Allogeneic Stem Cell Transplantation for Multiple Myeloma

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KEYWORDS

• Multiple myeloma • Allogeneic stem cell transplant • Autologous stem cell transplant
• Peripheral blood stem cells • Myeloablative transplant • Nonmyeloablative transplant

KEY POINTS

- Allogeneic stem cell transplantation can result in durable remissions for some patients with multiple myeloma; however, transplant morbidity and mortality limit its wider application.
- Reduced intensity allografts improve the safety, but are still limited by graft-versus-host disease and high rates of relapse.
- Prospective trials comparing autologous with allogeneic transplants based on donor availability have shown conflicting outcomes with respect to survival and disease-free intervals.
- Allogeneic stem cell transplants will remain investigational until improvements in conditioning regimens, and control of graft-versus-host disease and relapse are achieved.

INTRODUCTION

Despite significant progress in the treatment of multiple myeloma, most patients will have recurrent disease and die. New drugs and autologous stem cell transplantation (ASCT) have increased rates of remission, improved remission durations, and prolonged overall survival rates by 3 to 5 years. Relapses, however, continue for most patients, emphasizing the need for new drugs and treatment strategies. Allogeneic stem cell transplantation (AlloSCT) offers the potential of harnessing an immunologic graft-versus-myeloma (GVM) effect capable of controlling residual disease and offering the potential for cure. Unfortunately, the complexity, complications, and relatively poor outcomes of AlloSCT for myeloma have limited its application and relegated this therapy to investigational studies. As survival of patients with myeloma has improved with new drugs and ASCT, the role of AlloSCT, if any, in the treatment of myeloma has been further questioned.[1] This article reviews the current knowledge about AlloSCT for myeloma and discusses current research activities.

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HISTORY

An initial attempt at treating refractory myeloma with total body irradiation (TBI) and bone marrow from an unmatched cadaver, reported in 1957, was unsuccessful.[2] Success with AlloSCT for the treatment of multiple myeloma was first reported in 1982[3] and again in 1984.[4] One patient with progressive myeloma received cyclophosphamide and 800 cGy TBI followed by HLA identical sibling marrow and achieved engraftment and a remission. Two patients with advanced myeloma received cyclophosphamide and TBI followed by sibling bone marrow. Both patients engrafted with subsequent resolution of their myeloma; however, one died of disseminated zoster at 6 months, while the other relapsed at 3 years. These reports were followed by small series from Seattle[5] and the European Bone Marrow Transplant Cooperative Group (EBMT)[6] showing the feasibility of this procedure in myeloma. As experience accumulated in the 1980s and 1990s, it became clear that AlloSCT using ablative techniques was associated with high morbidity and mortality, as a consequence, many transplant centers abandoned myeloablative allograft conditioning for myeloma.[7] A US trial of early versus late ASCT had an option of AlloSCT for patients with matched sibling donors.[8] Patients received myeloablative conditioning with melphalan plus TBI. After 36 patients were enrolled in the AlloSCT arm, this group was closed to further accrual because of transplant-related mortality (TRM) exceeding 50%. Interestingly, after more than 7 years of follow-up, the overall survival (OS) rate of the AlloSCT group was 40%, better than either arm of the ASCT groups. Because of the GVM effect of AlloSCT, deeper and more durable remissions were observed, resulting in a reduced rate of relapse in the AlloSCT group compared with either ASCT group. Studies using patient-specific primers to look for minimal residual disease in myeloma patients achieving a complete response (CR) reported higher rates of minimal residual disease negativity among recipients of AlloSCT compared with ASCT. Furthermore, patients with minimal residual disease–negative remissions have much longer disease-free intervals than patients whose marrow is minimal residual disease positive at any time after transplant.[9,10]

By the mid-1990s the EBMT reported a retrospective comparison of 189 patients with myeloma who received myeloablative AlloSCT and were matched for gender and prior courses of chemotherapy with 189 patients with myeloma who received ASCT.[11] The groups were comparable except the median age of the AlloSCT group was 6 years younger, with 16-month longer median follow-up. OS was superior for the ASCT group (median, 34 vs 18 months; $P = .001$) because of a much higher TRM in the AlloSCT group (41% vs 13%; $P = 0001$). This higher TRM was not offset by the lower rates of relapse seen in the AlloSCT group (at 4 years, 50% vs 70%; $P = .04$).

Thus, the perception of an increase in morbidity and mortality after AlloSCT for patients with myeloma draws directly from outcomes of patients reported in the literature. Recently, this idea has been challenged by pooled analyses of 56,000 transplants reported to EBMT.[12] Patients were given a risk score of 0 to 7 based on age, disease stage, time from diagnosis to transplant, donor type, and donor-recipient gender. Patients with myeloma had a greater mortality risk after AlloSCT but were also observed to have a higher risk score because of more advanced age, longer interval from diagnosis to transplant, and more advanced disease stage. When similar risk score patients with myeloma or acute leukemia underwent transplant, the mortality was similar. Although interesting, as a practical matter, these observations are of limited benefit, because the diagnosis of myeloma is frequent at advanced age, and most patients do not achieve complete remission before transplant. Furthermore, the EBMT observed a marked reduction in nonrelapse mortality after 2 years