Multiple Myeloma: Role of Allogeneic Transplantation

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An estimated 14,600 new cases of multiple myeloma will be diagnosed in the United States in 2002. Multiple myeloma remains an incurable disease despite significant improvements in complete response rates and overall survival.

**Pretransplant Chemotherapy**

Conventional chemotherapy regimens in this setting have been stagnant for many years; the preferred initial regimen for potential transplant patients has long been infusional vincristine and doxorubicin with oral dexamethasone for 3 to 4 months.[2] Alkylator-based chemotherapy regimens such as MP (melphalan [Alkeran], prednisone) or VBMCP (vincristine, carmustine [BiCNU], melphalan, cyclophosphamide [Cytoxan, Neosar], prednisone) represent other commonly used standard regimens for initial treatment.[3,4]

In previously untreated patients, response rates with each of these regimens range from 50% to 60%, with comparable median survivals.[5] The major toxicity of alkylator-based therapy is myelosuppression, which may result in prolonged cytopenias and/or myelodysplasia/acute leukemia.[6,7] In addition, alkylator-based chemotherapy damages the stem cell compartment, decreasing the ability to collect adequate peripheral blood stem cells. Hence, alkylator-based chemotherapy may be more suitable for patients who are not considered candidates for transplantation.

A recent report from the Mayo Clinic has demonstrated that the combination of thalidomide (Thalomid) and dexamethasone pulsing resulted in response rates exceeding 70%.[8] The benefit of maintenance therapy is as yet uncertain. A number of poor prognostic factors associated with a short survival and/or inferior response to chemotherapy have been identified. These include elevated C-reactive protein and beta-2-microglobulin levels, abnormalities involving chromosome 13, increased soluble interleukin (IL)-6 receptor levels, high plasma cell labelling index, and high bone marrow microvessel density.

**Autologous Stem Cell Transplantation**

The use of high-dose therapy with autologous hematopoietic stem cell transplantation has improved outcomes in patients with newly diagnosed multiple myeloma. A randomized French trial of 200 newly diagnosed patients under 65 years old conclusively demonstrated that high-dose therapy with autologous hematopoietic stem cell transplant was superior to conventional therapy. Rates of overall response (81% vs 57%), complete remission (22% vs 5%), 5-year event-free survival (28% vs 10%), and overall survival (52% vs 12%) were all superior in the transplant group (all statistically significant, \( P < .05 \)).[9]

Investigators at the University of Arkansas reported the results of a pair-mate analysis comparing VAD chemotherapy (vincristine, doxorubicin [Adriamycin], dexamethasone) to tandem high-dose therapy with autologous hematopoietic stem cell transplant. They, too, showed superior results in the high-dose therapy group (event-free survival: 49 vs 22 months, overall survival: 62+ vs 48 months).[10]

Thus, high-dose therapy with autologous hematopoietic stem cell transplant is now considered the standard of care for newly diagnosed multiple myeloma patients. For patients younger than 78 years (per Health Care Financing Administration guidelines), an autologous peripheral blood stem cell transplant should be considered as consolidation of induction therapy, if there are no significant risks.
comorbidities precluding this option. It is preferable that hematopoietic stem cells be collected before exposing the patient to alkylating agents and/or prolonged periods (> 12 months) of chemotherapy.

Tandem high-dose therapy with autologous stem cell transplant has shown improved event-free and overall survival in nonrandomized studies,[11-13] and three randomized trials comparing single to tandem transplants are awaiting final analyses. Even with tandem transplant, a plateau on survival curves has not been achieved. Although approximately 50% of patients who undergo high-dose therapy are alive at 5 years, the relapse rate continues to increase over time.

In contrast to these studies, a retrospective Spanish Registry study in 77 patients with multiple myeloma (who were deemed transplant-eligible but who received conventional chemotherapy) demonstrated a 5-year median survival rate similar to that seen in the above trials.[14] Thus, patient selection may play an important role in response and survival with different treatment options.

**Allogeneic Transplantation**

As suggested above, there does not appear to be a plateau in disease-free survival after high-dose therapy with autologous hematopoietic stem cell transplant, indicating that cures even with tandem autologous transplantation are unlikely. This may be due to either infusion of stem cell grafts contaminated with myeloma cells or the inability to eradicate minimal residual disease. In an attempt to avoid tumor cell contamination in autografts, three different groups have studied the use of highly purified CD34+ cells (positive selection) to support single or tandem high-dose therapy. However, these trials have failed to demonstrate a significant improvement in progression-free or overall survival.[15,16,16a]

Allogeneic transplantation offers two advantages: the absence of tumor-containing grafts and the benefit of a graft-vs-myeloma effect.[16,17] However, allogeneic transplant is an option for a small minority of patients (5%-10%) who have human leukocyte antigen (HLA)-compatible donors and are under age 60.

**EBMT Registry**

The largest experience in allogeneic transplant data was reported by the European Group for Blood and Marrow Transplantation (EBMT). They initially reported on 266 patients with a 51% complete response, an overall treatment mortality rate of approximately 40%, and actuarial survival rates of 30% at 4 years and 20% at 10 years. An update of the EBMT database in over 600 patients showed complete remission rates of 15% (by stringent criteria) with a transplant-related mortality of 20% (1994-1998 data). The relapse rate after the first 2 years was small, but late relapses continue to occur.[18]

**Single-Institution Trials**

The largest single-institution studies have been reported by groups in Seattle (Bensinger et al) and Arkansas (Mehta et al). Bensinger et al reported the results of a trial in which 106 patients underwent allogeneic transplant.[19] Approximately 70% of these patients had chemotherapy-resistant disease, and the majority were very heavily pretreated. The investigators observed a 50% treatment-related mortality within the first 100 days and a 57% overall treatment-related mortality at 1 year. At a median follow-up of 4 years, 23% were alive, but only 16% were progression-free.

These results are similar to findings reported by the Arkansas group in patients with similar characteristics.[20] Table 1 shows results of single-institution trials with allogeneic transplants in multiple myeloma.[18-23] Again, late relapses have been observed.

**Larger Studies**

Alternative donor transplants have equally poor outcomes as those of HLA-identical sibling transplants. Ballen et al reported the National Marrow Donor Program experience in 71 myeloma patients undergoing unrelated donor transplant.[21] They reported a 40% transplant-related mortality. The relapse rate was 35% at 3 years, and only 17% were alive at 5 years posttransplant. Similarly poor results have been reported utilizing alternative donors by the Seattle group.[19] One of the debates surrounding the outcome of allogeneic transplants concerns the fact that they have routinely been performed in heavily pretreated patients, often after autologous transplant. This argument is not supported by the North American Intergroup trial (S9321), which allowed allogeneic transplantation in patients under 55 who had HLA-identical sibling donors. Patients underwent allogeneic transplant following four cycles of VAD and high-dose cyclophosphamide (4.5 g/m²). This arm of the study was prematurely closed when the transplant-related mortality reached 41% in the first 36 patients (R. Kyle, personal communication).
Case-matched comparative studies between allogeneic and autologous transplantation have been reported: All have shown superior outcomes with autologous transplant, given a higher transplant-related mortality associated with allogeneic transplant.[24-27] Of interest, Gahrton et al compared the outcomes of syngeneic (n = 25), allogeneic (n = 125), and autologous (n = 125) transplantation in the EBMT database. The overall 4-year survival from transplant with syngeneic transplantation was 77%, with autotransplantation, 46%, and with allotransplantation, 31%.[24]

**Recommending Allogeneic Transplant**

The selection of patients for allogeneic transplant entails a difficult clinical decision. Heavily treated patients and those with chemotherapy-resistant disease have a uniformly dismal outcome. Newly diagnosed patients with chemotherapy-sensitive disease may derive long-term remissions and potential cures. When the clinician is counseling his or her patient, it may be difficult to recommend the allogeneic approach, with its 20% to 50% early transplant-related mortality and less than 30% 5-year survival (compared with the superior data for autologous transplant).[less than 2% transplant-related mortality and projected 5-year median survival of over 50%). Perhaps patients with extremely poor prognostic features, chromosome 13 deletions, and elevated beta-2-microglobulin may be candidates for allogeneic transplant.

**Donor Lymphocyte Infusion**

It has become increasingly apparent that a significant part of the curative potential of allogeneic transplants is related to alloreactive T lymphocytes with activity against tumor cells. This is particularly true for B-cell malignancies and chronic myelogeneous leukemia, which is the prototype of allogeneic T-cell immunoreactivity against tumor cells. The most compelling clinical evidence consists of (1) higher relapse rates in syngeneic transplants with no graft-vs-host disease (GVHD); (2) the increased relapse rate in T-cell-depleted allografts resulting in reduced GVHD; and (3) the efficacy of donor lymphocyte infusions resulting in complete remission in nearly 70% to 80% of patients with cytogenetic relapse.

**Clinical Trials**

The effectiveness of donor lymphocyte infusion in inducing remissions in recurrent disease following allogeneic transplant has been demonstrated in most hematologic malignancies and some solid tumors, with success rates ranging from approximately 10% to 15% in acute lymphocytic leukemia to 70% to 80% in chronic myelogenous leukemia.[28] This principle has also been proven in patients who have relapsed after transplant from an unrelated donor.[29]

In multiple myeloma, it has been proven that immunoreactive T lymphocytes can induce clinical remissions in patients who have relapsed following allogeneic transplant.[16,17] The largest trial to demonstrate the efficacy of donor lymphocyte infusion in multiple myeloma was conducted by Lokhorst et al.,[17,30] who reported on 52 such procedures in 27 patients with relapsed disease. A total of 14 patients responded (52%), including six complete responses (22%). The median survival for the whole group was 18 months; five patients remained in remission at a median of 31 months post-donor lymphocyte infusion. Nevertheless, the procedure was associated with a significant incidence of GVHD acute cases in 56% and chronic cases in 26%.

Similar findings were updated by this group, who reported data on 39 patients receiving 68 donor lymphocyte infusions, with acute GVHD seen in 47% of patients and chronic GVHD in 33%.[30] Moreover, GVHD remains a problem after donor lymphocyte infusion in myeloma. Favorable prognostic factors reported by Lokhorst and colleagues were a T-cell dose exceeding $1.1 \times 10^8$ cells/kg, response to reinduction chemotherapy before donor lymphocyte infusion, and chemotherapy sensitivity prior to allotransplant. In an attempt to reduce the drawback of GVHD, Alyea and coworkers infused a purified donor lymphocyte graft consisting predominantly of CD4+ lymphocytes after depleting CD8+ lymphocytes.[31] The treatment-related mortality was only 3%, and five of six relapsed myeloma patients responded.

**Further Considerations**

Allogeneic transplant in multiple myeloma is associated with excessive toxicity, with transplant-related mortality ranging from 20% to 50%. In addition, even in the most favorable group of patients—i.e., those who have achieved complete remission prior to transplant, are less than 1 year from diagnosis, and have low beta-2-microglobulin levels—over 50% will relapse within 5 years. Thus, it remains to be proven whether allogeneic transplant alone is curative. As discussed above, donor lymphocyte infusions as immunotherapy for patients with relapsed disease results in response rates of over 50%. Unfortunately, many of these responses are not durable. In addition, donor lymphocyte infusion is associated with a significant risk of
Moderate-to-severe GVHD.

**Nonmyeloablative Transplants**

Due to the excessively high transplant-related mortality associated with conventional allogeneic transplants and the proven efficacy of immunoreactive donor T lymphocytes in inducing a graft-vs-myeloma effect, the current trend is to utilize nonmyeloablative transplants ("mini-transplants") for many hematologic malignancies including multiple myeloma. The basis of the mini-transplant is to provide sufficient immune suppression to allow donor engraftment and subsequent graft-vs-tumor effect.[32]

Preliminary data have shown a high rate of complete remission after nonmyeloablative transplantation, even in heavily treated patients with resistant disease. At the American Society of Hematology meeting in December 2000, a large number of abstracts described nonmyeloablative therapy using different conditioning regimens. Table 2 summarizes some of these trials.[33-39]

**EBMT Data**

The largest study of multiple myeloma patients undergoing nonmyeloablative transplants was reported by Lalancette et al, who presented the EBMT results in 50 patients.[33] All patients engrafted, and 20 of 27 evaluable patients achieved 95% donor engraftment. A new complete response was observed in 16 patients, continuous complete response in 1, new partial response in 7, and continuous partial response in 12.

Transplant-related mortality at 1 year was 32%, and the relapse incidence at 1 year was 13%.[33] Actuarial survival at 1 and 2 years was 54% and 40%, respectively. Patients with good-risk features (complete response or first or second partial response) had a 1-year overall survival, transplant-related mortality, and relapse rate of 83%, 13%, and 11%, compared to the poor-risk group (beyond a second partial response or refractory), with 25%, 67%, and 20%, respectively. Again, unfortunately, many of the observed responses were not durable.

**Arkansas Study**

Another recently reported series from the Arkansas group on 16 poor-risk multiple myeloma patients who received a nonmyeloablative conditioning regimen (with melphalan, 100 mg/m²) followed (in 14 patients) by donor lymphocyte infusion[4] given either to attain full donor chimerism or to eradicate residual disease[4] had a 75% overall response rate with five sustained complete responses at 1-year follow-up.[33] However, 10 patients developed acute GVHD, and most of this group progressed to chronic GVHD. Three patients died of GVHD complications.

Although currently very popular within the transplant community, nonmyeloablative transplants are probably not sufficient to produce cures in multiple myeloma patients. The transplant-related mortality is lower than that observed with conventional allogeneic transplant but remains substantially higher than that seen after autologous transplant (10%-67%). Even with donor lymphocyte infusion[4] whether preemptive in high-risk patients or for persistent disease/relapse[4] does not produce durable remissions in the majority of patients.

**Seattle Study**

The Seattle group reported an intriguing pilot trial of autologous transplant (with melphalan, 200 mg/m²) followed by nonmyeloablative allogeneic transplant.[38] This appealing strategy maximizes tumor cytoreduction with the autologous transplant to optimize the immunoablative graft-vs-myeloma effect and eradicate minimal residual disease. A total of 32 patients completed the planned two transplants, and nearly 100% donor chimerism was achieved by day 56. The complete response rate was 53%, and the transplant-related mortality, 16%. The median follow-up, however, was only 202 days. The Eastern Cooperative Oncology Group has initiated a multi-institutional protocol (E4A98) utilizing the same approach.

**Posttransplant Maintenance Therapy**

The efficacy of posttransplant maintenance therapy has not yet been established. A variety of treatments have been utilized, including interferon-alpha, chemotherapy, corticosteroids, and immunotherapy.[12,13,40] There is growing interest in thalidomide, with or without corticosteroids, as maintenance therapy, based on the cytoreductive activity of both types of agents as monotherapy. Thalidomide has been known to have activity in relapsed multiple myeloma, but has not been tested as posttransplant maintenance therapy.

**Immunomodulation**

An area of intense investigational interest is posttransplant immunomodulation, achieved via anti-idiotypic vaccines, DNA vaccines, or idiotype-pulsed dendritic cells. Studies of anti-idiotypic
vaccines have demonstrated the ability to generate humoral and/or cellular responses in some patients after transplantation. Whether this type of immune enhancement will result in a clinically relevant outcome remains to be proven. Another immunomodulation modality involves the use of lymphocyte and/or dendritic cell stimulatory cytokines, such as IL-12, IL-2 (Proleukin), or granulocyte-macrophage colony-stimulating factor (GM-CSF, Leukine), either alone or in combination. These studies are in their infancy.

Conclusions

Multiple myeloma remains a challenge for the oncologist due to the low proliferative rate of clonal plasma cells resulting in the progressive development of chromosomal abnormalities. These malignant plasma cells demonstrate native chemotherapy resistance even at the time of diagnosis, and this, in turn, accounts for the extremely low complete response rates (5%-10%) to conventional induction therapy. High-dose therapy with autologous hematopoietic stem cell transplantation results in improved response rates as well as increased event-free and overall survival. However, no plateau is appreciated even after tandem transplant. Allogeneic transplants are promising but associated with excessive transplant-related mortality. Nonmyeloablative transplant (mini-allograft) trials have been encouraging, showing prompt allogeneic engraftment and reducing transplant-related mortality, but longer follow-up is needed to compare survival data with other standard therapies. The use of donor lymphocyte infusion has shown impressive response rates even in refractory/relapsed myeloma, but GVHD seems to be a significant factor contributing to transplant-related mortality in this setting. Ultimately, a treatment strategy that utilizes maximal cytoreduction (autologous transplant), immunoablation by alloreactive T lymphocytes (nonmyeloablative therapy with donor lymphocyte infusion) followed by long-term immunomodulation to prevent disease recurrence (thalidomide with or without corticosteroids, cytokines, or vaccines) may provide the optimal control and potential cure of this challenging disease. In addition, we need to more fully understand the clinical implications of different prognostic factors, and use this information to stratify suitable treatment approaches to individual patients.

References:


40. Miller JS, Weisdorf D, Vesole DH, et al: Posttransplant immunotherapy in patients with multiple...
myeloma using concurrent lymphoid (IL-2) and antigen-presenting (GM-CSF) stimulation (abstract 4623). Blood 94(suppl 1):312b, 1999.

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