Symposium article

The role of high-dose chemotherapy in the treatment of multiple myeloma: A controversy*

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Summary

Background: Minimal criteria for the diagnosis of multiple myeloma are provided. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, primary systemic amyloidosis and metastatic carcinoma must be included in the differential diagnosis. Patients with multiple myeloma should not be treated unless they have an increasing M-protein in the serum or urine, development of anemia, hypercalcemia, renal insufficiency, lytic lesions, fractures or extramedullary plasmacytomas.

Patients and methods: This is a review of patients treated with chemotherapy, autologous stem-cell transplantation and allogeneic transplantation.

Results: Comparisons of melphalan and prednisone with a variety of combinations of therapeutic agents produces a higher response rate than with melphalan and prednisone but no significant difference in overall survival. Autologous stem-cell transplantation produces a higher response rate and some prolongation of survival but is not curative. Allogeneic transplantation is associated with a mortality of 40% and is not curative.

Conclusions: If the patient is younger than 70 years, the physician should consider the possibility of an autologous peripheral blood stem-cell transplant. Ideally, this should be done as part of a prospective study. Hematopoietic stem cells are damaged by alkylating agents so they must be collected before these agents are given. Autologous stem-cell transplantation does not produce a cure and most patients will relapse. The appropriate timing of an autologous stem-cell transplant has not been ascertained. Hopefully, better preparative regimens and the removal of contaminated tumor cells from the peripheral blood will make an autologous transplant more effective. Another major question is whether double (tandem) transplants are superior to a single autologous stem-cell transplant. A current French Myeloma Group Study randomized study should answer this question. Allogeneic transplantation for multiple myeloma must be made safer because the transplant-related mortality is 40%. The relapse of multiple myeloma following allogeneic transplant is a major problem and consequently the preparative regimens must be improved. The infusion of donor lymphocytes following relapse after an allogeneic transplant is useful. New approaches with immunologic aspects including the use of dendritic cells and vaccines are of potential importance for the future.

Key words: autologous and allogeneic transplantation, high-dose, multiple myeloma, therapy

Introduction

General criteria for the diagnosis of multiple myeloma consist of more than 10% plasma cells in the bone marrow or a plasmacytoma and one of the following: 1) M-protein in the serum (usually more than 3 g/dl), 2) M-protein in the urine, or 3) lytic bone lesions. These findings must not be related to metastatic carcinoma, lymphoma, connective tissue disorders or chronic infection. The patient must also have the usual clinical features of multiple myeloma.

Monoclonal gammopathy of undetermined significance (MGUS) [1], smoldering multiple myeloma (SMM) [2], primary systemic amyloidosis (AL) [3], Waldenström's macroglobulinemia (WM), lymphoma or metastatic carcinoma must be excluded. An M-protein < 3 g/dl, fewer than 10% bone marrow plasma cells, absence of lytic lesions, anemia, hypercalcemia or renal insufficiency in an asymptomatic patient are characteristic of MGUS. An M-protein value > 3 g/dl and more than 10% bone marrow plasma cells fulfill the diagnostic criteria for SMM in asymptomatic patients. SMM and MGUS must be recognized and no treatment given because they may remain stable for years.

Differentiation of MGUS and SMM may be difficult but the size of the M-protein in the serum and the urine and the number of bone marrow plasma cells are helpful. The plasma cell labeling index (PCLI) is useful in differentiating MGUS or SMM from multiple myeloma [4]. A monoclonal antibody (BU-1) reactive with 5-bromo-2-deoxyuridine identifies any cell that synthesizes DNA. This antibody does not require denaturation and, consequently, fluorescein-conjugated immunoglobulin antisera to kappa and lambda identify monoclonal plasma cells. An increased PCLI strongly suggests that the patient has or soon will develop symptomatic myeloma.

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loma. However, patients with symptomatic multiple myeloma may require chemotherapy and yet have a normal PCLI. Monoclonal plasma cells are detected in the peripheral blood of 80% of patients with symptomatic myeloma while those with MGUS or SMM have fewer or no circulating plasma cells [5].

No single test can differentiate a patient with MGUS from one in whom myeloma or other malignant disease will subsequently develop. Consequently serum and urine M-protein values must be measured periodically and clinical and other laboratory features should be evaluated to determine whether myeloma, AL, WM or other disorders have developed. Indications for therapy include an increasing M-protein in the serum or urine, development of anemia, hypercalcemia, renal insufficiency, lytic lesions, fractures or extramedullary plasmacytomas.

Treatment

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. If there is doubt about beginning treatment, it is best to reevaluate the patient in two months and to delay therapy until progressive disease is evident.

If the patient is younger than 70 years, the physician should discuss the possibility of an autologous peripheral blood stem-cell transplant. This should be done as part of a prospective study. 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 in whom transplantation is not feasible.

Melphalan and prednisone, given orally, produces an objective response in only 50%-60% of patients. I prefer to give melphalan orally in a dosage of 8-10 mg/d for seven days and prednisone, 20 mg/tid for the same seven days. Melphalan must be given when the patient is fasting. Leukocyte and platelet counts should be determined at three-week intervals after beginning therapy because the melphalan dosage must be altered until mid-cycle neutropenia or thrombocytopenia occurs. The melphalan and prednisone should be repeated every six weeks. At least 3 courses of melphalan and prednisone should be given before the regimen is discontinued unless the patient has evidence of progressive disease because an objective response may not be achieved for 6-12 months.

Various combinations of therapeutic agents have been tried because of the shortcomings of melphalan and prednisone. In an overview of individual data in 4930 persons from 20 randomized trials comparing melphalan and prednisone with a variety of combinations of therapeutic agents, the response rates were significantly higher with combination chemotherapy (60%) than melphalan-prednisone (53%) (P < 0.00001). However, there was no significant difference in overall survival. There was no evidence that any group of patients benefited from receiving combination chemotherapy. In fact, there was nothing to indicate that high-risk patients benefited from combination chemotherapy. There was also no significant difference in response duration between single and multiple agents [6].

Chemotherapy should be continued until the patient is in a plateau state or for at least one year. Continued chemotherapy may lead to the development of a myelodysplastic syndrome or acute leukemia. The duration of the plateau is prolonged with α2-IFN but survival is only slightly improved [Wheatly K, personal communication]. The patient should be monitored closely during the plateau phase and the same chemotherapy regimen should be reinstated if relapse occurs after six months.

Autologous transplantation

Autologous peripheral blood stem-cell transplantation has virtually replaced autologous bone marrow transplantation because engraftment is more rapid and there is less contamination of myeloma cells. Autologous peripheral stem-cell transplantation is applicable for more than half of patients with multiple myeloma. The two major shortcomings are 1) eradication of myeloma from the patient does not occur even with large doses of chemotherapy and total body radiation and 2) autologous peripheral blood stem cells are contaminated by myeloma cells or their precursors. Fortunately the mortality from autologous transplantation is currently 1% if patients are appropriately selected.

Most physicians initially treat the patient with vincristine, doxorubicin, and dexamethasone (VAD) for three to four months to reduce the number of tumor cells in the bone marrow and peripheral blood. Peripheral stem cells are then collected following high-dose cyclophosphamide and granulocyte colony-stimulating factor (G-CSF). One can then proceed with the transplant in which the patient is given high-dose chemotherapy and/or total body radiation 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 treat with α2-IFN or no therapy until early relapse. At that time the patient is given high-dose melphalan and/or total body radiation and the previously collected peripheral blood stem cells are infused. In a French study, 185 patients treated with three to four courses of VAD and then randomized to high-dose chemotherapy and autologous stem-cell transplantation or to conventional therapy with high-dose chemotherapy and autologous transplantation performed on primary resistant or relapsed patients showed no difference in the median overall survival of the two groups (65 vs. 64 months). The main advantages of early transplantation were a shorter period of chemotherapy and a longer median
event-free survival (39 vs. 13 months). There was no plateau of survival in either group suggesting that cure of the myeloma was an unusual event [7].

The largest single institution experience with autologous transplantation in myeloma included 496 patients enrolled in a tandem transplant program [8]. Complete response was obtained in 36% while the transplant-related mortality was 7%. The overall survival from the time of the first transplant was 41 months. This series was heterogeneous and included patients with resistant disease as well as those with disease sensitive to conventional chemotherapy. In a recent report of 231 patients receiving tandem transplants, the overall median survival was 68 months [9].

A randomized trial performed by the French Myeloma Group compared high-dose chemotherapy and autologous bone marrow transplantation with conventional chemotherapy in 200 previously untreated patients under the age of 65 years [10]. Data was analyzed on an intention to treat basis in which 25% of the patients randomized to transplantation did not receive the transplant. The rate of response (81% vs. 57%) and complete responses (22% vs. 5%) was superior in the transplant group. A higher rate of five-year event-free survival (28% vs. 10%) and overall survival (52% vs. 12%) occurred in the transplant group. However in another report, the median survival of 77 patients who were potential candidates for transplant (age <66 years, stage II or III, good performance status and disease responsive to initial chemotherapy) but who were treated with conventional chemotherapy was similar to the survival with autologous transplantation (five years) [11].

It has been suggested that better results could be obtained with two autologous peripheral stem-cell transplants. 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 transplantation. Four hundred patients younger than 60 years with untreated myeloma were randomized to receive a single autologous transplant after melphalan (140 mg/m²) and total-body irradiation (8 cGy) or a double transplant, the first with melphalan (140 mg/m²) and the second with melphalan (140 mg/m²) and total body radiation (8 cGy). The two groups were similar in regard to sex, age, stage, Ig isotype, β₂ microglobulin level, C-reactive protein value and bone marrow plasmacytosis. Analysis was performed on the first 200 patients with a median follow-up duration of two years from diagnosis. The complete response rate was 32% with a single transplant and 33% with a double transplant. The event-free survival was 54% in the single transplant group and 57% in the double transplant group. The overall survival was 71% vs. 67%, respectively. Thus, the double transplant did not improve response rate or event-free or overall survival [12]. However longer follow-up analysis of the total group is necessary.

The preparative regimen for the autologous stem-cell transplant patient 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 (TBI) or melphalan, 200 mg/m², no difference was found in remission status, event-free or overall survival [13].

The other major shortcoming of autologous stem-cell transplantation is the removal of myeloma cells and their precursors from the peripheral blood. Selection of CD34+ cells produces a lower number of tumor cells than no selection (P < 0.001). Fifty-four percent of the patients in the CD34+ selection group had no detectable tumor cells versus 21% for those without CD34+ selection [14]. However the use of purified hematopoetic stem cells may result in delayed engraftment [15]. The use of dendritic cells and vaccines may be of benefit following autologous transplantation.

Allogeneic bone marrow transplantation

Allogeneic bone marrow transplantation is advantageous because the graft contains no tumor cells that can lead to a relapse. Unfortunately, there is a mortality rate of approximately 25% within three months and an overall transplant-related survival rate of 40%. Furthermore, 90%-95% of patients with multiple myeloma are ineligible for an allogeneic transplant because of their age, lack of an HLA matched sibling donor or inadequate renal, pulmonary or cardiac function.

The European Blood and Bone Marrow Transplantation registry has had the most experience with allogeneic transplantation for multiple myeloma. In a report of 266 patients, 51% achieved a complete response. The overall treatment mortality rate was approximately 40%. Overall survival was 40% at two years, 30% at four years, and 20% at ten years. Females, who received one line or less of previous therapy, and those with a β₂ microglobulin level <4 μ/ml had a more favorable survival [16].

Thus, the mortality rate for allogeneic transplantation must be reduced before it can assume a major role in the treatment of multiple myeloma. A preparative regimen using fludarabine and melphalan may result in a lower mortality [17]. Use of T-cell depleted peripheral allogeneic blood stem cells decreases the incidence of graft-versus-host disease and apparently reduces transplant mortality. However, relapse may be more frequent due in part to lessening of the graft-versus-myeloma effect [18]. Graft-versus-myeloma effect has been demonstrated after donor peripheral blood mononuclear cells were given for relapse following allogeneic transplantation. Of 13 patients with relapsed multiple myeloma after allogeneic bone marrow transplantation, 8 responded to donor leukocyte infusions. Four of these eight patients obtained a complete response [19]. Allogeneic transplantation is associated with too high mortality at present and cannot be recommended as a routine procedure.
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References


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