliative treatment for uncontrolled pain, for impending pathologic fracture, or impending cord compression
    - Radiation doses should not preclude future total-body irradiation
  - Orthopedic consultation for impending fractures in weight-bearing axis or bony compression of spinal cord or vertebral column instability
- Hypercalcemia
  - Hydration and steroids supplemented with furosemide and bisphosphonates
- Hyperviscosity
  - Plasmapheresis as adjunctive therapy for symptomatic hyperviscosity
- Anemia
  - Erythropoietin considered for anemic patients with inappropriately low endogenous erythropoietin levels for the degree of anemia, especially in the setting of renal failure
- Infection
  - Intravenous immunoglobulin therapy considered in the setting of recurrent life-threatening infection
- Renal dysfunction
  - Maintain hydration to avoid renal failure
  - Avoid use of nonsteroidal antiinflammatory drugs

treatment within the context of a clinical trial, since optimal therapy within this context is undefined.

## REFERENCES

1. Kyle RA, Beard CM, O'Fallon WM, et al: Incidence of multiple myeloma in Olmsted County, Minnesota: 1978 through 1990, with a review of the trend since 1945. *J Clin Oncol* 12:1577-1583, 1994
2. Bataille R, Harousseau J-L: Multiple myeloma. *N Engl J Med* 336:1657-1664, 1997
3. Anderson K, Kyle RA, Berenson J: Lymphoproliferative disorders: Multiple myeloma, in *Hematology—1997. The Education Program of the American Society of Hematology*. San Diego, CA, December 5-9, 1997, pp 177-188
4. Joshua DE, Gibson J: Diagnosis and treatment of multiple myeloma, in Wiernik PH, Canellios GP, Dutcher JP, et al (eds): *Neoplastic Diseases of the Blood* (ed 3). New York, NY, Churchill Livingstone, 1996, pp 571-572
5. Oken MM: Standard treatment of multiple myeloma. *Mayo Clin Proc* 69:781-786, 1994
6. Oken MM, Harrington DP, Abramson DO, et al: Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma: Results of the Eastern Cooperative Oncology Group Study E2479. *Cancer* 79:1561-1567, 1997
7. Balmer C, Valley AW: Basic principles of cancer treatment and cancer chemotherapy, in Dipeiro JT, Talbert RL, Yee GC, et al (eds): *Pharmacotherapy: A Pathophysiologic Approach* (ed 3). Stamford, CT, Appleton & Lange, 1997, pp 2435-2440
8. Weaver CH, Zhen B, Schwartzberg LS, et al: Phase I-II



- evaluation of rapid sequence tandem high dose melphalan with peripheral blood stem cell support in patients with multiple myeloma. *Bone Marrow Transplant* 22:245-251, 1998
9. Raje N, Powles R, Kulkarni S, et al: A comparison of vincristine and doxorubicin infusional chemotherapy with methylprednisolone (VAMP) and the addition of weekly cyclophosphamide (C-VAMP) as induction treatment followed by autografting in previously untreated myeloma. *Br J Haematol* 97:153-160, 1997
  10. MacLennan ICM, Chapman C, Dunn J, et al: Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. *Lancet* 1:200-205, 1992
  11. Gregory WM, Richards MA, Malpas JS: Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma: An overview of published trials. *J Clin Oncol* 10:334-342, 1992
  12. Barlogie G, Smith L, Alexanian R: Effective treatment of advanced multiple myeloma refractory to alkylating agents. *N Engl J Med* 310:1353-1356, 1984
  13. Selby PJ, McElwain TJ, Nandi AC, et al: Multiple myeloma treated with high dose intravenous melphalan. *Br J Haematol* 66:55-62, 1987
  14. Attal M, Harousseau J-L, Stoppa A-M, et al: A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med* 335:91-97, 1996
  15. Seiden M, Schlossman R, Andersen J, et al: Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Leuk Lymphoma* 17:87-93, 1995
  16. Vesole DH, Barlogie B, Jagannath S, et al: High dose therapy for refractory multiple myeloma: Improved prognosis with better supportive care and double transplants. *Blood* 84:950-956, 1994
  17. Attal M, Payen C, Facon T, et al: Single versus double transplant in myeloma: a randomized trial of the "Inter Groupe Français du Myelome." *Blood* 90:1859A, 1997 (suppl 1, abstr)
  18. Mandelli F, Arvisi G, Amadori S, et al: Maintenance therapy with recombinant interferon alfa 2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 322:1430-1434, 1990
  19. Drayson MT, Chapman CE, Dunn JA, et al: MRC trial of  $\alpha 2b$ -interferon maintenance therapy in first plateau phase of multiple myeloma. *Br J Haematol* 101:195-202, 1998
  20. Kyle RA: Multiple myeloma: Review of 869 cases. *Mayo Clin Proc* 50:29-40, 1975
  21. McCloskey EV, MacLennan ICM, Drayton MT, et al: A randomized trial of the effect of clodronate on skeletal morbidity in multiple myeloma. *Br J Haematol* 100:317-325, 1998
  22. Berenson JB, Lichtenstein A, Porter L, et al: Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *N Engl J Med* 334:488-493, 1996
  23. Durie BGM: Multiple myeloma: A concise review of the disease and treatment options (booklet). Los Angeles, CA, International Myeloma Foundation.