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## **Hematopoietic Stem Cell Transplantation for the Treatment of Multiple Myeloma**

William I. Bensinger

University of Washington, The Fred Hutchinson Cancer Research Center, Seattle, USA

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The treatment of multiple myeloma has dramatically improved in the last 10 years. The availability of new drugs has broadened chemotherapy options, however complete remissions (CR) are infrequent and cure is still very rare. Success in the management of refractory hematologic malignancies with stem cell transplantation (SCT) led to the exploration of this treatment for patients with MM. Initial studies demonstrated that high dose melphalan followed by autologous SCT could produce high complete remission rates with the potential to improve survival. SCT from an allogeneic donor is associated with a “graft-versus-myeloma” (GVM) effect resulting in a higher response rate, more durable remissions and the potential for cure.

### **Autologous Stem Cell Transplantation**

Two large trials have demonstrated convincingly that 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 to continued conventional chemotherapy. Seven-year follow-up of one trial continues to show a survival advantage for patients in the SCT arm. The Medical Research Council Myeloma VII trial compared combination chemotherapy to combination chemotherapy followed by high dose melphalan and autologous SCT. This trial, with 407 patients randomized, demonstrated a 12 month improvement in the median survival ( $p=0.04$ ) and a similar improvement in event-free survival. A more recent US Intergroup trial with 560 patients randomized, showed similar

response rates between the conventional and high dose groups but better event-free survival with high dose. Overall survival between the 2 groups was similar but this was likely due to salvage transplants that were given to many of the patients who progressed after conventional chemotherapy.

Unfortunately, despite autologous SCT the majority of patients will relapse and die of recurrent disease. Relapses occur due to failure to eradicate disease in the patient or due to the reinfusion of malignant cells contained in the stem cell graft. One randomized study, which evaluated the effect of removing myeloma cells from autologous stem cell grafts on outcome, found no improvement in overall or progression free survival, despite the removal of 3-4 logs of tumor cells. Thus, residual host disease appears to be the major contributor to relapse, which will require more effective high-dose regimens. Currently, the best high dose regimen is melphalan 200 mg/m<sup>2</sup> as shown in a study comparing melphalan alone at 200 mg/m<sup>2</sup> v. melphalan 140 mg/m<sup>2</sup> plus 8 Gy total body irradiation (TBI).

Recent efforts to improve the ability to eradicate host disease have focused on innovative high dose therapy regimens. The French Intergroup compared a single autologous SCT after melphalan 140 mg/m<sup>2</sup> plus TBI to a double regimen of melphalan 140 mg/m<sup>2</sup>, stem cell infusion, followed 2-4 months later by melphalan 140 mg/m<sup>2</sup> plus TBI. The tandem transplant group had a projected survival at 7 years of 42% v. 21% for the single transplant group,  $p < 0.01$ . Improved survival was observed only for the subgroup of

patients who did not achieve major remissions after the first transplant.

Another technique for improving the ability to eradicate residual host myeloma involves the use of targeted radiation delivered by antibodies or chemically specific uptake. High energy, short acting radioisotopes linked to bone seeking compounds have been utilized in this manner. <sup>166</sup>Holmium or <sup>153</sup>Samarium, beta emitting radiometals linked to phosphonate chelates, achieve rapid and specific uptake in bone and bone surfaces. In phase 1-2 trials, high response rates have been reported.

### **Allogeneic Marrow**

Allogeneic transplants are attractive because of the well-known GVM effect which can result in more durable remissions. More than 1000 transplants from allogeneic donors have been performed worldwide for patients with MM. The EBMT registry analysis examined transplants performed on 334 patients from 1983-93 and 356 patients from 1994-98. Of the patients transplanted during the latter period 133 (37%) received peripheral blood stem cells (PBSC) rather than marrow. The most important observation was a marked reduction in transplant-related mortality (TRM) from 46% to 30%. The reduction in mortality was a result of fewer deaths from opportunistic infections and interstitial pneumonias. The overall survival after 3 years improved from 35% during the 1983-93 period to 56% during the 1994-98 period. Majolino et al. have reported a 67% event-free survival at 73 months in 30 patients with MM who received a busulfan and melphalan regimen followed by PBSC from matched siblings.

### **Non-Ablative Allogeneic Transplants**

Although high-dose chemoradiotherapy followed by allogeneic SCT is capable of producing remissions and long-term survival for patients with MM, the transplant-related mortality of 25-40%, even in "good-risk" patients, limits the application of this approach. Furthermore, since the majority of patients who develop multiple myeloma are greater than age 55 years and need closely

HLA-matched family members to serve as donors, less 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. Low intensity conditioning regimens, designed more for immunosuppression rather than cytoreduction, have been used to establish consistent donor engraftment with while minimizing toxicity and damage to normal host tissues.

A variety of low intensity regimens have been studied in small phase 1-2 trials. While there is no consensus on which regimen is preferred, it is clear that patients with relapsed or resistant disease benefit less than patients with chemoresponsive disease. One particular strategy for patients with MM who had not received a prior high dose regimen employs a "tandem" autologous, non-ablative allogeneic transplant approach. Patients first have autologous PBSC collected, followed by melphalan 200 mg/m<sup>2</sup> and reinfusion of PBSC to provide cytoreduction and some immunosuppression. Two to 4 months' later patients received the non-ablative regimen of 200 cGy TBI, mycophenolic acid and cyclosporine with allogeneic PBSC. Fifty-four patients ages 39-71 years, median age 55 years, received this tandem transplant strategy. All patients were stage II or III and 43% had refractory or relapsed disease. The day 100 TRM was 6% and the CR rate was 53%. Only 3 patients developed severe GVHD and the overall TRM was 18%. With a follow-up of 32 months after autograft, the survival was 70%, and the event-free survival 50%.

Non-ablative or reduced intensity regimens prior to allogeneic SCT for MM have been reported from other centers. One report utilized melphalan 100 mg/m<sup>2</sup> to prepare 45 patients prior to allografting. These patients had either failed 2 or 3 prior autologous transplants, or received the allograft as part of a planned tandem autologous-allogeneic transplant strategy (n=12). The patients had a median age of 56 years and donors were

all HLA matched; 34 were related. TBI and fludarabine were added to the regimens of patients receiving transplants from unrelated donors. The day 100 TRM was 13%, overall TRM 38% and 73% achieved CR or near CR. There was a significantly better 2 year survival for patients transplanted as part of the planned tandem strategy v. 1-2 failed autografts, 75% v. 20%. At least 2 other studies of non-ablative allografts from family or unrelated donors have confirmed that results are poor when patients have failed a prior autologous transplant or have chemotherapy resistant disease. Other regimen variations with fludarabine and melphalan with or without ATG have been utilized with both family members and unrelated donors .

Non-ablative allogeneic transplant regimens can result in reliable donor engraftment with lower transplant related mortality than with high dose regimens. It appears, however, that substantial cytoreduction pre-allografting is necessary due to a limited GVM effect. It will be important, however, to have longer follow-up of patients transplanted using non-ablative regimens in order to document the durability of these remissions and to document the rates and severity of chronic GVHD.

### **Future Directions**

High dose therapy with autologous SCT has improved the response rate and survival for patients with MM. Long-term disease free survival or cure is still an elusive goal for most autograft patients. Strategies that may increase the cure rate include targeted radiation, tandem transplant or post-transplant vaccines or immune stimulation.

One probable reason for the high transplant-related mortality after allografting for patients with MM may be related to the primary immunodeficiency in this disease. Thus improved sources of stem cells such as PBSC which 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 anti-tumor effects such as radioisotopes linked to bone seeking chelates. The studies using low intensity, non-ablative regimens appear to effectively reduce the early complications and mortality of allogeneic transplants, while retaining GVM effects sufficient 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. The tandem autologous, reduced intensity allogeneic transplant regimen looks very promising in terms of low mortality and high response rates. It will require longer follow-up to determine if these remissions are durable. Randomized trials will likely be required to determine the relative benefits of these treatments compared to autologous transplantation.