

Molly Pomerance. *Lunch*. Oil on canvas, 22" × 28".

Several novel agents and promising strategies are available or in development for the treatment of multiple myeloma.

Stem Cell Transplantation for Multiple Myeloma

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Background: Multiple myeloma (MM) is the second most common hematologic malignancy, affecting approximately 14,000 new patients in the United State per year. The median overall survival is 5 years, and cure is a realistic goal for only a small minority of patients.

Methods: A review of the literature was conducted that focused on treatment strategies for MM involving administration of high doses of chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplant.

Results: For over three decades, the standard treatment for MM has been a regimen of melphalan and prednisone (MP). Complete responses (CRs) have been rare, and 50% of patients have had disease that was resistant to treatment with MP. Attempts have been made to improve the outcome of MM by administering other combinations of standard doses of chemotherapy, but these treatments are equivalent in terms of overall survival. For patients who are candidates, high-dose therapy followed by autologous stem cell transplantation results in higher CR rates and improved long-term survival compared to treatment with standard doses of chemotherapy alone. While this strategy represents an advance in the treatment of MM, evidence-based reviews indicate that there are a number of issues to consider regarding the induction therapy, the collection of stem cells, and the timing, type, and number of high-dose therapies to use in this type of treatment strategy.

Conclusions: Advances have been made in autologous transplantation, allogeneic transplantation, anti-MM agents, and immunotherapy for MM. Combining these different strategies to achieve synergistic responses is an exciting possibility.

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Introduction

Multiple myeloma (MM) is a malignant B-cell disorder characterized by proliferation of atypical plasma cells in the bone marrow and the presence of monoclonal immunoglobulin protein in the serum and/or urine.¹ The annual incidence of MM is approximately 4 cases per 100,000 persons, with approximately 14,000 new cases and 11,300 deaths in the United States per year. The median age of affected patients is 65 years, and 20% of patients are over age 70.² A trend toward a higher incidence of MM in patients under age 55 has been reported, which implies that important environmental causative factors may have developed in the past 3 to 4 decades. The nature of these and other causative factors in the development of MM currently remains unknown. Prior reports suggested that Kaposi's sarcoma herpes virus was an etiologic agent in MM, but this has not been confirmed.^{3,4} In addition, while many of the biologic processes in MM remain to be defined, complex interactions between the MM cells and the microenvironment clearly play important roles in the pathogenesis of the disease (Fig 1).⁵ The underlying biology of the disease and the interactions between MM cells and the microenvironment may provide targets for treating the disease as well.

Multiple myeloma leads to progressive morbidity and death by lowering resistance to infection and by causing bone destruction, hypercalcemia, anemia, renal failure, and weight loss. Poor prognostic factors include stage III disease at diagnosis (using the Durie-Salmon classification system⁶), chromosome 13 abnormalities, and elevated β_2 -microglobulin, C-reactive protein, lactate dehydrogenase, and plasma cell labeling index levels.^{7,8} The median survival without therapy for patient with advance stage dis-

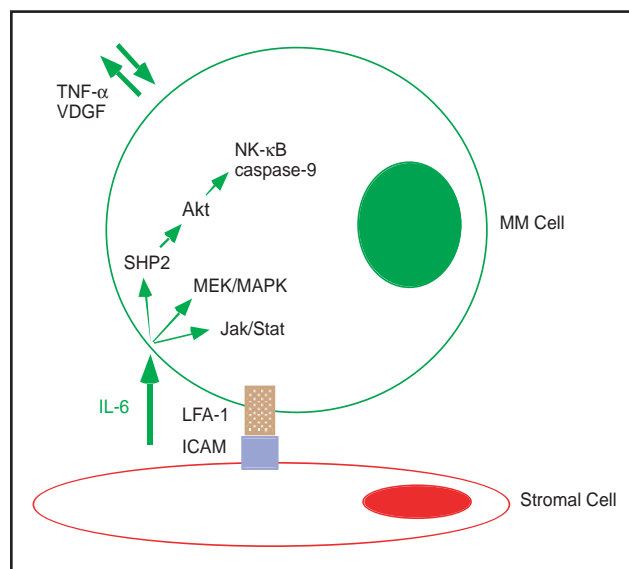


Fig 1. — Summary of important biologic processes in multiple myeloma. Adapted from Ryoo JJ, Cole CE, Anderson KC. Novel therapies for multiple myeloma. *Blood Rev.* 2002;16:167-174. Adapted with permission of Elsevier Science.

ease is less than 1 year. Although some patients may have indolent or smoldering disease, most patients with MM will ultimately develop active disease that requires treatment. At present, cure is a realistic goal for only a small minority of patients with MM.

For more than 3 decades, the standard treatment for MM has been the alkylating agent melphalan along with prednisone (MP) given as an intermittent oral outpatient regimen. Prospective trials demonstrated that MP yielded a 50% response rate (based on the criteria of a 50% reduction in the concentration of myeloma protein), a mean remission duration of 18 months, and a median survival of 24 to 30 months.⁹ Complete responses were rarely obtained, and 50% of patients had disease that was resistant to treatment with MP. Even those who responded invariably developed resistance, usually within 2 years. By 5 years, more than 80% of patients treated with MP had died. Given the limitations of MP, many attempts have been made to improve the outcome of MM by administering other combinations of standard doses of chemotherapy, including the combination of vincristine, doxorubicin, and dexamethasone (VAD) and combinations of alkylating agents.¹⁰ Despite this, meta-analyses of 6,633 patients treated in 27 comparative trials of MP vs combination chemotherapy have shown these treatments to be equivalent in terms of overall survival (Fig 2).¹¹

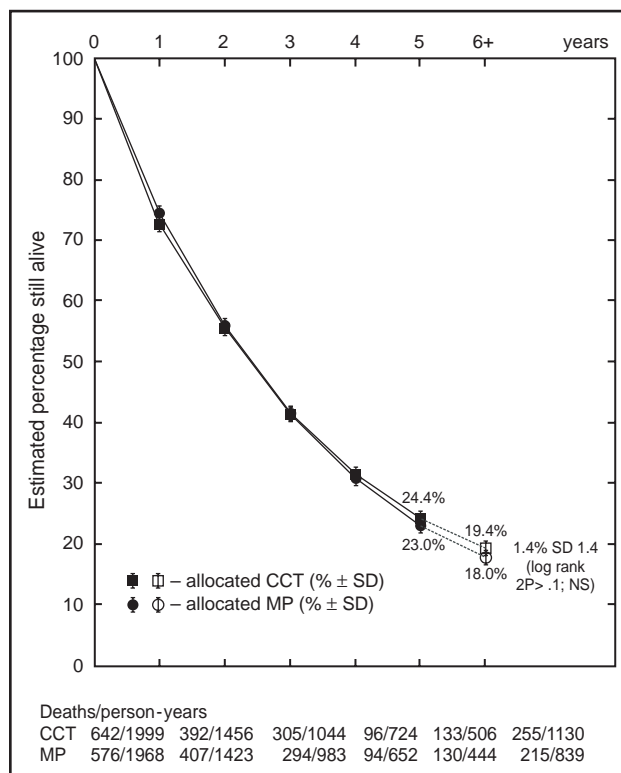


Fig 2. — Mortality meta-analysis of combination chemotherapy (CCT) vs melphalan plus prednisone (MP) for multiple myeloma. From Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. *J Clin Oncol.* 1998; 16:3832-3842. Reprinted with permission.

High-Dose Therapy and Stem Cell Transplantation

As an alternative to standard-dose chemotherapy, a variety of more intense treatment strategies have been developed that involve the administration of high doses of chemotherapy and/or total body irradiation (TBI) followed by autologous or allogeneic hematopoietic stem cell transplantation. For patients who are candidates, high-dose therapy followed by autologous stem cell transplantation results in higher complete response rates and improved long-term survival compared to treatment with standard doses of chemotherapy alone. For example, a randomized trial of 200 newly diagnosed patients in France demonstrated an improved response rate (81% vs 57%) and a 5-year probability of event-free survival (28% vs 10%) for patients undergoing high-dose therapy and autologous BMT compared with standard-dose chemotherapy (Fig 3A-B).¹² A second randomized trial conducted by the United Kingdom Medical Research Council, which enrolled 407 patients, found a significant survival benefit in overall survival for patients treated in the intensive arm (median 54.8 months vs 42.3 months, respectively).¹³ Data from a systematic review, performed by the Ontario Cancer Center, also support the conclusion that autologous transplant is better than standard chemotherapy, particularly in patients younger than 55.¹⁴ Several studies have confirmed that autologous stem cell transplantation after high-dose chemotherapy is equal-

ly well tolerated in groups of patients above 65 years of age, and the current acceptable upper age limit for performing autologous transplantation in MM is currently unclear.¹⁵⁻¹⁷ Based on these results, treatment with standard chemotherapy (ie, induction therapy) for several cycles followed by treatment with high-dose therapy and autologous stem cell transplant is the current treatment of choice for many patients with MM.

While this strategy represents a real advance in the treatment of MM, evidence-based reviews indicate that there are a number of issues to consider regarding the induction therapy, collection of stem cells, and the timing, type, and number of high-dose therapies to use in this type of treatment strategy.¹⁸

Which Induction Therapy Is Optimal and How Many Cycles?

The goal of induction therapy is to reduce the tumor burden prior to high-dose therapy and autologous transplant. Many groups have used administration of 2 to 4 cycles of VAD for this purpose.¹⁹ VAD has the important advantage of sparing hematopoietic stem cells relative to other chemotherapeutic regimens, particularly combinations of alkylating agents.²⁰ This increases the likelihood that sufficient autologous stem cells can be collected for transplantation. Other induction regimens that may also be useful for reducing the tumor burden and sparing stem cells include administration of 2 or more cycles of dexa-

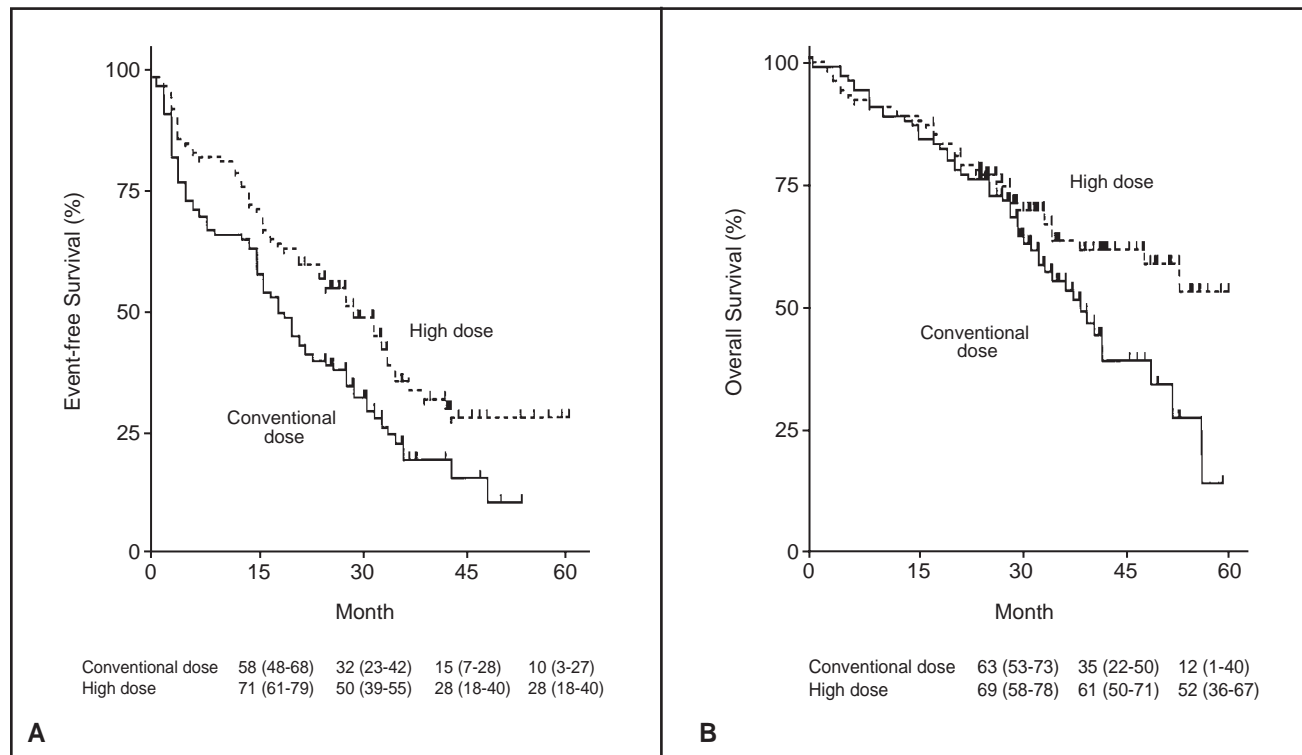


Fig 3. — Event-free (A) and overall (B) survival in patients with myeloma receiving either conventional-dose chemotherapy or high-dose chemotherapy with autologous transplant. The numbers shown below the time points are probabilities of overall and event-free survival and 95% confidence intervals. From Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med.* 1996;335:91-97. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

methasone either alone or with thalidomide.²¹ Currently, the optimal induction regimen and number of cycles of treatment are unclear. Further studies are underway to clarify this issue.

What Is the Preferred Time for Transplantation?

From the available data, the use of early high-dose therapy and transplantation immediately after induction chemotherapy appears to be preferential to performing transplant after disease relapse because it is associated with shorter periods of chemotherapy administration and lower toxicity.²² A randomized trial of 202 patients found an improved event-free survival and quality of life in patients who underwent high-dose therapy and autologous transplant early after initial therapy compared with patients who received conventional chemotherapy and transplant as a salvage therapy for relapsed disease.²³ Based on this and concerns about collecting sufficient stem cells for transplantation, most centers prefer to treat patients with only 2 to 4 cycles of standard induction chemotherapy prior to administering high-dose therapy and transplantation.

What Is the Best Way to Collect Autologous Hematopoietic Stem Cells?

Currently, stem cells collected from the peripheral blood (PBSCs) are preferred over those obtained from bone marrow (BM) because engraftment is more rapid and there is usually less contamination of the infused cells with tumor cells.²⁴ Several trials have shown that PBSC transplant reduces transplant-related toxicity and has overall response rates similar to autologous BMT transplants.²⁵⁻²⁷ There are several methods for collecting PBSCs, including administering cyclophosphamide followed by cytokines (G-CSF or GM-CSF) or simply using a cytokine alone. The use of cyclophosphamide or other chemotherapy offers the potential advantage of further reducing the tumor burden prior to transplant. However, it is associated with more toxicity, and several studies suggests that the use of cyclophosphamide does not improve overall outcome.²⁸ Since the use of chemotherapy coupled with cytokine administration has not been directly compared to cytokine administration alone in a randomized fashion, this issue remains unresolved. In addition, the timing, type, and dosing of the chemotherapy and cytokines are also unclear.²⁹⁻³³ Further studies are needed to define these important issues.

Should the Autologous Graft Be Purged of Multiple Myeloma Cells?

The safety and feasibility of transplanting PBSC preparations that were enriched for CD34⁺ stem cells or CD34⁺ subfractions has been explored in an effort to reduce the number of myeloma cells returned to the transplant recipient. While neutrophil and platelet engraftment

occurred at rates similar to unmanipulated PBSC transplants, some studies have reported a higher incidence of cytomegalovirus infection than expected, implying that immune function may be compromised more than usual in CD34⁺ selected grafts.^{34,35} So far, no studies have demonstrated a survival advantage for patients receiving CD34⁺ selected cells.³⁶⁻³⁹ Despite the lack of historical evidence for a benefit to purging, we believe this issue should be revisited for several reasons. The initial studies used heterogeneous induction and transplant conditioning regimens that limited the power of the statistical analyses. In addition, most of the disease relapse in both the purged and unpurged treatment arms was probably due to MM cells in the body that survived the induction and conditioning regimens rather than reinfusion of MM cells in the autograft. This would have significantly obscured the value of purging. There have also been recent improvements in purging technologies, such as isolating stem cells based on expression of the enzyme aldehyde dehydrogenase (ALDH), that may represent advances.⁴⁰ As the disease burden in the body is better controlled with improving induction and transplant conditioning regimens and as purging procedures improve, it may be useful to test again whether eliminating contaminating myeloma cells from the autologous graft can lead to a reduction in disease recurrence. Determining whether this is true will require a new generation of purging studies.

Is One High-Dose Therapy Preferable to Another?

High-dose melphalan as single agent or in combination with TBI has been the most widely used agent in high-dose therapy. TBI leads to a higher treatment-related mortality without any benefit with respect to response rate.^{41,42} Based on this, chemotherapy alone may be superior to using chemotherapy and TBI.¹⁸ Currently, most evidence favors using melphalan alone at doses of 200 mg/m², although the exact dose, schedule, and role of additional transplant conditioning agents all remain to be clarified.^{17,18} In addition, busulfan, cyclophosphamide, and other agents may also hold some promise as components of transplant conditioning regimens.^{43,44} Not surprisingly, patients who attain a complete response following transplant do better than those that do not, so achieving a remission with optimized induction and high-dose therapy is an important goal.

Are Two Transplants Better Than One?

An increasing body of evidence suggests that in selected subgroups of patients, tandem transplants may be more effective than single rounds of high-dose therapy and transplant.⁴⁵⁻⁵⁰ Evaluation of an uncontrolled series of 231 patients newly diagnosed with MM who underwent tandem stem cells transplants suggested that the timely application of a second transplant extended both event-free

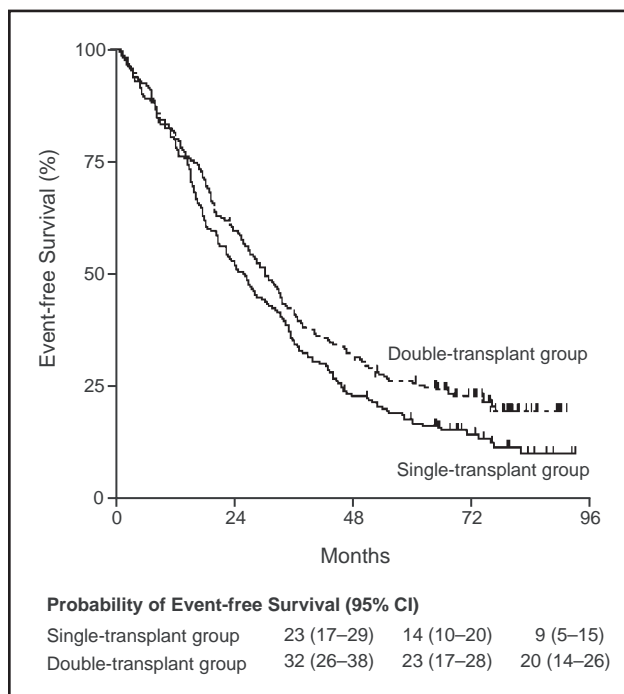


Fig 4. — Tandem transplant in multiple myeloma: Kaplan-Meier estimates of event-free survival in single- vs double-transplant. From Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem cell transplantation for multiple myeloma. *N Engl J Med*. 2003;349:2495-2502. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

and overall survival independent of cytogenetics and β_2 -microglobulin in some patients (Fig 4).⁴⁶ From the initial studies, it appears that only patients who do not achieve a complete response to the first transplant will benefit from a second transplant. Defining the exact populations that may benefit from tandem transplants as well as the type and timing of the tandem transplants remains to be clarified. Numerous studies are now underway to delineate these important factors in this exciting treatment approach to myeloma. Again, it will be important to define the optimal high-dose therapies used with each transplant and their timing.

Allogeneic Transplantation and Multiple Myeloma

Myeloablative Allogeneic Transplants

Sibling or unrelated allogeneic transplants have several potential advantages relative to autologous transplants, including no chance that the transplant will reinfuse MM cells and the possibility that donor cells may mediate immunologic antitumor effects. The complete response rates after allogeneic transplant in patients with myeloma range from 22% to 67%, and it appears that some of these patients may be cured of their disease.⁵¹⁻⁵⁵ A number of observations suggest that graft-vs-myeloma effects occur following allogeneic transplantation, including the identification of myeloma-specific cytotoxic T cells in transplant

recipients and clinical responses to donor lymphocyte infusions.⁵⁶⁻⁵⁹ For example, Tricot et al⁵⁷ described a patient with MM refractory to standard chemotherapy and autologous transplantation who received a matched unrelated T-cell-depleted transplant. Posttransplant, the patient developed a transient and incomplete response with evidence of rapidly progressive disease. However, after receiving a small number of donor peripheral blood mononuclear cells (PBMCs) without any further cytotoxic therapy, the patient developed acute graft-vs-host disease (GVHD) and achieved a complete remission.

Despite these encouraging results, myeloablative allogeneic transplantation has not been widely applied because the treatment-related toxicity is too high (in the 35% to 50% range), primarily related to complications of the high-dose conditioning regimens and GVHD.⁶⁰ Other limitations to allogeneic transplantation include the lack of available acceptable donors for many patients and the relatively advanced age of most patients with MM, which increases the risk of GVHD and other problems. To minimize toxicity and make allogeneic transplantation acceptable in older patients, several strategies are being pursued. One strategy for improving outcomes with allogeneic transplant is to deplete T cells responsible for GVHD from the graft prior to transplant.⁶¹⁻⁶⁴ However, T-cell depletion and other graft engineering strategies are technically difficult and may lead to posttransplant problems such as graft failure, lymphoproliferative diseases, or an increased incidence of infections.

Nonmyeloablative Allogeneic Transplants

Another strategy designed to avoid these concerns and minimize the toxicity of myeloablative conditioning regimens is to use nonmyeloablative conditioning regimens. Several nonmyeloablative preparative regimens have been developed that facilitate engraftment of hematopoietic stem cells from both related and unrelated donors. Einsele et al⁶⁵ recently reported on 22 patients with myeloma who received reduced-intensity conditioning followed by allogeneic stem cell transplantation. All patients had previously undergone autologous transplant. Seven patients received a transplant from a human leukocyte antigen (HLA)-sibling and 15 patients from unrelated donors, including 3 patients from HLA-mismatched unrelated donors. On day 30 following transplant, analysis of chimerism showed complete donor chimerism in unfractionated blood leukocytes in 20 of 22 patients. Eight patients developed acute GVHD and 7 developed chronic GVHD. The transplant-related mortality rate was 23%. Thirteen of 22 patients achieved a partial or complete response, and the median event-free survival was 24 months. Chemo-refractory disease prior to allogeneic stem cell transplantation and the absence of chronic GVHD were associated with shorter event-free survival. The authors concluded that long-term disease control can be achieved, but it is restricted to patients responding to

prior salvage chemotherapy. Badros et al⁶⁶ reported on 31 patients with myeloma who received nonmyeloablative conditioning followed by infusion of bone marrow or PBSCs. Complete donor chimerism was established in 25 of 31 patients at day 30 after transplantation. Nineteen patients achieved an excellent tumor response, including 12 complete remissions. Eighteen patients developed significant acute GVHD, and 10 developed chronic GVHD. The median event-free survival and overall survival were both 15 months. The best outcomes were noted in those patients who had received only one autologous transplant prior to treatment. Similar reports have been published by other groups.

These initial results are encouraging and support the feasibility and efficacy of nonmyeloablative allogeneic transplant in the management of MM. Nevertheless, several issues need to be addressed regarding this strategy prior to its widespread use as a standard therapy. These include improving the prophylaxis and treatment of GVHD, as well as defining the patient populations that may benefit, the optimal timing of transplant, the type and schedule of induction chemotherapy, and the optimal nonmyeloablative conditioning regimen. One promising new strategy is to perform an autologous transplant to reduce the tumor burden and then perform a second nonmyeloablative transplant to create graft-vs-myeloma effects. Kroger et al⁶⁷ reported on 17 patients treated initially with 200 mg/m² of melphalan and autologous transplant followed by dose-reduced regimen of fludarabine, melphalan, and antithymocyte and either related or unrelated donor allogeneic transplant. The treatment-related mortality rate was 11% at a median follow-up of 13 months from allografting. Thirteen patients were alive and 12 were free of relapse or progression. Maloney et al⁶⁸ reported on 54 patients treated with 200 mg/m² of melphalan and autologous transplant followed 40 to 229 days later with 2 Gy TBI and an HLA-identical sibling transplant. At a median follow-up of 552 days from allografting, the overall survival rate was 78% with no treatment-related deaths. One patient died of progressive disease prior to day 100. The Bone Marrow Transplant Clinical Trials Network in the United States is currently conducting a study to compare tandem autologous stem cell transplants vs a single autologous stem cell transplant followed by matched sibling nonmyeloablative allogeneic stem cell transplant (Protocol #0102). This study and other similar studies will begin to define how and when to apply these new stem cell transplant-based approaches to treating myeloma.

Multiple Myeloma Immunotherapy and Stem Cell Transplant

Another promising strategy to enhance the activity of transplant in the treatment of MM is by attacking the MM

directly with immune agents or by enhancing host antimyeloma immunity. Interferon has been used in many trials of MM treatment for its immunologic effects against myeloma.⁶⁹ A meta-analysis of the effectiveness of interferon in MM demonstrated a modest but significant improvement in progression-free survival as both induction and maintenance therapy.⁷⁰ In addition, overall survival was modestly prolonged (median = 4 months) with interferon, and this immunomodulatory agent is still in use in selected settings. Currently, there are several other immunotherapy approaches under active investigation including antibody-mediated therapy of myeloma and vaccination against myeloma.

Alemtuzumab and Myeloma

Several antibodies have been investigated as agents in the treatment of MM, including anti-CD19, CD20, CD38, CD40, CD45, and CD138 (syndecan).⁷¹⁻⁷⁸ While CD20 (rituximab) antibodies have been widely used in the treatment of lymphoma and other B-cell disorders, only a minority of MM cells express CD20, and less than a third of patients have responses to this treatment.^{77,78} Studies using anti-CD38 and anti-syndecan are ongoing.

Another therapeutic antibody that has the potential for use in MM is alemtuzumab (Campath-1H), a humanized monoclonal antibody directed against the CD52 cell surface protein.⁷⁹ CD52 is abundantly expressed on T- and B-lymphocytes and has been found on a subpopulation (<5%) of granulocytes but not on erythrocytes, platelets, or hematopoietic stem cells. Alemtuzumab can cause cell lysis and growth inhibition of primary cells and malignant cells via a variety of mechanisms including complement fixation and antibody-dependent cell-mediated cytotoxicity.^{77,78} Alemtuzumab has been utilized to treat patients with a number of lymphoid malignancies including advanced chronic lymphocytic leukemia, T-prolymphocytic leukemia, and low-grade non-Hodgkin's lymphoma with response rates of 40% to 90%.⁷⁹⁻⁸⁶ Recent studies have found that CD52 is expressed at variable levels on MM cells.^{87,88} It has also been demonstrated that cross-linking the CD52 receptor with alemtuzumab can induce direct growth inhibitory and apoptotic effects in myeloma cell lines and primary MM cells and may have a modest effect as a single agent in treating patients with MM (C.G., unpublished data, 2004).⁸⁸ As in other settings involving alemtuzumab administration, it will be necessary to either observe patients closely or provide prophylaxis against opportunistic infections and cytopenias.⁸⁹ If alemtuzumab is found to be safe and have clinical activity in patients with MM, then it may be used to treat MM either alone or in combinations with chemotherapeutic agents, biologic agents, or other therapeutic antibodies either before or after autologous or allogeneic transplantation. In allogeneic transplants, alemtuzumab treatment in the peritransplant period may also help to prevent GVHD and graft rejection as well as reduce the MM tumor burden.⁹⁰

Multiple Myeloma Tumor Vaccines

Another approach to enhancing host antimyeloma immunity is via MM tumor vaccines. In animal studies, both antibodies and T cells have been described that are capable of regulating the growth of the myeloma clone by specific recognition of the idiotypic portion (Id) of the myeloma-specific immunoglobulin protein (MM-Ig).⁹¹ Vaccination with Id conjugates can trigger Id-specific humoral and T-cell responses in mouse models and in some patients with myeloma, even after high-dose therapy and autologous transplantation.⁹¹⁻⁹⁵ In the setting of allogeneic transplant, it is possible to vaccinate the donor against the patient's idiotypic protein and to transfer myeloma-specific immunity at the time of allografting. In the autograft setting, modest immunologic responses against Id vaccines have been noted.⁹⁵

Dendritic cell (DC) vaccines are another intriguing type of tumor vaccine. The rationale behind this approach is that DCs are the most potent antigen-presenting cell in the body and, when pulsed with tumor derived antigens, may elicit specific antitumor responses. In one form of this strategy, DCs are generated *ex vivo* from the patient PBMCs, pulsed with tumor-derived antigens, and then reinfused or injected subcutaneously back into the patient. This strategy has been used in patients with MM using Id as the target antigen.⁹⁶⁻¹⁰⁰ The DC vaccine generated both immunologic and clinical responses in some patients.

While DCs appear to be safe and possibly potent cellular vaccines, the use of myeloma-associated idiotype as the tumor antigen is limited by several factors. Patients with elevated myeloma Id may be tolerized to the protein. In addition, not all myeloma cells express Id, particularly the stem cells that sustain the disease. Lastly, idiotype may not be the most potent of the myeloma tumor-associated antigens. Investigators at our center have recently developed a novel technology involving transfection of DCs with tumor-derived RNA that circumvents the limitations associated with using defined tumor-associated antigens.¹⁰¹ This strategy has been tested both *in vitro* and *in vivo* in both animal models and in patients with solid tumors.¹⁰²⁻¹⁰⁶ DCs transfected with RNA were found to be potent antigen-presenting cells and capable of eliciting clinically relevant antitumor activity against a variety of murine tumors. In pilot clinical studies using DCs transfected with tumor RNA derived from prostate cancer, immunologic responses have been observed without apparent toxicity.¹⁰⁶ Based on these observations, we have undertaken preclinical studies to examine the effectiveness of autologous DCs pulsed with autologous RNA to elicit cytotoxic T-cell (CTL) responses *in vitro*. We have found that functional DCs can be generated from most patients with MM and can elicit CTLs *in vitro* when pulsed with MM RNA. Once technical issues relating to obtaining sufficient MM RNA are addressed, we will initiate a clinical study using vaccina-

tion with autologous DCs pulsed with MM RNA following autologous PBSC transplant.

New Agents With Multiple Myeloma Activity and Their Role in Stem Cell Transplantation

While autologous and allogeneic transplant represent clear areas of advance in the treatment of MM, most patients will still ultimately die of disease relapse. Other strategies to improve the outcome for these patients and to reduce their risk of relapse following transplantation must be investigated. Several newer agents including thalidomide and bortezomib have been developed over the last several years that may have activity in either the post- or pre-transplant setting. Singhal et al¹⁰⁷ initially reported that thalidomide had anti-MM activity in a series of 84 patients who had relapsed following autologous PBSC transplantation. A number of additional studies have since confirmed this original report and suggest that approximately 30% to 45% of patients with relapsed or refractory disease after transplant will achieve a partial response to single-agent thalidomide.¹⁰⁸⁻¹¹³ Thalidomide has also been used in combinations with other drugs, including dexamethasone, with compelling response rates.^{113,114} The major potential problem associated with thalidomide use is peripheral neuropathy, which requires prompt discontinuation of the drug. Other side effects include thromboembolic events, sedation, constipation, birth defects, neutropenia, hypothyroidism, rash, and bradycardia. The optimal dose of thalidomide has not been defined, but one report demonstrated that responses could occur even with low doses of thalidomide in some patients.¹¹⁵ Thalidomide and dexamethasone can be given prior to autologous stem cell transplant without significantly compromising the stem cell collection, although a slight delay in platelet engraftment may occur.¹¹⁶ Based on these data, thalidomide alone or in combination may play an important role prior to transplant, as part of an induction therapy, as well as following transplant, as either maintenance therapy or as treatment of resistant disease.

Bortezomib (Velcade; also known as PS-341 and MLN-341) is a reversible inhibitor of the proteasome, a large protein complex that degrades ubiquitinated proteins.¹¹⁷ Dysregulating the degradation of such proteins has profound effects on tumor growth and causes cells to undergo apoptosis. Bortezomib is cytotoxic to a variety of cancer cell types *in vitro* and causes a delay in tumor growth *in vivo* in animal models of MM.¹¹⁷⁻¹²⁰ In several clinical studies, the overall response rate of patients was in the 30% to 50% range.¹²¹ Studies involving the planned administration of bortezomib in both the pre- and post-transplant setting are ongoing, but preliminary data suggest that this agent may play an important role as an adjunct to transplant in the treatment of MM.

Conclusions

A host of novel agents and strategies are either available or in development for the treatment of MM. Advances have been made in autologous transplantation, allogeneic transplantation, the development of novel anti-MM agents, and immunotherapy for MM. Combining these different strategies to achieve synergistic responses will be particularly exciting. Future efforts should produce further advances in the combined application of transplantation, novel agents, and immunotherapy in the treatment of MM. It is not unreasonable to hope that over the next decade, MM will become a manageable chronic disease for many and perhaps a curable disease for some.

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