Original Article

The Role of Hematopoietic Stem Cell Transplantation in the Treatment of Multiple Myeloma

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Multiple myeloma, stem cell transplantation, graft-versus-myeloma

Abstract
The treatment of multiple myeloma has dramatically improved in the past 10 years. The availability of new drugs has broadened chemotherapy options; however, complete remissions (CR) are infrequent, and cure is still rare. High-dose therapy followed by autologous or allogeneic stem cell transplant has emerged as a promising means to increase remission rates and improve survival. Autologous transplants have not always shown survival benefits in randomized studies because the majority of patients who undergo transplant relapse, and patients given conventional therapy can receive salvage transplants at the time of relapse. CR has been found to reliably predict survival and thus the efforts to improve remission rates using autologous transplant include tandem transplants, targeted radiation, cytoprotective agents, or posttransplant immunotherapy. Only allogeneic hematopoietic stem cell transplantation is potentially curative, because of an immunologic graft-versus-myeloma effect. High transplant-related mortality associated with allogeneic stem cell transplantation is currently the major limitation to wider use of this modality. Although patients who receive either allogeneic or autologous stem cell transplants for multiple myeloma have similar 3- to 5-year survivals, only allograft recipients appear to enjoy long-term disease-free survival. Promising approaches designed to improve the therapeutic index of allografts include the use of nonablative conditioning regimens, peripheral blood cells rather than bone marrow, graft engineering, and targeted conditioning therapies such as bone-seeking radioisotopes. (*JNCCN* 2004;2:371–378).

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Multiple myeloma (MM), a clonal B-cell tumor involving plasma cells, responds to alkylating agents, corticosteroids, radiation therapy, and several new agents including thalidomide and bortezomib. With conventional chemotherapy, complete responses are uncommon, and cure is only rarely achieved. Success in the management of refractory hematologic malignancies with stem cell transplantation (SCT) led to the exploration of this treatment for patients with MM.[1–4] A graft-versus-myeloma (GVM) effect may be associated with allogeneic SCT for patients with MM.[5–7] In contrast, SCT from autologous or syngeneic donors provide little or no GVM effects requiring the intensive application of chemotherapy with or without radiation to accomplish eradication of disease.

Autologous Stem Cell Transplantation

Several prospective randomized trials have been conducted comparing conventional chemotherapy with high dose therapy (HDT) using autologous stem cell support for patients with MM.[8–10] The French intergroup study showed that high-dose melphalan and total body irradiation (TBI) followed by autologous SCT, when applied as consolidation therapy after conventional chemotherapy induction, resulted in higher response rates, longer disease-free intervals, and better overall survival compared with continued conventional chemotherapy for up to 1 year.[8] Seven-year follow-up evaluation of that study continues to show a survival advantage for patients in the SCT arm.[11]

The Medical Research Council Myeloma VII trial compared combination chemotherapy with combination chemotherapy followed by single-agent high-dose melphalan and autologous SCT.[12] This large trial, with 407 patients randomized, showed a 12-month improvement in the median survival (P = .04) and a similar improvement in event-free survival. A smaller study reported

higher response rates in the HDT arm but no differences in event-free or overall survival.[13]

The results of a large U.S. intergroup trial were recently reported.[10] This trial enrolled 899 patients newly diagnosed with MM, of whom 805 received VAD induction for 4 cycles followed by mobilization and collection of peripheral blood stem cells (PBSC) after cyclophosphamide (CY) 4.5 g/m^2. Patients (n = 510) were then randomized to receive standard dose vincristine, BCNU, melphalan, CY, and prednisone (VBMCP) or melphalan 140 mg/m^2, and 12 Gy TBI followed by autologous PBSC infusion. This trial allowed patients who received conventional dose VBMCP to receive salvage autologous transplant at disease progression.

Progression-free survival was better with upfront high-dose therapy (25 vs. 21 months), but overall survival rates were similar. The complete response rates after high-dose therapy were disappointing at 17%, most likely because of the use of melphalan plus TBI combination, which is considered inferior to melphalan 200 mg/m^2.

This trial confirmed the results of a previously reported French study that salvage transplant produced similar survival to upfront transplantation.[14] Another trial compared conventional therapy with HDT and SCT in patients aged 55 to 65 years. Although there was a trend favoring event-free survival was seen in the HDT plus SCT group (P = .07), the overall survival rates were not statistically different.[15]

The Dutch/Belgian cooperative group, HOVON, took a somewhat different approach by first giving intensified melphalan 70 mg/m^2 without stem cell support for 2 cycles followed by a cycle of HDT with CY, TBI, and autologous SCT.[16] Patients receiving HDT had a higher CR rate but without differences in event-free or overall survival. Although not really a comparison of conventional dose chemotherapy versus HDT, this study does indicate that intermediate-dose melphalan is an alternative to high-dose melphalan.

A confounding feature of many of these randomized studies is the use of HDT and SCT for patients in the conventional therapy arm for salvage, and the significant (20% to 25%) dropout rate for patients who were randomized to receive HDT and SCT, but who never received it. This reduces the power to measure effects on disease-free intervals, but overall survival may not be affected if combined HDT and SCT as salvage therapy are effective at prolonging survival.

Unfortunately, despite autologous SCT, the majority of patients with MM will experience relapse and die of recurrent disease. Relapses occur because of failure to eradicate disease or because of the reinfusion of malignant cells contained in the stem cell graft. One randomized study evaluated the effect of removing myeloma cells from autologous stem cell grafts on outcome and found no improvement in overall or progression-free survival.[17] These results occurred even though the purging technique removed 3 to 4 logs of tumor cells from the grafts, which implies that residual host disease is the major contributor to relapse. Although attempts are being made to further deplete stem cell grafts of residual myeloma cells,[18] purging, even if 100% effective, will not have much impact on outcomes until improvements are made in the ability to eradicate residual host disease.

Multiple studies have shown that obtaining a complete response (CR) is the most important factor for long term survival.[8,19–21] In the study by Attal et al.,[8] the 5-year probability of survival after transplantation was 72% among patients who achieved a CR or very good partial response compared with 39% among patients who only achieved a partial response (PR; P = .0001). A large retrospective study by the Spanish registry and several smaller studies have shown the benefit of immunofixation-negative CR on event-free and overall survival.

Complete remission requires serum or urine monoclonal proteins that are undetectable by sensitive assays, usually immunofixation, stable or improved bone disease, and no monoclonal plasma cells detectable in marrow.[22,23] In an effort to improve the detection of minimal disease, researchers have used polymerase chain reaction (PCR)-based primers using IgH fingerprinting or custom primers from individual patients to study marrow and blood from allograft recipients after successful BMT. PCR negativity appears to be associated with prolonged disease-free survival.

Corradini et al.[24] studied results for 70 patients who had received an allogeneic transplant. In 48 patients, the generation of clone specific molecular markers was successful. In 16 patients, persistent PCR negativity was obtained (33 %); 13 patients (27%) showed a persistent PCR positive status, and 19 (40%) showed a mixed pattern. The cumulative incidence of relapse at 5 years was 0% in persistently negative and 100% in consistently positive patients, and it was 33% in patients with a mixed pattern.[24] Relatively few patients who undergo autologous SCT (7%–16%) actually ex-

perience a molecular remission. These studies indicate that the eradication of minimal residual host disease is crucial to long-term disease-free survival.

Recent efforts to improve the ability to achieve CR have focused on innovative HDT regimens or immunotherapy approaches to deal with minimal disease present after SCT. A randomized trial that compared melphalan alone at 200 mg/m^2 versus melphalan 140 mg/m^2 plus 8 Gy TBI showed survival at 45 months to be 66% for patients receiving melphalan alone and 45% for patients receiving melphalan and TBI.[25]

In another strategy, the French Intergroup compared a single autologous SCT after melphalan 140 mg/m^2 plus TBI with a double-transplant regimen of melphalan 140 mg/m^2, followed 2 to 4 months later by melphalan 140 mg/m^2 plus TBI.[26] The CR rate was 50% among the double transplant group compared with 42% in the single transplant group (P = NS). The tandem transplant group had a projected 7-year survival of 42% versus 21% for the single transplant group ($P < .01$). Subgroup analysis of this trial showed that patients already in CR after transplant number 1 who had a second transplant had a survival identical to patients in CR who received only a single transplant. The major survival benefit was for patients who were not in CR after the first of 2 planned transplants. These observations confirmed a prior retrospective comparison of 1 versus 2 transplants.[27] Other randomized trials of one or two transplants have not shown survival benefits, although this may be because of limited follow-up evaluation.[28,29] Nevertheless, tandem autologous transplants represent one potentially useful therapeutic strategy for the treatment of MM. A trial in 40 patients given 280 mg/m^2 melphalan (which is considered above the maximum tolerated dose) along with the cytoprotective agent amifostine, reported a CR rate of 60% with no deaths or grade 3 toxicities caused by the regimen.[30]

Another technique for improving the eradication of residual myeloma involves the use of targeted radiation delivered by antibodies or bone-seeking isotopes. Holmium-166 (^{166}Ho), a beta-emitting radio metal with a half-life of 26 hours, has been linked to DOTMP, a tetra phosphonate chelate, to achieve rapid and specific uptake in bone and bone surfaces. In phase 1 and 2 trials, increasing doses of ^{166}Ho-DOTMP were given along with high dose melphalan and this was followed by autologous SCT.[31] A CR rate of 38% was seen, with a median overall survival in excess of 24 months. Sammarium-153, another high energy isotope, was linked to EDTMP, another tetra phosphonate chelate, and studied in 7 patients with MM, 2 of whom received allogeneic marrow.[17] CR resulted in 4 of 7 patients. Further studies with targeted radioisotopes are warranted.

After autologous SCT, immunotherapeutic manipulations are attractive theoretical methods to deal with both residual host disease and reinfused tumor cells. Boosting host immune responses after SCT could help patients eliminate cells that survive high-dose therapies, and patients still recovering from the effects of transplantation should be better able to tolerate these treatments as opposed to further chemotherapy. After SCT, the host immune system is still recovering, but studies show that T cells reactive against residual myeloma can be isolated from peripheral blood. Research in patients recovering from SCT showed that the patients' tumor-specific idiotype (id) protein can be used for vaccination after autologous SCT and generate id-reactive T cells.[32–34] This id also has been used to pulse autologous dendritic cells and generate similar responses.[32–34] Although these approaches are attractive, none have yet been shown to result in clinically important responses.

Recent work indicates that myeloma cell biology, namely the presence of chromosome 13 deletions, could have an important impact on survival equal to the attainment of CR.[35]

Allogeneic Marrow Transplantation

The EBMT Registry has reported the largest series of patients receiving allogeneic transplants for MM with 690 patients.[36] The EBMT registry analysis examined transplants performed on 334 patients from 1983 to 1993 and 356 patients from 1994 through 1998. Of the patients undergoing transplantation during the latter period, 133 (37%) received peripheral blood stem cells (PBSC) rather than marrow. The most important observation was a reduction in transplant-related mortality (TRM) from 46% to 30% between the time periods. The reduction in mortality was a result of fewer deaths from opportunistic infections and interstitial pneumonias. This was caused, in part, by better patient selection with less previous treatment and improvements in supportive care. The improvement in results did not appear to be a result of the introduction of PBSC. The overall survival after 3 years improved from 35% during the 1983 to 1993 period to 56% during the 1994 to 1998 period. A phase 2 study

using high-dose busulfan and melphalan followed by allogeneic PBSC from matched sibling donors in 30 patients with MM, reported a reduced transplant related mortality.[37] The TRM was 16% at 100 days, 30% overall, with an 81% CR rate. Survival and progression-free survival at 6 years were 65% and 70%, respectively.

The largest single center series of patients receiving allografts for MM comes from Seattle, where 136 patients were treated between 1987 and 1999. Risk factor analysis has been reported on the initial 80.[38] The median age for patients in these studies was 47 years, with all patients younger than 60 years old. In the Seattle experience, only 21% of 136 patients had chemotherapy-sensitive disease responsive to initial treatment; the remaining patients were beyond a first response or had chemotherapy-resistant disease. For all 136 patients, the probabilities of survival and RFS were 22% and 14% at 8 years, respectively. The CR rate was 34%, and for patients who achieved a CR (n = 46), the survival and event-free survival rates at 5 years were 48% and 37%, respectively.

Because only 25% to 30% of patients with MM will have a matched related donor, researchers have shown interest in exploring the potential for matched unrelated donors (MUD) to substitute for family members. MUD transplants are associated with higher rates of rejection, graft-versus-host disease (GVHD), and mortality, and relatively few patients have received these transplants. Patients selected for transplant from MUD usually have advanced disease and may have undergone one or more failed autologous transplants.

In a survey conducted by the National Marrow Donor Program, 71 patients with MM received transplants from unrelated donors over an 11 year period.[39] Patient ages ranged from 22 to 60 years, with a median of 45 years. One third had undergone a prior failed autologous transplant. Twenty-four percent of the donors were class 1 or class 2 mismatched. T cell depletion was used in 38% and TBI was used in 63%. Nine percent experienced graft rejection. A CR was achieved in 55%, but transplant-related mortality by 100 days was 41%. The projected overall survival was only 17%. These results indicate a greater need for strategies to reduce infectious complications, organ toxicity, and GVHD.

Graft-Versus-Myeloma Effect

Small series of patients with MM who developed post allograft relapses and who subsequently underwent infusion with allogeneic leukocytes from the original stem cell donors (DLI) have clearly shown a GVM effect associated with GVHD.[5–7,40,41] Between 50% and 70% of patients receiving DLI for relapsed MM were reported to experience CR,[7,42,43] although, in a more recent survey of 25 patients at 15 centers, CRs were obtained in only 7 (28%) of patients who received one or more DLI infusions.[41] In a review of DLI for relapsed MM, a GVM effect was noted in 18 of 22 patients who developed GVHD compared with only 2 of 7 patients who did not develop GVHD (P = .02).[44] That study and the previous retrospective study of 37 patients suggest that, although GHVD may not be essential for GVM, the relationship between the two is very strong.

Minimizing GVHD

T cell depleted grafts are, in theory, an attractive approach to preventing GVHD and its associated morbidity. Unfortunately, most studies of T-cell depletion used for allogeneic SCT for patients with MM have reported continuing problems with GVHD, high mortality from infections, and attenuated GVM effects. A retrospective study of 66 patients from Dana-Farber/Partners CancerCare indicated that the risk of mortality was greater than with autologous transplants because of GVHD and infection. Furthermore, relapses at 2 years were similar to those for autologous transplantation, indicating that T cell depletion may have interfered with a GVM effect.[45]

In another study of T cell depleted allografting for MM performed in the Netherlands, 56 patients were reported to have a survival rate inferior to those for comparable autograft patients because of high TRM (32%) and lack of GVM effect.[46] This lack of GVM could, in theory, be overcome by pre-emptive DLI given shortly after transplantation.[47]

Nonablative Allogeneic Transplants

The transplant-related mortality of 25% to 50% after high-dose therapy and allografting, even in younger patients, limits the application of this approach. Because the majority of patients who develop MM are older than age 55 years and need closely HLA-matched family members to serve as donors, fewer than 10% of patients are even eligible for allogeneic SCT. The high-intensity conditioning regimens customarily used

before allogeneic transplants are designed to produce cytoreduction and immunosuppression sufficient to allow establishment of the donor graft. The demonstrated efficacy of DLI in relapsed allograft patients suggests that the allogeneic GVM effect is a major reason cure can be achieved. This has led to the exploration of low-intensity conditioning regimens, designed more for immunosuppression rather than cytoreduction, with the aim of establishing consistent donor engraftment while minimizing toxicity and damage to normal host tissues.

Specific low-intensity regimens used vary widely and include melphalan 100 to 140 mg/m^2, often with added fludarabine, and total body irradiation 200 cGy with fludarabine or sometimes with added cyclophosphamide. Currently, no consensus exists on which of these regimens is superior in terms of toxicity or efficacy.

A regimen using fludarabine, low-dose TBI (200 cGy), and a combination of 2 potent immunosuppressive drugs, including mycophenolic acid (MMF) and cyclosporine, showed that engraftment was reproducible with low TRM, but also showed poor response rates, suggesting that additional cytoreduction was necessary.[48,49] A new strategy was adopted for patients with MM who had not received a previous high-dose regimen using a "tandem" autologous, nonablative allogeneic transplant approach. Patients undergo autologous PBSC collection followed by melphalan 200 mg/m^2 and SCT to provide cytoreduction and some immunosuppression. Two to 4 months later, after patients recovered from the effects of the HDT regimen, they received a nonablative regimen of 200 cGy TBI, MMF, and cyclosporine with allogeneic PBSC. Fifty-four patients aged 29 to 71 years (median age, 52 years) received this tandem transplant strategy. All patients were considered stage II or III, and 48% had refractory or relapsed disease. One patient died of CMV pneumonia after the autograft, and 52 received the nonablative transplant. With a follow-up of 18 months after allografting, the survival at 24 months was 78%, overall TRM was 22%, and the CR rate was 57%. Only four patients developed severe GVHD, and chronic GVHD developed in 46%.[50]

Nonablative or reduced-intensity regimens before allogeneic SCT for MM have been reported from other centers. One report used melphalan 100 mg/m^2 to prepare 45 patients before allografting. The median age was 56 years, and donors were HLA matched; 12 were MUD. TBI and fludarabine were added to the regimens of patients receiving transplants MUD. The overall TRM was 38%, and 64% achieved CR or near CR. Overall survival at 3 years was only 36%. A significantly better survival for patients transplanted was seen as part of the planned tandem strategy versus 2 failed autografts (86% vs. 31%; P = .01).[51] Studies of nonablative allografts from family or unrelated donors have confirmed that results are poor when patients have experienced failure of a prior autologous transplant or have chemotherapy-resistant disease.[52–54] Two German studies and a study from M. D. Anderson Cancer Center confirmed 2-year survival rates of 26% to 50% for patients after 1 or more autologous transplants had failed.

Conversely, CR and survival rates were good when a planned tandem, reduced-intensity allograft approach was used.[55,56] Other regimen variations with fludarabine and melphalan with or without ATG have been used, with both family members and unrelated donors.[55,56] One study used the anti-CD52 antibody alemtuzumab added to TBI and fludarabine in 20 patients with MM who underwent reduced-intensity allografting as part of front-line therapy.[57] Fourteen of 20 patients were given DLI after transplantation for residual or progressive disease. Although TRM and survival rates at 2 years were acceptable at 15% and 71%, respectively, the CR rates at 10% were disappointing. Relapses have occurred in 80% of patients at a median of 9.3 months after transplantation.[10] The low response rate may have been caused by the addition of alemtuzumab, which may have interfered with the GVM effect.

Recommendations for Clinicians

The NCCN strongly encourages clinicians to enroll patients in clinical trials whenever possible to improve the treatment of patients with MM. Current evidence supports the use of single HDT using melphalan 200 mg/m^2 and autologous SCT as either the initial therapy or salvage therapy at disease progression after conventional therapy. Tandem autologous transplants may be beneficial for patients who achieve less than a very good PR to the first transplant. It is currently not possible to routinely recommend allogeneic transplant outside the context of a clinical trial. Patients with poor risk features, such as chromosome 13 deletions, should be enrolled in trials comparing autologous or allogeneic SCT.

Future Areas of Investigation

High-dose therapy with autologous SCT has improved the response rate and survival for patients with MM. Long-term disease-free survival or cure, however, is still elusive for most autograft patients. Strategies that may increase the CR rate and cures include tandem transplants, targeted radiation, cytoprotective agents, and posttransplant vaccines or immune stimulation.

Future studies of allogeneic marrow transplantation in MM should focus on regimens that are less toxic but able to preserve anti-tumor effects such as radioisotopes linked to bone-seeking chelates.[17,58] Improved sources of stem cells, such as PBSC, which result in earlier engraftment and immune reconstitution[59] should reduce infectious complications. Studies using low-intensity, nonablative regimens appear to effectively reduce the early complications and mortality associated with allogeneic transplantation. GVM effects are limited and it appears that prior cytoreduction is required to induce remissions. Such treatments could be combined with infusions of allogeneic donor lymphocytes or subsets of lymphocytes in the form of "engineered grafts" (for example, CD4 lymphocytes), which may have a GVM effect without increasing GVHD.[60] The tandem autologous, reduced-intensity allogeneic transplantation regimen looks very promising in terms of low mortality and high response rates. It will require longer follow-up evaluation to determine if these remissions are durable and the long-term impact of chronic GVHD. Randomized trials will be required to determine the relative benefits of these treatments compared with autologous transplantation.

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