New Questions About Transplantation in Multiple Myeloma: Review 2

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Multiple myeloma is now the most common indication for autologous stem cell transplantation (ASCT) in North America, with over 5,000 transplants performed yearly (Center for International Blood and Marrow Transplant Research [CIBMTR] data). While the role of ASCT as initial therapy in multiple myeloma has been established by randomized studies, newer therapies are challenging the traditional paradigm. The availability of novel induction agents and newer risk stratification tools, and the increasing recognition of durability of remissions are changing the treatment paradigm. However, even with arduous therapy designed to produce more complete remissions for example, tandem autologous transplants we have seen no plateau in survival curves. A tandem autologous procedure followed by maintenance therapy may be performed in an attempt to sustain remission. Sequential autologous transplants followed by nonmyeloablative allotransplants are pursued with the hope of "curing" multiple myeloma. We examine how the key challenges of increasing the response rates and maintaining responses are being addressed using more effective induction and/or consolidation treatments and the need for maintenance therapies after ASCT. We argue that given the biologic heterogeneity of multiple myeloma, risk-adapted transplant approaches are warranted. While the role of curative-intent, dose-intense toxic therapy is still controversial, conventional myeloablative allogeneic transplants need to be reexamined as an option in high-risk aggressive myeloma, given improvements in supportive care and transplant-related mortality.

Major progress has been made in the last 20 years in the treatment of multiple myeloma.[1] The introduction of high-dose therapy and, more recently, a variety of new agents including thalidomide (Thalomid)[2] and other immunomodulatory drugs,[3,4] bortezomib (Velcade),[5,6] and immunologic approaches means patients have a variety of treatment strategies available today.[7] Still, multiple myeloma remains incurable, and clinicians face unique challenges in placing new information into context, to determine a rational approach to the use of autologous and allogeneic stem cell transplantation for patients with the disease. Hari and colleagues distill the clinical questions surrounding transplantation for myeloma in a succinct yet thorough review. With their well-written assessment, the authors cover most of the key areas of controversy surrounding the role of autologous stem cell transplantation (ASCT) in this setting.

Risk-Adapted Therapy
The desire to prospectively distinguish patients destined to have an indolent disease course from those with aggressive myeloma has led to the identification of a number of prognostic features, including beta-2 microglobulin, serum albumin, plasma cell labeling index, and several cytogenetic abnormalities.[8-12] As our genetic understanding of multiple myeloma becomes more sophisticated, new classifications will emerge. The challenge is how to best use available information to ensure that patients with good prognosis are not subjected to unnecessarily toxic therapies and patients with poor prognosis are treated aggressively and appropriately. The Mayo Clinic definition of high-risk multiple myeloma includes patients with one or more of the following adverse prognostic factors: deletion 13 or hypodiploidy on conventional karyotypic analysis; t(4;14), t(14;16), or 17p on molecular genetic studies; or a plasma cell labeling index of at least 3%.[13,14] We have recommended that patients with high-risk myeloma be considered for novel treatment strategies.[14]

Novel Induction Regimens
The development of novel active agents for multiple myeloma has resulted in a plethora of new combination regimens. The high response rates observed with these regimens have raised questions on whether we should still be offering ASCT to patients as initial therapy. The first new combination regimen to show such promise was thalidomide and dexamethasone (Thal/Dex), which has been shown to be superior to dexamethasone alone in the Eastern Cooperative Oncology Group (ECOG) E1A00 trial.[15]
Combinations of thalidomide, lenalidomide (Revlimid), bortezomib, and traditional alkylating agents are summarized in Table 2 of the review by Hari and colleagues. Response rates in excess of 90% are not uncommon, rivaling responses seen with ASCT. Unfortunately, these high response rates do not equate with cure. No plateau is seen in survival curves in any of the trials, showing that the disease invariably relapses and patients can expect to be treated with multiple different regimens during the course of their illness. For this reason, we do not expect that ASCT will become obsolete any time soon.

High response rates are not the only factor determining the desirability of using ASCT. All new regimens have unique toxicities, and quality-of-life measures should be included in all future randomized trials. In transplant trials, some of the most important information to emerge has included recognition of the benefit to patients' quality of life with early transplant approaches.[16] This was best quantified in the French Group Myelome-Autogreffe (MAG) trial comparing early to late transplant, which showed improved TWiSTT (time without symptoms, treatment, and toxicity) among patients transplanted early.[16]

**Autologous Stem Cell Transplantation**

Two well-designed prospective randomized trials have demonstrated an advantage for ASCT over conventional chemotherapy, including improved complete remission (CR) rates, event-free survival, and overall survival.[17,18] Most studies that failed to show these benefits allowed salvage transplant at relapse or randomized only responding patients, as discussed in the review by Hari and colleagues. The MAG study,[16] as well as the US Intergroup study,[19] clearly show that survival is the same whether the transplant is done early or late, but the MAG study showed that the most compelling reason for early ASCT is superior quality of life.

Data from multiple single-center studies support the finding that ASCT offers high responses rates to patients with multiple myeloma refractory to initial induction therapy. This group of patients may well account for the improved overall survival seen in the Intergroupe Francophone du Myelome (IFM)[17] and Medical Research Council (MRC)[18] randomized trials but not the Programa para el Tratamiento de Hemopatas Malignas (PETHEMA) trial.[20] Controversy still surrounds the role of tandem ASCT. The original rationale for tandem ASCT was improved CR rates resulting in improved overall survival. The IFM94 trial did not show a significant difference in CR rates, but did show improved event-free and overall survival rates.[21] Both the IFM94 and the Bologna 96[22] trials show that tandem ASCT is beneficial to patients who did not achieve CR or near CR following the first transplant. Patients in CR or near CR following the first transplant did not appear to benefit from the second transplant. The survival advantage in the IFM94 trial did not emerge in the tandem transplant arm until 4 years' follow-up, at which time the survival curves diverged. Hari and colleagues appropriately point out that the difference in survival may not be due to improved CR rates, but rather, may be due to improved duration of response. This observation raises the question of whether low-risk patients are the patients most likely to benefit from an aggressive approach and runs counter to conventional wisdom, which advocates tailoring therapy according to prognostic variables in order to minimize toxicity for low-risk patients.

We agree with the recommendation that tandem transplantation should be considered primarily in patients who have not achieved a CR or near CR with the first transplant. Of note, there are no randomized trials comparing planned upfront tandem ASCT to single ASCT with salvage transplant at relapse—an approach that has been widely adopted in clinical practice.

**Allogeneic Transplantation**

Allogeneic transplant is offered to select patients with multiple myeloma. It is not widely applicable due to the advanced age of most patients with the disease, concerns about acute and late toxicity, and lack of available donors. Nonmyeloablative stem cell transplant can be used alone or in tandem following ASCT.[23] Studies show low early transplant-related mortality. However, the 1-year transplant-related mortality for most studies ranges from 15% to 40%. Furthermore, none of the published trials show a plateau in survival curves, and relapse accounts for the major source of mortality. Well-designed clinical trials are need to clarify the role of nonmyeloablative stem cell transplant in the treatment of multiple myeloma.

Conventional myeloablative allogeneic transplant has been shown to have a plateau in progression-free survival in the US Intergroup and European Bone Marrow Transplant (EBMT) trials.[19] Transplant-related mortality with myeloablative allogeneic transplant has decreased significantly. We agree that there may still be a role for this modality in select patients.

**Future Directions**

Significant progress has been made in the treatment of multiple myeloma in recent years. However,
significant challenges remain. Transplantation offers a meaningful adjunct to new therapies. We look forward to new advances in stem cell mobilization, conditioning regimens, and posttransplant maintenance that will improve care for patients with multiple myeloma. With improved understanding of the underlying biology of the disease, we anticipate further advances in risk-adapted and molecularly targeted therapies.

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References:


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