Multiple Myeloma: Role of Allogeneic Transplantation

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By Stefano R. Tarantolo, MD [2] and Ralph Hauke, MD [3]

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Shortcomings of Current Therapy
Multiple myeloma remains an incurable disease despite advances in systemic therapy and supportive care. Although standard-dose chemotherapy provides palliative benefit, the median survival is approximately 29 months, and few patients achieve a complete remission. Randomized trials have demonstrated improved response rates, low toxicity, and increased survival with autologous transplant as consolidation, compared with standard chemotherapy.[1] Tandem autologous transplants produce a superior complete remission rate compared to single transplants, but overall survival is equivalent (with the exception of patients with low beta-2-microglobulin, in whom overall survival is improved). Nevertheless, relapse due to minimal residual disease continues to be the main reason for failure.

New insights into factors that control the growth and survival of plasma cells as well as their critical interaction with the microenvironment have led to innovative therapies with thalidomide (Thalomid), proteasome inhibitors, and bisphosphonates. While unlikely to cure myeloma, these agents offer the possibility of stabilizing minimal residual disease.

Staging Modifications
The current staging system for multiple myeloma groups patients into three categories based on paraprotein volume, skeletal lesions, and laboratory parameters. However, the highly variable clinical course of similarly staged patients underscores the need to revise this classification system. Modification of the current system to incorporate such characteristics as chromosome 13 abnormalities and beta-2-microglobulin levels should provide the framework for a prognostic model to discriminate between low-, intermediate-, and high-risk patient groups. Gene expression profiles generated by DNA microarray analysis will likely emerge as a method to identify clinically relevant subsets among patients with otherwise indistinguishable myeloma.

Graft-vs-Myeloma Effect
Proof of a graft-vs-myeloma effect can be inferred from clinical experience. Fewer relapses occur after allogeneic transplant, and remissions can be established with the withdrawal of immunosuppression or with the occurrence of acute graft-vs-host disease. Similarly, fewer relapses occur with the development of chronic graft-vs-host disease, and remission can be established with donor lymphocyte infusions.[2-5] Furthermore, vaccinating donors with idiotypic proteins can stimulate the development of donor immunity against myeloma that can be transferred to recipients.[6]

Overcoming Treatment Related Toxicity
The graft-vs-myeloma effect makes allogeneic transplantation an attractive and potentially curative therapy for multiple myeloma patients. However, for unclear reasons, myeloma patients suffer from a higher treatment-related mortality rate than do patients with other hematologic malignancies. This results in relatively poor overall and event-free survival rates. If the results of allogeneic transplantation are to be improved, one logical step—as Pandit and Vesole point out—would be to reduce treatment-related mortality. Registry data suggest that treatment-related mortality decreases as a function of the increase in clinical experience.[7] Autologous transplantation offers a low mortality rate (less than 2%); approximately half of the patients who undergo such treatment are alive at 5 years with an excellent quality of life. The authors are correct to emphasize that the high treatment-related mortality and morbidity of chronic
graft-vs-host disease makes it difficult to recommend allogeneic transplantation. Much interest has been generated by nonmyeloablative (“mini-allo”) transplants as a means of reducing the toxicity of allogeneic transplantation for myeloma patients. Reports by Badros and Lalancette noted significant treatment-related mortality and graft-vs-host disease in this setting.[8,9] Although Badros originally reported no mortality at 100 days, a recent update at the International Myeloma Workshop showed a 33% 1-year mortality rate.[10] Lalancette’s review of registry data from the European Group for Blood and Marrow Transplantation (EBMT) reports a similarly high mortality rate. The interpretation of these data is complicated by the heterogeneity of patients and treatment methods. The Seattle group treated 32 myeloma patients with autologous transplantation for cytoreduction followed by a nonmyeloabative allogeneic transplant. The preliminary results reported at the 2001 American Society of Hematology meeting are encouraging, with a low 100-day mortality.[11] However, the incidence of graft-vs-host disease was high, and donor lymphocyte infusions were required for some patients with persistent disease. The Dana Farber group has demonstrated that T-cell manipulation of both the original graft and donor lymphocyte infusions has diminished treatment-related mortality and morbidity, but at the expense of a higher relapse rate. Although these results are encouraging, the follow-up period was relatively short.[12] Nonetheless, they provide the platform for future improvements.

**Future Directions**

A better understanding of the pathogenesis of myeloma has improved supportive care and response rates. However, many challenges remain for the management of myeloma patients. Conventional myeloablative allogeneic transplantation is associated with significantly high morbidity and mortality precluding its widespread use. Nonmyeloablative transplantation requires further scrutiny before this approach can be embraced as a standard of care. Randomized trials are necessary to establish the role of nonmyeloablative transplants. That said, recent advancements in this area offer renewed optimism for pursuing allografting in selected patients. Components for designing safer allogeneic transplant protocols include mobilized allogeneic blood stem cells, improved antifungal agents, methods of viral surveillance, T-cell depletion strategies, vaccination of donors with patient-specific vaccines, creation of suicide lymphocytes, and improved immunosuppressive agents. One area that requires particular attention is the prevention of graft-vs-host disease, because its incidence is much higher in myeloma patients. Our clinical experience indicates the need for a prognostic model that incorporates specific patient and tumor characteristics such as chromosomal abnormalities (including microarray analysis) and beta-2-microglobulin levels. This change in "staging" criteria will enable stratification of patients to specific treatment plans that have the highest likelihood of producing a response, while minimizing side effects.

The eradication of myeloma cells has proven to be a daunting task. The failure of current therapies suggests that future therapy for myeloma patients will require a multimodality approach. Such a strategy will probably incorporate cytoreduction with autologous transplant, immunotherapy with allogeneic transplant, and/or maintenance therapy directed at eliminating minimal residual disease (ie, immunomodulatory drugs, cytokines, monoclonal antibodies, vaccines, and angiogenesis and proteasome inhibitors). Recent innovations have provided the framework for transforming myeloma into a chronic yet stable disease. Indeed, the outlook for myeloma patients has never been brighter.

**References:**


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