

Update on the Treatment of Multiple Myeloma

ROBERT A. KYLE

Division of Hematology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

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ABSTRACT

The patient with multiple myeloma should be carefully evaluated from the standpoint of symptoms, physical findings, and laboratory data. If there are no symptoms or evidence of early or impending complications, the patient should not be treated. He or she should be followed and treatment delayed until progression of the disease occurs. If the patient is younger than 70 years, autologous peripheral blood stem cell transplantation should be considered. Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents. If the patient is older than 70 years, chemotherapy is indicated. The two major shortcomings of autologous stem cell transplantation are: A) failure to eradicate myeloma, and B) contamination of autologous peripheral blood stem cells. Most physicians initially treat the patient with vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD) for three to four months and then collect the peripheral blood stem cells. One can then proceed with transplant or treat the patient with alkylating agents and delay the transplant until the patient progresses. In a

prospective trial comparing autologous bone marrow transplantation with conventional chemotherapy, five-year overall survival favored the transplant group (52% versus 12%). In a randomized trial of 400 patients from France, there was no difference in event-free or overall survival between double and single autologous stem cell transplant when evaluated at two years. In a subsequent evaluation, patients with a low β_2 -microglobulin value at diagnosis appeared to have better results with a double transplant. There is no evidence that combinations of chemotherapeutic agents are more effective than melphalan and prednisone. Allogeneic transplantation is associated with a high mortality. Depletion of T-cells or a mini-allogeneic transplant may be beneficial in an effort to reduce mortality. Thalidomide produces objective response in approximately 30% of refractory patients. The use of intravenous bisphosphonates is recommended for patients with skeletal lesions. Hypercalcemia and renal failure must be treated promptly. *The Oncologist* 2001;6:119-124

INTRODUCTION

Although most patients with multiple myeloma have symptomatic disease at diagnosis and require therapy, some are asymptomatic and should not be treated. All symptoms, physical findings, and laboratory data must be considered before beginning therapy. An increasing level of the M-protein in the serum or urine suggests that therapy will be needed in the near future, whereas the development of significant anemia, hypercalcemia, renal insufficiency, lytic bone lesions, or extramedullary plasmacytomas are all indications for immediate treatment. If there is doubt about beginning treatment, it is best to reevaluate the patient in two months and delay therapy until progressive disease is evident.

AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT

If the patient is younger than 70 years, the physician should discuss the possibility of an autologous peripheral

blood stem cell transplant with the patient. Hematopoietic stem cells should be collected before the patient is exposed to alkylating agents. Chemotherapy is the preferred initial treatment for symptomatic multiple myeloma in patients older than 70 years or in younger patients for whom transplantation is not feasible.

Peripheral blood stem cells are preferable to bone marrow for transplantation because engraftment is more rapid and there may be less contamination of the infused cells with tumor cells. The absolute number of CD34⁺ cells per kilogram of recipient weight is the most reliable and practical method for determining the adequacy of a stem cell product. Autologous peripheral stem cell transplantation is applicable for more than half of patients with multiple myeloma. The two major shortcomings are: A) that eradication of myeloma from the patient does not occur even with large doses of chemotherapy and/or total body irradiation, and B) that autologous peripheral blood stem cells are

Correspondence: Robert A. Kyle, M.D., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. e-mail: kyle.robert@mayo.edu Received October 12, 2000; accepted for publication November 1, 2000. ©AlphaMed Press 1083-7159/2001/\$5.00/0

contaminated by myeloma cells or their precursors. Fortunately, mortality from autologous transplantation is only 1%-2% if patients are appropriately selected.

Most physicians initially treat the patient with VAD—vincristine, doxorubicin (Adriamycin), and dexamethasone—for 3 to 4 months to reduce the number of tumor cells in the bone marrow and peripheral blood. Dexamethasone with or without thalidomide is being evaluated for initial therapy. Peripheral stem cells are then collected after administration of high-dose cyclophosphamide and G-CSF. One can then proceed with the transplant, in which the patient is given high-dose chemotherapy and/or total body irradiation followed by infusion of the peripheral blood stem cells. The other choice is to treat the patient with alkylating agents after stem cell collection until a plateau is reached and then give the patient α_2 -interferon or no therapy until early relapse. At that time, the patient is given high-dose melphalan and/or total body irradiation and the previously collected peripheral blood stem cells are infused.

One hundred eighty-five patients were treated with three or four courses of VAD and then randomized to high-dose chemotherapy and autologous stem cell transplantation or conventional chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation for patients with primary resistance to or relapse after conventional chemotherapy. There was no difference in the median survival of the two groups (65 versus 64 months). The main advantage of early transplantation was a shorter period of chemotherapy. There was no plateau of survival in either group [1].

In a series of 177 patients less than 75 years of age with IgG myeloma, C-VAMP, high-dose chemotherapy with or without stem cell rescue, and maintenance interferon were given. The overall survival was 4.9 years. Serum β_2 -microglobulin levels less than 2.7 mg/l and age less than 52 years predicted survival [2]. In another report of 231 patients receiving tandem transplants, the overall median survival was 68 months [3].

A randomized trial by the French Myeloma Group compared high-dose chemotherapy and autologous bone marrow transplantation with conventional chemotherapy in 200 previously untreated myeloma patients under the age of 65 years [4]. Data were analyzed on an intention-to-treat basis in which 25% of the patients who were randomized to transplantation did not receive a transplant. The response rate (81% versus 57%) and complete responses (22% versus 5%) were superior in the transplant group. The five-year event-free survival (28% versus 10%) and overall survival (52% versus 12%) were superior in the transplant group. It must be kept in mind that patient selection plays an important role

in response and survival. In a report of 77 patients with multiple myeloma who fulfilled the criteria for transplant (age less than 66 years, stage II or III, good performance status, and disease responsive to initial chemotherapy) but who were treated with conventional chemotherapy, survival was five years, which is similar to that seen for autologous stem cell transplantation [5].

In an uncontrolled series of 231 newly diagnosed multiple myeloma patients who received a second transplant, 51% had a complete response and 95% had a complete or partial response. The authors felt that the double transplant extended both event-free and overall survival, even in patients with unfavorable cytogenetics and β_2 -microglobulin values [3]. The use of dendritic cells and vaccines may be of benefit following autologous transplantation.

In a randomized trial of 400 patients from France, there was no difference in event-free or overall survival between double and single autologous stem cell transplant on evaluation at two years. Four hundred patients younger than 60 years were randomized to receive a single autologous transplant or a double transplant. The two groups were similar in age, gender, stage, Ig isotype, β_2 -microglobulin value, C-reactive protein level, and bone marrow plasmacytosis. Complete response rate was 32% with a single transplant and 33% with a double transplant. At two years, the event-free survival was 54% versus 57% and the overall survival was 71% versus 67%, respectively [6]. In a subsequent evaluation, patients with a low β_2 -microglobulin value at diagnosis appeared to have better results with the double transplant.

The preparative regimen for an autologous stem cell transplant must be improved because it is likely the source of relapse in the majority of patients. In a comparison (non-randomized) of melphalan 140 mg/m² plus total body irradiation with melphalan 200 mg/m², no difference was found in remission status, event-free survival, or overall survival [7]. Today, most physicians give melphalan in a dosage of 200 mg/m² as the preparative regimen because there is no apparent survival advantage in using total body irradiation, and toxicity, especially mucositis, is less.

CHEMOTHERAPY

Various combinations of therapeutic agents have been used because of the shortcomings of treatment with melphalan and prednisone which produces an objective response in 50% to 60% of patients. In an overview of individual data from 4,930 persons from 20 randomized trials comparing melphalan and prednisone with various combinations of chemotherapeutic agents, the response rates were higher with combination chemotherapy (60%) than with melphalan and prednisone (53%) ($p < 0.00001$). However,

there was no significant difference in overall survival or evidence that any group of patients benefited from receiving combination chemotherapy. Duration of response was not different in the single-agent and multiple-agent regimens. Furthermore, there was no evidence that high-risk patients benefited from combination chemotherapy.

Chemotherapy should be continued until the patient is in a plateau state or for one year. Continued chemotherapy may lead to a myelodysplastic syndrome or acute leukemia. The possible benefit of maintenance therapy with α_2 -interferon following conventional chemotherapy is controversial because of conflicting results and the frequency of undesirable side effects. In a large meta-analysis, *Wheatley* [8] reported a survival benefit in both induction ($p = 0.05$) and maintenance ($p = 0.03$), with an increase in median duration response of 6 months in both settings. Patients should be monitored closely during the plateau, and the same chemotherapy regimen should be reinstated if relapse occurs after 6 months.

ALLOGENEIC BONE MARROW TRANSPLANTATION

The major advantage with allogeneic bone marrow transplantation is that the graft contains no tumor cells that can lead to a relapse. Unfortunately, over 90% of patients with multiple myeloma are ineligible because of their age, lack of an HLA-matched sibling donor, or inadequate renal, pulmonary, or cardiac function. Furthermore, there is presently a mortality rate of at least 25%.

In a report of 266 patients from the European Blood and Bone Marrow Transplantation registry, 51% obtained a complete response. The overall treatment mortality rate was approximately 40%. The actuarial survival was 30% at 4 years and 20% at 10 years. Patients with a β_2 -microglobulin level of less than 4 $\mu\text{g/ml}$, those who had received one line or less of prior therapy, and female patients had a more favorable outlook [9].

It is obvious that the mortality rate for allogeneic transplantation must be reduced before this approach can assume a major role in the treatment of multiple myeloma. A "mini-allo" transplant using a preparative regimen of fludarabine and melphalan may result in a lower mortality [10]. Depletion of T-cells decreases the incidence of graft-versus-host disease and reduces transplant mortality. However, relapse may be more frequent because the graft-versus-myeloma effect is reduced [11]. The graft-versus-myeloma effect has been noted after the administration of donor peripheral blood mononuclear cells for relapse following allogeneic transplantation. Eight of 13 patients with relapse of myeloma after an allogeneic bone marrow transplantation responded to donor lymphocyte infusions. Four of the patients had a complete response [12]. At present, a conventional allogeneic

transplant is not recommended because of its high mortality. Efforts are necessary to reduce that mortality.

TREATMENT OF REFRACTORY MULTIPLE MYELOMA

Patients who are initially refractory to alkylating agent therapy or who become so have a low response rate to subsequent chemotherapy and limited survival. The highest response rates in patients with multiple myeloma resistant to alkylating agents have been obtained with VAD. Vincristine and doxorubicin are given by continuous infusion for 4 days, and dexamethasone, 40 mg daily, is given on days 1-4, 9-12, and 17-20 each month. Because of toxicity, dexamethasone is often given only on days 1-4 in even-numbered cycles. Dexamethasone can be given as the only therapeutic agent and probably accounts for 80% of the effect of VAD. Intravenous pulse methylprednisolone (2 g three times weekly for a minimum of 4 weeks) is helpful in patients with pancytopenia and refractory disease. We find fewer side effects with this approach than with dexamethasone [13]. Vincristine, 2 mg, carmustine (BCNU), 30-40 mg, and doxorubicin, 30-40 mg, on day 1 and prednisone daily for 5 days every 3 to 4 weeks produces benefit in about one-third of patients. Thalidomide produced benefit in 32% of 84 patients with previously treated, progressive multiple myeloma. After 12 months of follow-up, 22% of patients remained event-free and 58% were alive [14]. Thalidomide was given in an initial dosage of 200 mg daily which was gradually increased to 800 mg daily. Constipation, weakness or fatigue, sleepiness, and peripheral neuropathy were undesirable side effects. The use of thalidomide in conjunction with dexamethasone is being explored. In the majority of patients, response occurs within 6 weeks and with only 400 mg daily.

SUPPORTIVE CARE

Skeletal Complications

Skeletal involvement often leads to pain, pathologic fractures, hypercalcemia, or cord compression [15]. These complications result from increased osteoclastic bone resorption. The increase in osteoclastic activity in multiple myeloma is mediated by the release of osteoclastic stimulating factors including interleukin 1 (IL-1), IL-6, and tumor necrosis factor.

Bisphosphonates are specific inhibitors of osteoclastic activity and have been evaluated as adjunctive therapy to chemotherapy for multiple myeloma. In a prospective study, 377 patients were randomized to receive pamidronate, 90 mg intravenously every 4 weeks, or placebo. All patients had stage III myeloma with at least one lytic lesion. The patients were stratified at entry into those receiving first-line chemotherapy (stratum 1) and those who failed first-line

chemotherapy on subsequent therapy regimens (stratum 2). The skeletal events were defined as pathologic fractures, need for surgery to treat or prevent pathologic fractures, need for radiation to bone, or spinal cord compression. Patients receiving pamidronate had significant reduction in both the proportion of patients experiencing skeletal events and the number of skeletal lesions per year. The pamidronate group also had a reduction in the number of patients developing new pathologic fractures and requiring radiation therapy, and they had a significant decrease in bone pain, a lesser requirement for analgesic drugs, and improved quality of life [16]. Bisphosphonates may induce apoptosis in human myeloma cell cultures and thus exert a direct effect on multiple myeloma [17]. Patients with multiple myeloma who have lytic lesions or osteopenia should receive pamidronate, 90 mg intravenously over 2 hours every 4 weeks. Use of the drug should be continued indefinitely. Pamidronate is well tolerated, but cost is a factor [18].

Patients should be encouraged to be as active as possible, but they must avoid undue trauma. Fixation of fractures or pending fractures with an intramedullary rod and methylmethacrylate has produced good results. Bone pain should be treated with analgesics or narcotics, as necessary.

Hypercalcemia

Hypercalcemia occurs in 15% of patients with multiple myeloma at diagnosis and should be suspected in the presence of anorexia, nausea, vomiting, polyuria, polydipsia, increased constipation, weakness, confusion, or stupor. If hypercalcemia is untreated, renal insufficiency develops. Hydration plus prednisone (25 mg q.i.d.) is effective in most cases. The prednisone should be reduced in dosage and then discontinued as soon as the serum calcium becomes normal. If hypercalcemia persists, the patient should be treated with pamidronate.

Renal Failure

Approximately 20% of patients with multiple myeloma have a creatinine level of 2.0 mg/dl or more at diagnosis. The two major causes of renal insufficiency are “myeloma kidney” and hypercalcemia. Myeloma kidney is characterized by the presence of large, waxy, laminated casts in the distal and collecting tubules. These casts consist of large amounts of monoclonal light chains and small amounts of albumin, Tamm-Horsfall protein, and fibrinogen. The renal tubules dilate and atrophy, and the entire nephron becomes distorted and nonfunctional. The extent of cast formation correlates with the severity of renal insufficiency, and often with the quantity of monoclonal urinary light chains. No consistent relationship has been found between the isoelectric point of the light chains and renal insufficiency. Even

though some light chains are very nephrotoxic, no specific amino acid sequence of the light chain has been associated with nephrotoxicity.

Dehydration, infection, nonsteroidal anti-inflammatory agents, and roentgenographic contrast media may contribute to acute renal failure. The risk of renal failure with roentgenographic contrast media is minimal if dehydration is avoided. Hyperuricemia may contribute to renal insufficiency but can be treated easily with allopurinol. Amyloid deposition occurs in 10% of patients with multiple myeloma and often causes nephrotic syndrome, renal insufficiency, or congestive heart failure. The physician must determine whether proteinuria in a patient with multiple myeloma consists mainly of a monoclonal light chain or only albumin, because a large amount of albumin indicates the presence of a nephrotic syndrome. Nephrotic syndrome rarely occurs in multiple myeloma unless amyloidosis is present.

Maintenance of a high urine output (3 l/day) is important for preventing renal failure in patients with Bence Jones proteinuria. Prompt treatment of hypercalcemia and correction of dehydration and electrolyte imbalance are crucial.

Acute renal failure should be treated with appropriate fluid and electrolyte replacement. Alkalinization of the urine is useful. A prospective randomized trial in which renal biopsies were performed found that by the time cast formation reached an advanced stage, irreversible renal damage had already occurred and few of the patients responded to vigorous plasmapheresis [19]. Patients with acute or subacute renal failure should be treated with VAD—vincristine and doxorubicin by continuous infusion for 96 hours plus dexamethasone, 40 mg daily on days 1-4, 9-12, and 17-20. A trial of plasmapheresis in younger patients with acute renal failure is recommended because renal biopsy is impractical in most instances. Hemodialysis or peritoneal dialysis is necessary in the event of symptomatic azotemia.

Anemia

Anemia occurs in almost all patients during the course of multiple myeloma. A prospective, randomized, placebo-controlled blind clinical trial was performed involving 25 patients with a hematocrit of less than 30% and in a stable phase of multiple myeloma. They were given erythropoietin, 150 U/kg, or a placebo subcutaneously 3 times weekly. After 6 weeks, the code was broken for all patients and those who had been randomized to placebo were crossed over to an open-label phase in which they were given erythropoietin. Overall, 9 of 20 patients (45%) who could be evaluated had a complete response and two had a partial response [20]. *Österborg et al.* [21] reported a 60% response in patients with multiple myeloma or non-Hodgkin's lymphoma treated with erythropoietin. They found that the serum erythropoietin

concentration was the most important factor predicting response. *Cazzola et al.* [22] stated that 62% of patients receiving erythropoietin responded. Approximately three-fourths of patients with low erythropoietin levels responded, whereas only one-fourth of those with adequate erythropoietin levels did so. *Ludwig et al.* [23] reported beneficial effects with erythropoietin in anemia associated with multiple myeloma. They also found a significant improvement in the patients' quality of life and an improved sense of well-being as measured by a self-assessment questionnaire [24]. In another study, one-third of severely anemic patients with advanced multiple myeloma unresponsive to chemotherapy benefited from erythropoietin therapy [25].

Infection

Patients should receive pneumococcal and influenza vaccinations despite their suboptimal antibody response. Prompt and appropriate therapy of bacterial infections is essential. Patients who present with a high fever and chills should have blood and urine cultures and a chest x-ray. Antibiotics should be started immediately and changed as results of cultures indicate. Prophylactic daily oral penicillin often benefits patients with recurrent pneumococcal infections. Since many infections occur in the first 2 months after the start of chemotherapy, the use of daily oral trimethoprim-sulfamethoxazole is helpful [26]. Intravenously administered gamma globulin may be beneficial for patients with recurrent infections, but it is inconvenient and very expensive.

Neurologic Disorders

Spinal cord compression should be suspected in patients with severe back pain who develop weakness or paresthesias

of the lower extremities, or have bladder or bowel dysfunction. Magnetic resonance imaging (MRI) or computed tomography must be done immediately. MRI is particularly useful in demonstrating extramedullary plasmacytoma. Radiation therapy and dexamethasone are usually effective, and surgical decompression is rarely necessary.

Hyperviscosity

Hyperviscosity is characterized by oral or nasal bleeding, blurred vision, paresthesias, headache, or congestive heart failure. It may result from high concentrations of IgA or, rarely, IgG. Serum viscosity levels do not correlate well with symptoms or clinical findings. Consequently, a decision to perform plasmapheresis depends on the symptoms and changes in the ocular fundus. Plasmapheresis promptly relieves the symptoms and should be done regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity [27].

Emotional Support

All patients with multiple myeloma need substantial and continuing emotional support. The physician's approach must be positive in emphasizing the potential benefits of therapy. It is reassuring for patients to know that some survive for 10 years or more. It is vital that the physician caring for patients with multiple myeloma has the interest in and capacity for dealing with an incurable disease over the span of years with assurance, sympathy, and resourcefulness.

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