



[haematologica reports]
2006;2(7):111-112

B. BRUNO
M. BOCCADORO

On behalf of Gruppo Italiano
Trapianti di Midollo (GITMO)*,
Italy

Emerging role for reduced intensity allotransplant in multiple myeloma

Allografting for multiple myeloma appears a more potent anti-tumor treatment than autografting with more frequent molecular remissions. However, the curative potential of myeloablative allografting for myeloma patients has not fully been elucidated because of the unacceptably high transplant-related mortality, primarily as a consequence of infection and graft versus host disease.¹⁻³ Moreover, as it is performed in patients under 50 years of age, this procedure is only for a minority of myeloma patients. Indeed, mortality rates have decreased in the last decade because of advances in supportive care and a trend toward transplant earlier during the disease course. However, the best reported analysis, by Garthon *et al.*, still showed a transplant-related mortality of 21% at 6 months with a 55% 3-year survival for patients transplanted between 1994-1998.⁴ The median age in this cohort was 44 (range 18-57) years whereas the median age of newly diagnosed patients is approximately 65-70.

The graft-versus-myeloma effects that have been shown in myeloma following allografting have also the potential to consolidate the often incomplete responses achievable with preceding high dose chemotherapy.⁵⁻⁶ The observation that the allogeneic engraftment can be achieved without myeloablation have led to the exploration of novel approaches employing reduced intensity conditioning regimens in the attempt to reduce transplant-related mortality and increase the eligible age for transplant.⁷⁻⁹ However, the role and timing of reduced-intensity stem cell transplantation within current treatment strategies, including the so called new drugs, for the management of myeloma have yet to be defined. Initial application has generally been in patients with advanced disease and only a few studies have addressed the issue of allografting in newly diagnosed patients.

The Seattle Consortium originally developed a two-step approach in which high dose chemotherapy with autografting was temporally separated from a total body irra-

diation based non-myeloablative allogeneic transplant from an HLA identical sibling.⁹ The rationale was to capture the benefits of autografting (disease response and prolonged survival) together with the benefits of allografting (establishment of full donor chimerism and graft versus myeloma effects) reducing transplant toxicity. This approach has also been employed in a larger multi-center study by the GITMO group.

Briefly, after induction chemotherapy, patients undergo G-CSF mobilized autografting with high dose melphalan (200 mg/m²) followed, 60-120 days later, by low dose 2 Gy total body irradiation, peripheral blood stem cell infusion from HLA-identical siblings, and immunosuppression with mycophenolate mofetil and cyclosporin. From December 1999 to June 2005, 110 patients (median age 55) from 14 Italian Transplant Centers entered the study. One-hundred-two patients had completed both transplant procedures by January 2006. After a median follow up of 30 months (2-68) post allografting, overall survival was 83% (85/102). Best response rate was 86%, with 59% complete remission, defined as the disappearance of the monoclonal serum and/or urine paraprotein by immunofixation, and 27% partial remissions. Time to complete response was slow indicating a gradual graft versus myeloma effect. Disease recurrence was observed in 23% of patients, in all cases except one in patients with chemo-resistant disease. Importantly, patients in complete remission at the time of allografting had better progression free and overall survival. Grade II acute graft versus host disease (GVHD) and grade III-IV GVHD developed in 28% and 12%, respectively. Chronic GVHD requiring therapy developed in 48% (22/53). Overall, transplant related mortality was 13%, day 100 transplant related mortality <1% (1/102). Main causes of death were steroid refractory GVHD and infectious complications. Two patients developed lung carcinoma. Our study shows that low dose TBI based non myeloablative allografting is feasible

in older myeloma patients with high response rates and reduced toxicity compared to conventional allografting. Relapse remains an issue in patients with chemo-resistant disease. The integration of allografting with new drugs such as bortezomib and thalidomide may increase the percentage of complete remissions at transplant and/or consolidate response post allografting further increasing overall survival. Longer follow up is needed to determine if patients in prolonged complete remission will eventually be cured.

***Appendix**

The following Divisions of Hematology contributed to the GITMO study: Alessandria (Dr. Levis/Dr. Allione); Bergamo (Prof. Rambaldi/Dr.ssa Barbui), Bolzano (Prof. Coser/Dr Casini), Candiolo – Istituto Tumori (Prof. Aglietta/Dr Carnevale), Cuneo (Dr. Gallamini/Dr Mordini), Milano, Ospedale Maggiore (Prof. Soligo), Milano, Istituto Tumori (Prof. Corradini); Monza (Prof. Pogliani), Pescara (Dr. Di Bartolomeo/Dr.ssa Bavaro), Roma – Università Tor Vergata (Prof. De Fabritiis); Roma – Università La Sapienza (Prof. Foa, Dr.ssa Iori); Torino, Ospedale Maggiore (Prof. Gallo/Dr. Falda), Torino, Università (Prof. Boccadoro, Dr. Bruno) Udine (Prof. Fanin/Dr.ssa Patriarca).

References

1. Bensinger WI, Buckner CD, Anasetti C, Clift R, Storb R, Barnett T, et al. Allogeneic marrow transplantation for multiple myeloma: An analysis of risk factors on outcome. *Blood* 1996; 88:2787-2793.
2. Gahrton G, Tura S, Ljungman P, Belanger C, Brandt L, Cavo M, et al. Allogeneic bone marrow transplantation in multiple myeloma. *N Engl J Med* 1991; 325:1267-73.
3. Gahrton G, Tura S, Ljungman P, Blade J, Brandt L, Cavo M, et al. Prognostic factors in allogeneic bone marrow transplantation for multiple myeloma. *J Clin Oncol* 1995; 13:1312-22.
4. Björkstrand BB, Ljungman P, Svensson H, Hermans J, Alegre A, Apperley J, et al. Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma - a retrospective case-matched study from the European Group for Blood and Marrow Transplantation. *Blood* 1996; 88:4711-8.
5. Badros A, Barlogie B, Siegel E, Cottler-Fox M, Zangari M, Fassas A, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. *J Clin Oncol* 2002;20:1295-303.
6. Kröger N, Sayer HG, Schwerdtfeger R, Kiehl M, Nagler A, Renges H, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood* 2002;100:3919-24.
7. Maloney DG, Molina AJ, Sahebi F, Stockerl-Goldstein KE, Sandmaier BM, Bensinger W, et al. Allografting with non-myeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. *Blood*. 2003, 102, 3447-54
8. Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: Proof of principle. *Blood* 1996; 87:1196-8.
9. Aschan J, Lonnqvist B, Ringden O, Kumlien G, Gahrton G. Graft-versus-myeloma effect (Letter). *Lancet* 1996; 348:346.