Hematopoietic Cell Transplantation for Multiple Myeloma

William I. Bensinger, MD

Studies have shown that autologous hematopoietic stem cell transplantation has improved response rates and survival for selected patients with multiple myeloma.

**Background:** Multiple myeloma (MM) is a malignant plasma cell disorder with a median survival of three years. Despite the development of numerous conventional chemotherapy regimens and interferons, there has been little progress in improving the survival of patients with MM. Very high-dose chemoradiotherapy and autologous or allogeneic hematopoietic stem cell transplantation (HSCT) can result in high complete remission rates, even in patients with advanced disease.

**Methods:** A prospective, randomized study has shown that autologous HSCT results in superior response rates, progression-free survival, and disease-free survival compared with conventional chemotherapy. This is the first real advance in the treatment of this disease in 30 years. Unfortunately, few, if any, patients with MM who receive autologous HSCT are cured.

**Results:** Allogeneic HSCT can be curative for a fraction of patients with MM. However, very high transplant-related morbidity and mortality limit the application of allografts to younger patients with compatible donors.

**Conclusions:** Challenges for the future include the development of less intensive or more disease-specific chemotherapy regimens that preserve the antitumor activity but are less toxic, improvement in the control of graft-vs-host disease in the case of allografts and, for autologous graft recipients, the development of vaccines and cytotoxic lymphocytes to augment a graft vs myeloma effect.

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**Introduction**

Multiple myeloma (MM) is a clonal B-cell tumor of plasma cells. The median age at diagnosis of MM is 66 years. The disease is highly sensitive to alkylating agents, corticosteroids, and radiation therapy, but cure has not been achieved with conventional doses and schedules of these agents, and the median survival is only three years. Several lines of evidence provide a rationale for the treatment of younger patients less than 65 years of age with MM using myeloablative chemotherapy with or without total body irradiation (TBI) and hematopoietic stem-cell transplantation (HSCT). Early transplants using high-dose cyclophosphamide (CY) and TBI followed by bone marrow (BM) from syngeneic donors demonstrated that it may be possible to cure a small fraction of patients with refractory MM. In the Seattle experience, two of 12 syngeneic marrow recipients are surviving at nine and 16 years after transplant; one has no evidence of disease, while the other has had a very small, persistent monoclonal spike for more than 15 years. High-dose chemoradiotherapy and autologous HSCT can cure a variety of hematologic malignancies including acute myelogenous or lymphocytic leukemias and Hodgkin’s and non-Hodgkin’s lymphomas.

Allogeneic HSCT may be curative for 10% to 20% of patients with refractory hematologic malignancies and for a larger proportion of patients who are transplanted in remission. In certain diseases such as chronic myeloid leukemia (CML), allogeneic HSCT from HLA-matched or partially matched family members or phenotypically matched unrelated donors has become the treatment of choice. A “graft-vs-myeloma” effect may be associated with allogeneic HSCT or secondary donor lymphocyte infusions (DLIs) in patients receiving allografts for MM.

**Criteria for Response to Treatment**

Complete response (CR) is currently defined as a serum or urine monoclonal protein that is undetectable by sensitive assays, usually immunofixation. In addition, the percentage of narrow plasma cells must be reduced to normal levels of <5%. Response of bone disease has been difficult to evaluate. Patients with lytic bone lesions rarely normalize their skeletal radiographs even after prolonged disease-free intervals, thereby negating evaluation of bone disease in response criteria. Recently, magnetic resonance imaging and computed tomography have been used to supplement the information obtained from skeletal surveys. These studies indicate a higher degree of sensitivity for active disease and could be used prospectively to follow responses to HSCT.

The requirement for immunofixation to define a CR allows for a more rigorous disease response categorization for MM than almost any other malignancy except CML. However, limited studies have been performed using custom fabricated polymerase chain reaction (PCR)-based primers to study marrow from allograft recipients after successful HSCT. These studies indicate that most patients remain PCR positive in the first year following allogeneic transplant. With continued follow-up, however, PCR tests may become negative in subsequent years. The complete disappearance of the M protein is not an absolute requirement for long-term disease-free survival as evidenced by the 16-year progression-free interval following syngeneic transplantation in a patient who continues to produce a consistent, low level of abnormal protein. Presumably, in certain situations, residual plasma cells can produce abnormal proteins without the ability to divide and proliferate.

**Autologous HSCT**

Pioneering studies by McElwain and Powles in the early 1980s demonstrated high response rates to the administration of intravenous melphalan with or without autologous HSCT in patients with advanced MM. Subsequently, others reported high response rates in patients with resistant MM using melphalan at 90 to 200 mg/m² with or without TBI, making it the most widely used high-dose regimen. A variety of other regimens have been used, including busulfan (BU) alone or with CY or thiotepa, and TBI with CY. Response rates of 60% to 90% have been reported with true CR rates of 20% to 50%, which are generally higher in patients with or without TBI.
offered transplant as first-line therapy. In 1995, approximately 400 autologous transplants for MM were reported to the North American Bone Marrow Transplant Registry. The actual number of autologous transplants performed for patients with MM is unknown since many small centers and private practitioners perform such transplants without reporting their data to registries or in journals.

Despite the very high rate of CR after autologous transplant, the majority of patients will relapse within three to four years and few, if any, enjoy long-term remissions of more than five years. Because of the inability to cure patients with autologous HSCT, critics have argued that the inherent selection bias of patients entered on high-dose therapy studies explains the favorable results of phase II studies. A recently completed randomized study, however, was reported by the Intergroupe Francais du Myelome (IFM) in 200 patients with newly diagnosed MM.\(^{25}\) Patients with stage II or III MM were given four to six cycles of conventional chemotherapy followed by random assignment either to continued conventional therapy for 12 more months or to HSCT using TBI and 140 mg/m\(^2\) of melphalan. Analyzed on an intention-to-treat basis, patients who received HSCT had significantly better rates of remission, event-free survival, and overall survival than conventionally treated patients. In a recent update with a median of 60 months of follow-up,\(^{24}\) the group receiving HSCT had a six-year probability of event-free survival of 24% compared with 15% for the group receiving conventional chemotherapy (P < .001), and overall survival at six years was 43% vs 21%, respectively. The most important factor for prolonged survival was the attainment of a CR or very good partial response (ie, >90% reduction in monoclonal protein). Unfortunately, this trial also demonstrated the inability to prevent disease progression in most patients.

In the United States, an ongoing intergroup trial is evaluating the role of timing of autologous HSCT for patients with MM. Newly diagnosed patients with MM undergo induction with conventional chemotherapy followed by a single-dose C and granulocyte–colony stimulating factor for stem-cell harvest. After patients are collected, they are assessed for either HSCT or 140 mg/m\(^2\) of melphalan and TBI or to continued conventional chemotherapy for one year. Patients who progress in the conventional chemotherapy arm are offered HSCT. When completed, this study should provide confirmatory evidence of superior response rates and event-free survival for the early HSCT group. In addition, this study should indicate whether transplantation early after diagnosis or at the time of disease progression has a favorable influence on survival. If survival is equivalent in the two arms, patients could then be spared the morbidity and risk of mortality with early HSCT.

Since the IFM trial and others demonstrated the importance of attaining a CR for survival, efforts have focused on methods of attaining CR for an increasing fraction of patients. One approach utilizes a so-called “tandem” transplant consisting of two successive cycles of high-dose therapy with an infusion of marrow or peripheral blood stem cells (PBSC) after each cycle.\(^{25}\) The regimens have generally included 140 to 200 mg/m\(^2\) of melphalan for the first cycle with a second cycle of either melphalan alone or with TBI. Although the CR rate was improved in some phase II studies, it is not clear that this has translated to an increase in disease-free survival or cure for any appreciable fraction of patients. In some phase II studies, tandem transplants have been shown to result in superior event-free survival compared with conventionally treated patients, but whether two cycles of high-dose therapy are superior to one cycle remains unclear.\(^{30}\) The IFM is attempting to answer this question with a trial of 140 mg/m\(^2\) of melphalan plus TBI (8 Gy) vs a tandem HSCT using 140 mg/m\(^2\) of melphalan for cycle 1 and 140 mg/m\(^2\) of melphalan plus TBI (8 Gy) for cycle 2. With 200 of a planned 400 patients analyzed, the CR and very good PR rates were 32% and 5%, respectively, for the single-cycle group vs 33% and 10%, respectively, for the tandem group.\(^{27}\) Although this study will require further follow-up, these preliminary results suggest that it is unlikely that a tandem transplant approach will improve survival.

### Purging Stem Cells

Although HSCT has become an important treatment modality for a variety of hematologic and solid malignancies, relapse due to inadequately treated disease remains the principal cause of treatment failure. Relapses could be fostered by tumor cells infused in the graft.

Since it is easier to deplete the graft of tumor than to eradicate disease in the patient, intense research activity has been devoted to developing purging methodologies. More than 1,000 articles dealing directly or indirectly with purging technology have been published in the last 15 years. CD34+ cell selection,\(^{28}\) chemical purging with 4-HC\(^{29}\) or maphosphamide,\(^{30}\) and antibodies linked to immunomagnetic beads\(^{31}\) or utilized with complement\(^{24}\) to kill tumor cells have been extensively evaluated in clinical trials with BM or PBSC. Less widely evaluated technologies include CD34+ cell selection with immunomagnetic beads, high-speed cell sorting, physical separation (density gradient), \textit{in vitro} culturing, or cell expansion and incubation with antisense DNA.

In clinical trials, gene marking studies have documented that tumor cells from BM grafts can contribute to relapses following autologous stem cell transplantation in patients with AML, neuroblastoma, and CML.\(^{32,33}\) However, patients with a high probability of graft contamination also have a high probability of not being cured by current treatment regimens, even if normal syngeneic or allogeneic stem cells were infused. Thus, interpreting the effectiveness of purging techniques is difficult, if not impossible. CD34+ cell selection has been used to remove putative tumor cells from PBSC grafts from patients with MM.\(^{26}\) Although 2-3 logs of tumor cells are removed, there is as yet no evidence of improved outcomes for patients so treated. This subject has been recently reviewed.\(^{35}\)

Purging technologies have been intensely researched despite the lack of evidence that infused tumor cells in unpurged grafts contribute significantly to relapses after autologous BM or PBSC transplants. In addition, there is only scant documentation that any selection or purging technology has a significant impact on transplant outcome in any disease. All purging technologies are labor intensive, have the potential to damage the graft and, if routinely adopted, would add significantly to the overall cost of performing autologous PBSC transplants. Therefore, it is important to critically evaluate the role of purging technologies and to demand proof of efficacy in randomized clinical trials rather than accept the ability of a technology to remove tumor cells from the graft as a surrogate measurement of clinical effectiveness.

### Results With Allogeneic Transplants

The status of autologous bone marrow transplantation (BMT) for MM has been the subject of several reviews.\(^{1,36-39}\) More than 500 transplantations from allogeneic donors have been performed worldwide in patients with MM. The largest numbers of patients come from the European Group for Blood and Marrow Transplantation (EBMT) Registry in which more than 360 patients are included (outcome data have been reported on only 162 patients)\(^{37,40,41}\) and from the International Bone Marrow Transplant Registry (IBMTR) in which at least 265 patients have been reported (B. Durie, personal communication, 1997). Considerable overlap of patients exists between the two registries, thus making it difficult to determine the exact numbers and outcomes of patients. The largest single center series of patients receiving allografts for MM comes from Seattle where more than 117 patients have been treated.\(^{42,43}\) These patients are not included in the IBMTR or the EBMT Registry, nor are the results of transplant performed at the Dana-Farber Cancer Center in Boston or the University of Arkansas. The median ages of patients in these studies range from 43 to 48 years, with all patients being less than 60 years old.

In the EBMT Registry, the outcomes for 162 patients with MM receiving autologous transplants in 40 transplant centers in Europe and South Africa have been reported. Approximately half the patients were considered to have chemotherapy-responsive disease prior to transplant. Of the 162 patients, 117 patients were conditioned with TBI and chemotherapy, and the remainder were treated with high-dose chemotherapy alone. Graft–vs–host disease (GVHD) prophylaxis was accomplished with cyclosporine (CSF) and methotrexate (MTX) in 108 patients (45%), while T-cell depletion alone or with CSF was used for the remaining patients. Early transplant-related mortality was approximately 45%, with deaths due mainly to infection, GVHD, or regimen-related toxicities (RRT). The CR rate was 44%.
overall and 60% in evaluable patients. Relapse-free survival at six years for the patients entering CR was 34%. Actuarial survival for all patients was 28% at seven years. Patient gender had an important effect on outcome; at four years, women had a better survival (41%) compared with men (26%).

The EBMT has performed a recent analysis of 265 patients receiving HLA-identical sibling transplants for MM between 1988 and 1993 (B. Durie, personal communication, 1997). At four years of follow-up, the probability of survival was 35% for patients with Karnofsky performance scores of >70 pretransplant and approximately 15% for patients with scores <=70. In univariate analysis, other factors associated with improved four-year survival were a pretransplant serum creatinine of <1 mg/dL, a serum albumin of >3 gm/dL, chemotherapy-sensitive disease, and a good response of the disease to transplant. Among patients surviving at least one year from transplant, the best four-year survival (80%) occurred in patients with chemotherapy-sensitive disease.

In the Seattle experience, only 27% of 117 patients had chemotherapy-sensitive disease. All patients received BU and CY with or without TBI using lung and liver shielding. GVHD prophylaxis was CSP plus MTX. Mortality within the first 100 days occurred in 49% of patients due to RRT, GVHD, hemorrhage, or infection. Late transplant-related deaths (beyond 100 days) occurred in another 15% due to chronic GVHD or infection. Asperillus was a particularly troublesome organism that accounted for 11 deaths. For all 117 patients, the probabilities of survival and relapse-free survival were 21% and 18%, respectively, at five years. The CR rate was 33%, and for patients who achieved a CR (n = 39), the relapse-free survival at five years was 39%.

Investigators at the University of Arkansas have reported on outcomes of 80 patients with MM receiving HLA-matched allogeneic transplants. These results are complicated by the fact that two thirds of the patients had received a prior single or double autograft. They observed a 54% early death rate, and 26% of patients achieved CR. They found that an albumin of <3.5 g/dL and resistant disease prior to allograft were significant predictors of disease progression after transplant.

Investigators at Dana-Farber Cancer Center transplanted 21 patients with chemotherapy-responsive disease. The preparative regimen was CY and TBI for all but two patients. Marrow was T-cell depleted with an anti-CD6 monoclonal antibody and complement, which removed 1.5 logs of T cells. Transplant-related mortality was low with two deaths (10%) -- one from veno-occlusive disease of the liver and another from graft rejection. The CR rate was 33%, with three patients remaining disease-free between three and four years from BMT.

In Vancouver, 19 patients received allogeneic BMT from HLA-matched siblings. Eighty percent of patients had chemotherapy-sensitive disease. All patients received BU and CY with or without melphalan. GVHD prophylaxis was CSP with MTX or methylprednisolone. Transplant-related mortality was 16%, the CR rate was 58%, and the relapse-free survival was 40% at three years.

The Toronto group reported the results of 22 patients receiving allogeneic BMT from HLA-matched related donors. Patients were mainly chemotherapy sensitive and received BU and CY (n = 8) or CY and TBI (n = 14) with CSP and MTX for GVHD prophylaxis. The transplant-related mortality in the first 90 days was 27%, but an additional seven patients (32%) died of causes not related to myeloma. The CR rate was 42%, and the three-year survival and relapse-free survival were 32% and 22%, respectively.

Published results indicate that 33% to 58% of all patients receiving HLA-matched allografts achieve a CR and that 30% to 50% of those achieving a CR remain disease-free for three to six years after BMT (Table). It can be concluded that by carefully selecting patients with chemotherapy-responsive disease, transplant-related mortality can be reduced to less than 30%. Unfortunately, such selection excludes the majority of candidates from allografting. Since approximately 14,000 new cases of myeloma are diagnosed annually in the United States (SEER data), less than 2% of patients with MM receive allografts.

### Table: Sibling HLA-Matched Allografts for Multiple Myeloma

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of Patients</th>
<th>Age Median (Range)</th>
<th>Responsive Disease</th>
<th>Number Early Deaths</th>
<th>CR After Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBMT Registry</td>
<td>162</td>
<td>43 (23-59)</td>
<td>84 (52%)</td>
<td>73 (45%)</td>
<td>72 (44%)</td>
</tr>
<tr>
<td>IBMT Registry</td>
<td>265</td>
<td></td>
<td></td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Seattle</td>
<td>117</td>
<td>44 (23-58)</td>
<td>52 (27%)</td>
<td>57 (49%)</td>
<td>39 (33%)</td>
</tr>
<tr>
<td>Arkansas*</td>
<td>80</td>
<td>45 (29-68)</td>
<td>18 (23%)</td>
<td>43 (54%)</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>Boston</td>
<td>21</td>
<td>43 (37-55)</td>
<td>21 (100%)</td>
<td>2 (9%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Vancouver**</td>
<td>19</td>
<td>48 (28-54)</td>
<td>15 (80%)</td>
<td>3 (16%)</td>
<td>11 (58%)</td>
</tr>
<tr>
<td>Toronto**</td>
<td>22</td>
<td>43 (25-53)</td>
<td>16 (73%)</td>
<td>6 (27%)</td>
<td>9 (42%)</td>
</tr>
</tbody>
</table>

* Two thirds of patients had received a prior autograft.

** Data also reported to EBMT Registry or IBMT.

The development of GVHD, both acute and chronic, accounts for significant morbidity and mortality in the majority of reports. The EBMT study found a 14% incidence of grade 3-4 acute GVHD when no T-cell depletion methods were used and 9% among recipients of T-cell depleted marrow. Patients with grade 3-4 acute GVHD had a significantly poorer survival than patients who had no GVHD or grades 0-2. In the Seattle experience, acute or chronic GVHD contributed to death in 14% of patients. The Vancouver study found a 68% incidence of grades 2-4 acute GVHD among the 19 matched allograft recipients, with death due to GVHD in 11%.

The use of selective T-cell depletion using an anti-CD6 monoclonal antibody technique is intriguing. In a report by Anderson et al., only 2 (10%) of 21 patients developed severe GVHD, with no deaths attributable to GVHD. This very good outcome may be related to patient selection. Nevertheless, GVHD remains a significant problem after allografting in part because patients with MM comprise an older population. Improvements in prevention of GVHD are needed.

### Conditioning Regimens for Allogeneic Transplants

The preparative regimens used for cytoreduction and immunosuppression have been limited to TBI with alkylating agents or alkylating agents alone for both autologous and allogeneic HSCT. The regimens for autologous transplant have tended to be less intense due to the older age of patients and because immunosuppression is not needed for hematopoietic recovery. The EBMT studies of allografts found no particular advantage for TBI-based regimens compared to BU plus CY regimens in terms of response rates or survivals. Similarly, the use of TBI vs chemotherapy was not significantly different for day 100 mortality, relapse,
progression, survival, or progression-free survival by univariate analysis in the Seattle studies of allografts or autografts. The TBI given in Seattle uses a linear accelerator to deliver photons with lung and liver shielding to 90% of delivered dose followed by electron beam therapy to the rib cage covered by shielded areas. The results of this modified TBI were no better than following chemotherapy, but the modified TBI regimen was used mainly in patients with the most advanced disease. Investigators in Germany have recently used this modified TBI regimen with 12 mg/kg of BU and 120 mg/kg of CY followed by autologous HSCT. They reported no transplant-related mortality and a 44% CR rate in previously untreated patients.

The Vancouver group reported a particularly high complete response rate (58%) using BU, CY, and melphalan as the preparative regimen prior to allografting. This report suggests that this regimen is particularly active and well tolerated in a group of chemotherapy-sensitive patients with MM. This regimen was also reported to be highly active in patients with MM who received autologous HSCT but was associated with severe veno-occlusive disease in three of 14 patients.

The optimal conditioning regimen for preparing patients with MM prior to allografting has yet to be identified. Novel strategies such as the use of high-energy radioisotopes conjugated to bone-seeking chelates are being explored.

Alternative Donors

Since relatively few patients with MM have HLA identical siblings, the ability to increase the safety of transplants from partially matched related and phenotypically matched unrelated donors would increase the number of patients who could be offered curative-intent therapy. From the EBMT Registry, six alternative donor transplants (three from HLA-mismatched related donors and three from HLA-matched unrelated donors) have been reported. Death occurred less than 75 days from transplant in five recipients, with the sixth patient surviving 200 days after transplant.

In Seattle, 14 patients have been transplanted from one antigen mismatched (n = 10) or two antigen mismatched (n = 4) related donors. Deaths from GVHD (n = 1), RRT (n = 2), infection (n = 2), or hemorrhage (n = 1) occurred in six recipients mismatched for one HLA antigen, and one patient died from progressive disease. Three of 10 survive disease-free from one to nine years after BMT. Among four recipients of related marrow mismatched for two HLA antigens, two died of transplant-related complications, one of progressive disease, and one survives disease-free three years after transplant.

Sixteen patients with MM have been transplanted with marrow from fully HLA-matched (14 patients) or minor mismatched (two patients) unrelated donors. Eleven of the 14 HLA-matched recipients died: three of GVHD, three of RRT, three of infection, and two of progressive disease at three years. HLA-matched unrelated donor recipients survive one to seven years after transplantation. One of two recipients of marrow from HLA-mismatched unrelated donors survives disease-free at two years.

The Vancouver group has reported on outcomes for seven patients transplanted from three HLA partially matched relatives or four matched unrelated donors. The preparative regimens were chemotherapy for the related donors and CY and 12 Gy of TBI for the unrelated donor transplants. Grades 2-4 acute GVHD occurred in all seven recipients and was the cause of death in two patients. Two later deaths from chronic GVHD occurred, and one patient died from disease progression. Two of seven patients survive, one in partial response at four months and one in CR at 30 months.

Allografting from partially matched or unrelated donors is limited and is usually performed in patients with advanced refractory MM. For this reason, it is not unexpected that transplant-related mortality is high. Some recipients are surviving free of disease at two to nine years after transplant, which suggests that further studies designed to improve outcome are warranted.

Graft-vs-Myeloma Effect

Due to small numbers and heterogeneity of risk factors in registry data, no transplant studies to date have been able to identify a graft-vs-myeloma effect. However, three case reports of five patients with post-allograft relapses who were infused with autologeneic leukocytes from their original donors have demonstrated an antmyeloma effect that was associated with GVHD. Complete remissions were obtained in three of five cases, and partial responses occurred in the remaining two cases. Several other small series of patients receiving donor lymphocyte infusions for relapsed MM indicate that approximately 50% of patients will achieve CRs. These results are similar to the now universally recognized graft-vs-leukemia effect observed with leukocyte infusions for patients with CML. These small studies should pave the way for innovative strategies involving the infusion of selective subsets of autologeneic T cells, as has been described in CML.

Peripheral Blood Stem Cells

Due to ease of collection and faster hematopoietic recovery, PBSCs have already supplanted BM as the primary source of cells for autologous HSCT. Some reports have suggested that fewer circulating myeloma cells are detectable in PBSC compared to BM, although as previously noted, the impact of this finding on clinical outcome remains unclear. To date, results of autologeneic PBSC transplantation suggest that this technique can produce substantially more rapid engraftment than that obtained with BM. Furthermore, contrary to widespread expectations, acute GVHD has not been intolerable, even with unmanipulated PBSCs that contain many more T cells than are present in a normal BM graft. Although GVHD remains a formidable problem for patients with MM who receive allografts, the earlier recovery of neutrophils and platelets has the potential to reduce infectious complications, which should encourage cautious exploration of this new source of stem cells in patients with MM.

Allotransplants vs Autotransplants

In an EBMT Registry study, autologeneic HSCT was compared to autologous HSCT for patients with MM. Patients were matched for the most important prognostic factors for autologeneic transplantation, ie, according to the sex of the patient and the number of treatment regimens before transplantation. A total of 189 autologeneic transplant recipients were compared with an equal number of matched autotransplant recipients. A comparison showed that most pretransplant prognostic factors were well matched. However, the median age in the autotransplant group was somewhat higher (49 years) than for the allotransplant group (43 years). The follow-up time was shorter for autotransplant recipients than for allotransplants since autotransplantation was not performed until 1986, while allotransplantation began in 1983. The CR rate and the time from transplant to CR was similar in both groups. The most striking difference was a higher transplant-related mortality in the autologeneic group, amounting to more than 41% compared with 13% in the autotransplant group. This high incidence resulted in a significantly better median survival for autologeneic transplantation (34 months from time of transplant) than for autologeneic transplantation (18 months). At approximately four years, however, the two curves merged with no significant difference in survival. Relapses continue to be observed among autograft recipients, while a fraction of recipients of allografts, the only known potentially curative therapy for this disease, remains disease-free. However, only a small fraction of patients can undergo allografting.

Future Directions
One probable reason for the high transplant-related mortality in patients with MM may be related to the primary immunodeficiency in this disease. It is not likely that age plays a significant role since the median age of patients who have undergone allogeneic transplantation is 48 years, which is not significantly different from the median age of patients transplanted for CML. Furthermore, patients with CML, although of similar age to patients with MM, have had relatively little chemotherapy prior to transplant and often have large granulocyte reserves in blood and other tissues than may protect against early infections. Thus, improved sources of stem cells, such as PBSC, that result in earlier engraftment and immune reconstitution should reduce infectious complications.

Future studies of allogeneic marrow transplantation in MM should focus on regimens that are less toxic but able to preserve antitumor effects such as external beam TBI with lung and liver shielding or radioisotopes linked to bone-seeking chelates. These measures should include efforts for more effective prevention of GVHD and infections, possibly with the use of allogeneic PBSC. Such treatments could be combined with a return of allogeneic donor lymphocytes or subsets of lymphocytes (eg, CD4 lymphocytes) that may have a graft-vs-myeloma effect without increasing GVHD. Outcomes after autologous transplantation could be improved by the use of posttransplant vaccines or the infusion of autologous cytotoxic lymphocytes specific for myeloma cells.

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References


*From the Fred Hutchinson Cancer Research Center, Seattle, Wash.*

*Address reprint requests to William I Bensinger, MD, Fred Hutchinson Cancer Research Center, 1124 Columbia St, M-185, Seattle, WA 98104.*