

Multiple Myeloma: Current Perspectives on Therapeutic Management

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Introduction

Multiple myeloma is a disseminated monoclonal plasma cell malignancy in which the tumor cell progenitors circulate in the peripheral blood but home to and reside primarily in the bone marrow and adjacent bone. The median age at diagnosis in the U.S. is in the range of 62-65 and 70 in Scandinavia. Growth promotion of myeloma is stimulated by interleukin-6 and other cytokines. There appears to be a strong paracrine relationship between non-neoplastic macrophages and osteoclasts in the bone marrow and the growth and invasiveness of tumor cells into bone matrix. Bone erosion is mediated by osteoclasts under the influence of pro-inflammatory cytokines. Common presenting features include weakness due to anemia and bone pain. Laboratory findings typically include the presence of a monoclonal Ig in the serum (IgG, IgA, IgD or IgE) and/or the presence of either kappa or lambda light chain dimers in the urine. Hypercalcemia and/or renal failure may also be identified by laboratory findings, and evidence of osteolytic bone lesions or osteoporosis is identifiable on radiologic studies. Bone scans are not recommended as they are of little or no value in myeloma as the disease is largely osteolytic, whereas radionuclides used for bone scanning are taken up only into areas of osteoblastic activity. The only imaging procedure that is more sensitive than standard x-rays is magnetic resonance imaging (MRI). MRI is capable of detecting myelomatous involvement in the spine even in instances where the bone x-rays are normal. Accordingly, they are occasionally useful for distinguishing between the premalignant condition known as monoclonal gammopathy of unknown significance (MGUS) from multiple myeloma as there is an overlap in some instances in clinical presentation of MGUS and myeloma in patients who do not have laboratory abnormalities identifiable other than the presence of the monoclonal protein in the serum or urine, and whose standard skeletal x-ray surveys do not show abnormalities of myeloma. MRI is also useful for identifying extradural spinal cord compression by myelomatous lesions, although computerized tomography (CT) can also be used for this purpose. In an emergency, whichever procedure (MRI or CT) can be done most expeditiously should be chosen. Myeloma can be most simply staged with the use of the clinical staging system developed by Durie and Salmon,⁽¹⁾ although use of the serum beta-2 microglobulin can also be used for pretreatment evaluation or stratification. However, serum beta-2 macroglobulin results often take days to weeks to obtain, whereas clinical staging can usually be completed very rapidly and is often already available at the time of diagnosis.

Treatment

Standard Therapy for Remission Induction

Treatment for myeloma is indicated if the patient is symptomatic or if there are clear-cut signs that the disease is progressing aggressively. Therefore, treatment should be

considered optional (and often not indicated) for patients with stage I myeloma. The primary approach to remission induction therapy of myeloma is with systemic chemotherapy with alkylating agents (e.g., melphalan or cyclophosphamide) plus a glucocorticoid, although the VAD regimen (vincristine, doxorubicin and dexamethasone) represents a useful alternative for younger patients and induces more rapid remissions than standard alkylating agent therapy. High dose glucocorticoids alone can also be used for remission-induction therapy.

Although interferon- α (IFN- α) is known to have some activity in myeloma patients in relapse, the recombinant forms of IFN- α have had only limited study in previously untreated patients. Two randomized trials comparing initial therapy with IFN- α to chemotherapy have shown IFN- α monotherapy to be less active than standard chemotherapy.^(2,3) Recombinant IFN- α has also been integrated into combination chemotherapy with alkylating agent and prednisone combinations.⁽⁴⁾ This study as well as that by the Myeloma Group of Central Sweden failed to show overall benefit from the addition of IFN- α to melphalan-prednisone.⁽⁵⁾ Several more recent trials have also failed to show significant overall survival benefit in myeloma by adding IFN to commonly used multi-agent induction chemotherapy regimens. A trial conducted by the Eastern Cooperative Oncology Group (ECOG) evaluated the addition of IFN- α 2 or high-dose cyclophosphamide to the VBMCP regimen as compared to VBMCP. While this large randomized trial reported a higher “complete remission” rate with the IFN-containing combination as compared to VBMCP alone (17 vs. 10%), there was no difference in overall response or survival as compared to the other induction regimens tested.⁽⁶⁾ An additional recent randomized trial conducted in France⁽⁷⁾ using the VMCP/VBAP regimen with or without interferon- α also failed to show any benefit from the addition of IFN.

High-Dose Chemotherapy

For more than a decade, it has been clear that use of high-dose chemotherapy (e.g., with intravenous melphalan at 2-3 times the normal dosage range) either used alone or with autologous hematopoietic stem cell rescue could improve the apparent “complete remission” rate for patients with multiple myeloma in relapse.⁽⁸⁾ Such results have been obtained at the cost of the substantial toxicity associated with severe bone marrow aplasia, which routinely occurs after high-dose chemotherapy. A number of single institutions and groups have since conducted studies of high-dose chemotherapy with melphalan and/or other agents along with the use of hematopoietic growth factors and autologous hematopoietic stem cell rescue with peripheral blood stem cells (PBSC) or bone marrow stem cells (BMSC) or the combination for previously untreated patients with myeloma. Use of hematopoietic growth factors plus stem cells in general permits higher doses to be administered than with high-dose chemotherapy alone, and shortens the time required for recovery of bone marrow function after chemotherapy-induced marrow aplasia. These programs were initiated after it was determined that, in refractory patients, high-dose chemotherapy with autologous stem cell rescue could be initiated with a relatively low mortality rate associated with the procedure.⁽⁹⁻¹³⁾ A variety of regimens have been used in such high-dose chemotherapy efforts. In general, patients are first brought into at least a partial remission with combination chemotherapy (e.g., VAD),

after which hematopoietic stem cells are collected for subsequent engraftment. It is not clear whether tumor cell contamination of the autograft is more significant when PBSC or BMSC are utilized, although most groups now prefer the use of PBSC that are obtained and cryopreserved from leukopheresis collections after stem cell mobilization with high doses of cyclophosphamide and growth factor priming with either recombinant human granulocyte-monocyte colony-stimulating factor (GM-CSF) or recombinant human granulocyte colony-stimulating factor (G-CSF). In vitro techniques to enrich the graft for CD34+ hematopoietic stem cells as well as incubation of the cell suspension with anti-tumor drugs and/or monoclonal antibodies have been used in order to deplete the autograft of contaminating myeloma cells.⁽¹⁴⁾ Prior to performing the autologous transplant, the patient receives a “conditioning regimen” such as high-dose melphalan (HDM) (e.g., 140-180 mg/m²) either alone or combined with total body irradiation (e.g., 10 Gys).

The role of high-dose chemotherapy plus autologous or allogeneic stem cell transplantation remains controversial. However, a recent French trial suggests that high-dose chemotherapy with autologous stem cell rescue may be superior to standard chemotherapy.⁽¹⁵⁾ A large randomized U.S. intergroup trial (SWOG 9321) for patients of age 65 or younger is currently addressing the same question and is comparing induction therapy with VBMCP to high dose chemotherapy with autologous stem cell support. In general, because of toxicity, high-dose chemotherapy/autologous transplantation programs are restricted to patients under age 65 who show a favorable response to initial chemotherapy. Patients with other adverse factors (e.g., very high serum creatinine) are often also excluded. As age 65 is close to the median age at diagnosis (which usually ranges from 62-70 in various countries), the high-dose approach is currently something that can be considered for somewhat less than half of all newly diagnosed myeloma patients. Even within this subset of patients it will be important to evaluate relative efficacy, toxicity, and quality of life achieved with conventional versus high-dose chemotherapy with autologous stem cell rescue.

Allogeneic Bone Marrow Transplantation

Bone marrow transplantation (BMT) from a histocompatible donor has proven to be an effective means to achieve long-term disease control or cure in patients under age 55 with some forms of leukemia who have a histocompatible donor available.^(16,17) One of the potential benefits of allogeneic transplants above and beyond the high-dose therapy and stem cell rescue alone is the “allogeneic effect” which for certain neoplasms may include a “graft-versus-tumor reaction” in which donor lymphoid cells seek out and destroy residual tumor cells.^(18,19) Additionally, an allogeneic graft from a healthy donor does not have contaminating tumor cells. While only a relatively small minority of patients with myeloma fulfill current criteria for allografting, this is nonetheless a procedure worthy of evaluation in formal clinical trials involving suitable patients referred to recognized centers for bone marrow transplantation.⁽²⁰⁾ The European Registry for Blood and Bone Marrow Transplantation recently analyzed prognostic factors important for outcome after transplantation from a total of 162 myeloma patients who had allotransplants from human leukocyte antigen (HLA)-compatible siblings between 1983 and 1993 at a large number of cooperating hospitals that provided data to the registry.⁽²¹⁾

The report includes a heterogeneous patient population including myeloma patients treated with different stages or timing of transplant during the course of their disease, as well as varying induction chemotherapy, conditioning regimens and treatments for graft-versus-host disease, etc. Forty-four percent of patients achieved complete remission, but there was a high early mortality rate with about half of the patients dying during the first year after BMT. Actuarial survival was 32 percent at 4 years and 28 percent at 7 years. While the time from diagnosis to transplant was not significant for survival, patients who were transplanted later than six months from diagnosis tended to do worse than those who were transplanted earlier. The most important adverse factor was the development of grade III or IV graft-versus-host disease. The results reported with allogeneic BMT for stage I patients with alloBMT appear to be inferior to reported results of standard chemotherapy, where the median survival for stage I myeloma is in the range of seven years. Follow-up is insufficient to determine whether outcome is better with BMT than with more conservative therapy and whether patients receiving BMT for myeloma can be cured with this procedure as they can be with chronic myeloid leukemia. A major issue for stage I patients is whether any therapy should be employed until clear evidence of symptomatic disease progression occurs.

Remission Maintenance Therapy

Patients who are induced into remission with chemotherapy and then followed symptomatically generally have remissions that last from 1-2 years before signs of relapse begin to emerge. It has long been recognized that maintenance chemotherapy is not associated with a better survival than is an unmaintained remission followed by re-induction therapy at the first signs of early relapse.⁽²²⁻²⁵⁾ Use of recombinant IFN- α for remission maintenance was reported by the Italian Multiple Myeloma Study Group.^(26,27) In this study, 70 patients with remissions induced with chemotherapy were randomized to recombinant IFN- α 2 or to no treatment. IFN was administered at a dosage of 3×10^6 IU/m² s.c. three times weekly.⁽²⁷⁾ After 27 months of follow-up, 24% evaluable patients receiving IFN and 59% on no maintenance had relapsed ($p < 0.01$).⁽²⁷⁾ A marginal survival advantage was claimed, but further published follow-up is required. A far larger study of IFN maintenance by the SWOG used 3×10^6 of IFN- α 2 s.c. with the same schedule but showed no advantage of IFN over observation only for either remission duration or survival.⁽²⁸⁾ Other subsequent IFN- α studies for remission maintenance have failed to show an improvement in overall survival, although several suggest an increase in the time from start of maintenance to relapse.^(29,30) As IFN- α has significant side effects and is expensive, there is currently no consensus regarding its use as a single agent for myeloma maintenance therapy.

Supportive Care

Several important advances in supportive care have recently been made in myeloma. These include the use of erythropoietin to treat anemia and the use of potent diphosphonates (e.g., pamidronate) to treat both hypercalcemia and to prevent skeletal complications of myeloma (such as fractures and need for radiation therapy for pain control).⁽³¹⁾ The exciting results with pamidronate suggest that effective treatment of

myeloma should be directed at the “soil” (the bone) as well as the “seed” (the malignant cell).

References

1. Durie BGM and Salmon SE: A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment and survival. *Cancer* 36:842-852, 1975.
2. Ludwig H, Cortelezzi A, Van Camp BGK, et al: Treatment with recombinant alpha 2c. Multiple myeloma and thrombocythaemia in myeloproliferative diseases. *Oncology* 42 (suppl 1) 19-25, 1985.
3. Ahre A, Bjorkholm M, Mellstedt H, et al: Human leukocyte interferon and intermittent high-dose melphalan-prednisone administration in the treatment of multiple myeloma. A randomized clinical trial from the Myeloma Group of Central Sweden. *Cancer Treat Rep* 68:1331-1338, 1984.
4. Cooper MR, Fefer A, Thompson J, et al: Alpha-2 interferon/melphalan/prednisone in previously untreated patients with multiple myeloma: A phase I-II trial. *Cancer Treat Rep* 70:473-476, 1986.
5. Osterborg A, Bjorkholm M, Bjoreman M, et al: Natural interferon- α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: A randomized study from the Myeloma Group of Central Sweden. *Blood* 81:1438-1434, 1993.
6. Oken MM, Leong T, Kay NE, et al: The effect of adding interferon (IFN- α 2) or high dose cyclophosphamide to VBMCP to treat multiple myeloma: results from an ECOG phase III trial. *Blood* 80(1):441a, 1995 (abstr 1749).
7. Cassus PH, Pegourie-Bandelier B, Sadoun A, et al: Randomized comparison of interferon- α with VMCP/VBAP regimen as the induction phase of untreated multiple myeloma: results of the KIF multicentre trial. *Blood* 80(1):441a, 1995 (abstr 1750).
8. McElwain TJ, Powles RL: High-dose melphalan for plasma-cell leukemia and myeloma. *Lancet* 2:822, 1983.
9. Selby PJ, McElwain TJ, Nandi AC, et al: Multiple myeloma treated with high-dose intravenous melphalan. *Br J Haematol* 66:55-62, 1987.
10. Barlogie B, Alexanian R, Dicke KA, et al: High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. *Blood* 70:869-872, 1987.
11. Femand JP, Levy Y, Gerota J, et al: Treatment of aggressive multiple myeloma by high dose chemotherapy and total body irradiation followed by blood stem cells autologous graft. *Blood* 73:20-23, 1989.
12. Attal M, Huguet F, Schlaifer D, et al: Intensive combined therapy for previously untreated aggressive myeloma. *Blood* 79:1130-1136, 1992.
13. Harousseau J-L, Attal M, Divine M, et al: Autologous stem cell transplantation after first remission induction treatment in multiple myeloma: A report of the French Registry on autologous transplantation in myeloma. *Blood* 85:3077-3085, 1994.
14. Anderson KC, Anderson J, Soiff R, et al: Monoclonal antibody-purged bone marrow transplantation therapy for multiple myeloma. *Blood* 2568-2576, 1993.

15. Attal M, Harousseau JL, Stoppa AM, et al: High dose therapy in multiple myeloma: A prospective study of the "Intergroup Francais du Myelome." *Blood* 82 (suppl 1): 198a, 1993.
16. Ringden O, Horowitz MM, Gale RP, et al: Outcome after allogeneic bone marrow transplant for leukemia in older adults. *J Am Med Assoc* 270:57-60, 1993.
17. Gratwohl A, Hermans J, Niederwieser D: Bone marrow transplantation for chronic myeloid leukemia: Long-term results. *Bone Marrow Transplant* 12:509-516, 1993.
18. Weiden PL, Sullivan KM, Flournoy N, et al: Antileukemic effect of chronic graft-versus-host disease: Contribution to improved survival after allogeneic marrow transplantation. *N Engl J Med* 304:1529-1533, 1981.
19. Horowitz MM, Gale RP, Sondel PM, et al: Graft-versus leukemia reactions after bone marrow transplantation. *Blood* 75:555-572, 1990.
20. Bensinger WI, Buckner CD, Clift RA, et al: Phase I study of busulfan and cyclophosphamide in preparation for allogeneic marrow transplant for patients with multiple myeloma. *J Clin Oncol* 10:1492-1497, 1992.
21. Gahrton G, Tura S, Ljungman P, et al: Prognostic factors in allogeneic bone marrow transplantation in multiple myeloma. *J Clin Oncol* 13:1312-1322, 1995.
22. Alexanian R, Gehan E, Haut A, et al: Unmaintained remissions in multiple myeloma. *Blood* 51:1005-1011, 1978.
23. Southwest Oncology Group Study: Remission maintenance therapy for multiple myeloma. *Arch Intern Med* 135-147, 1975.
24. Belch A, White D, Bergsagel D, et al: The role of maintenance chemotherapy for multiple myeloma. *Proc Am Soc Clin Oncol* 3:268, 1984 (abstr c1050).
25. Cohen JH, Bartolucci AA, Forman WB, et al: Consolidation and maintenance therapy in multiple myeloma: Randomized comparison of a new approach to therapy after initial response to treatment. *J Clin Oncol* 5:888-899, 1986.
26. Tribalto M, Mandelli F, Cantonetti M, et al. In: Bernasconi C (ed): *New trends in the therapy of leukemia and lymphoma*. Pavia, Italy, Edizione Medic Scientifiche, 1987, p 61-68.
27. Mandelli F, Tribalto M, Cantonetti M, et al: Recombinant alpha 2b interferon as maintenance therapy in responding multiple myeloma patients. *Blood* 70 (suppl 1) 247a, 1987.
28. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B: Combination chemotherapy, glucocorticoids and interferon alpha in the treatment of multiple myeloma. A Southwest Oncology Group Study. *J Clin Oncol* 12(11):2405-2414, 1994.
29. Ludwig H, Cohen AM, Polliack A, et al: Interferon-alpha for induction and maintenance in multiple myeloma: Results of two multicenter randomized trails and summaries of other studies. *Annals of Oncology* 6:4676-476, 1995.
30. Westin J for the Nordic Myeloma Study Group: Interferon-alfa-2 in addition to melphalan-prednisone for initial and maintenance treatment in multiple myeloma: A randomized Nordic trial. *Blood* 86 (suppl 1): 441a, 1995, (abstr 1751).
31. Berenson JR, Lichtenstein A, Porter L, et al: Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. *New Engl J Med* 334:488-493, 1996.