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Editorials and Views

Allogeneic bone marrow transplantation for paroxysmal nocturnal hemoglobinuria

Whether or not to undertake allogeneic bone marrow transplantation (allo-BMT) is an extremely difficult decision facing the patient with paroxysmal nocturnal hemoglobinuria (PNH) and the doctor looking after that patient. Currently, allo-BMT is the only intervention which offers the chance of a cure; at the same time, allo-BMT may mean replacing an old set of problems with new problems, and it involves balancing immediate serious risks versus the hope of a longer and better future. Since disease recurrence has not been reported after allo-BMT, one might expect that as this procedure becomes safer over time, it will become an increasingly attractive option. On page 59 of this journal, Raiola *et al.* report that 7 out of 7 patients are alive after receiving HLA-matched grafts from siblings in the 1990s, lending support to such optimism.

PNH is a chronic disorder, with a median survival of 10-15 years.[1] Chronic hemoglobinuria, a feature of PNH, is to a large extent harmless in itself, and anemia can be controlled by appropriate blood transfusion management. If bone marrow failure becomes severe, it is potentially treatable not only with allo-BMT but also with immunosuppression.[2,3] Venous thrombosis may be controlled by anticoagulation and may respond to thrombolysis,[4] but it is still potentially life-threatening.

Raiola *et al.* now report that, between 1991 and 1999, they transplanted 7 PNH patients, with 100% survival at a mean follow-up of 51 months. All of these patients had been receiving transfusions and had vigorous hemolysis, as reflected by marked LDH elevation. Four patients had hypocellular marrow, but only 1 had a platelet count below 50×10^9/L. Graft-versus-host disease (GvHD) developed in all patients, and 5 of the patients are still receiving immunosuppression. Two of the 7 suffer from extensive chronic GvHD, but all are able to work, with Karnofski's score of 90-100%. Compared to the results recently published on behalf of the IBMTR,[5] these are better. This is often the case when results from a single institution are compared with data from many institutions, as in the case of the IBMTR data. Even though the number of patients transplanted by Raiola *et al.* is relatively small, we believe that this difference reflects, at least in part, real progress in allo-transplantation.

What is the mechanism by which allo-transplantation might cure PNH? While we cannot review the pathophysiology of PNH in detail here, suffice it to say that PNH is clearly related to acquired aplastic anemia (AAA),[6,7] and there is mounting evidence that an element of bone marrow failure is always present in PNH. Therefore, allo-BMT may be playing 3 distinct roles simultaneously: (i) eliminating the PNH clone(s) (just as one hopes to do in patients with leukemic clones); (ii) providing normal hematopoiesis (as it would do in AAA itself); and (iii) producing intense immunosuppression (as can also be achieved with alternative approaches, such as ATG/cyclosporin). In PNH the therapeutic importance of these 3 mechanisms is perhaps in reverse order. In fact, we surmise that immunosuppression destroys auto-reactive immune cells that exert negative pressure against normal stem cells;[8] once that happens, normal hematopoiesis can be restored and the PNH clone automatically loses its relative advantage. This model is supported by the observations that the PNH clone can undergo spontaneous regression,[1] and that syngeneic transplantation *without* conditioning has been followed by relapse.[9]

Therefore, it may be appropriate to consider the optimal conditioning regimen carefully. Ringden *et al*.[10] have recently reported a randomized trial demonstrating the superiority of cyclophosphamide/TBI over busulfan/cyclophosphamide in terms of venous obstructive disease (VOD), obstructive bronchiolitis, and chronic GvHD.[10] But perhaps more important, do we need a myeloablative regimen? The main purpose of BMT is not to kill the PNH clone, which is not in itself a malignancy: indeed, PNH clones can be found even in normal individuals[11] and they do not have a growth advantage in mouse models.[12,13] If there is always bone marrow failure in PHN, and if the PNH clone is not malignant, it would seem logical to use a conditioning regimen like in AAA, such as cyclophosphamide with ATG, as recommended by Bacigalupo himself[14] and by others.[15]

Avoiding a myeloablative regimen would spare the patients at least some of the risk of pulmonary disease, VOD, infertility, and secondary malignancy.[16] In fact, Antin *et al.*[17] and Kawahara *et al.*[18] have achieved complete long-term remissions with the non-myeloablative regimen that they used in PNH patients with hypocellular marrows.

Do we now have a rational basis for confronting the therapeutic dilemma of allo-BMT?*

If we compare the actuarial curve of the *natural history* of PNH – drawn from a cohort of patients who received only supportive therapy[1] – with the actuarial survival curve after allo-BMT from the IBMTR[5] (see Figure 1), we glean an important message. In the short term the transplanted patients fare worse, meaning that some patients would still be alive if

**At the moment, the dilemma only exists for patients who have an HLA-identical sib. Patients transplanted from mismatched/unrelated donors were not included in Raiola's series: but in the IBMTR series 6 out of 7 such patients died; and we know of a number of additional unpublished unsuccessful outcomes. Alternative donor BMT for PNH is yet another challenge.*

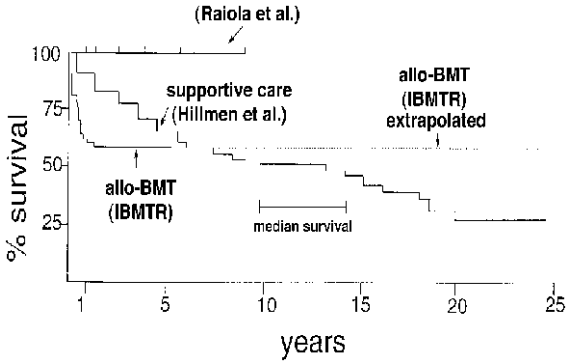

Figure 1. Prospects for PNH patients as a function of management.

they had not received allo-BMT. However, at about 6 years, the two curves cross and in the long term, the transplanted patients have a better chance of survival, assuming a plateau on the curve, though some of these patients will develop chronic GvHD and a few may develop secondary malignancies. In advising patients today, one must point out that recent progress in allo-BMT and supportive care may shift both curves upward, perhaps minimizing the differences in survival between them. Likewise, with highly effective methods of GvHD prophylaxis (i.e., T-cell depletion) and semen and embryo (and now perhaps oocyte cryopreservation) differences in quality of life between the two approaches may decrease.

After extrapolating data from survival curves, important questions remain for the individual patient. At what point in the disease should a transplant be performed? Should a 40-year old receiving transfusions undergo allo-BMT upon diagnosis, or wait to see whether he develops thrombocytopenia or thromboses, at which time he might be considered *too old* for the procedure? Is allo-BMT still *safe* after a patient has sustained a portal or hepatic vein thrombosis? What should be the indications for allo-BMT in those with only an unrelated donor? While counselling patients with PNH will always be a challenge, perhaps we can look forward to a time when we can help as many as possible either by allo-BMT or by targeting the cause of their bone marrow failure.

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References

1. Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333:1253-8.
2. Stoppa AM, Vey N, Sainty D, et al. Correction of aplastic anaemia complicating paroxysmal nocturnal hemoglobinuria: Absence of eradication of the PNH clone and dependence of response on cyclosporin A administration. Br J Haematol 1996; 93:42-4.
3. Paquette RL, Yoshimura R, Veiseh C, Kunkel L, Gajewski J, Rosen PJ. Clinical characteristics predict response to antithymocyte globulin in paroxysmal nocturnal haemoglobinuria. Br J Haematol 1997; 96:92-7.
4. McMullin MF, Hillmen P, Jackson J, Ganly P, Luzzatto L. Tissue plasminogen activator for hepatic vein thrombosis in paroxysmal nocturnal haemoglobinuria. J Intern Med 1994; 235:85-9.
5. Saso R, Marsh J, Cevreska L, et al. Bone marrow transplants for paroxysmal nocturnal haemoglobinuria. Br J Haematol 1999; 104:392-6.
6. Dacie JV, Lewis SM. Paroxysmal nocturnal haemoglobinuria; clinical manifestations, haematology, and nature of the disease. Ser Haematol 1972; 5:3-23.
7. Dameshek W. Riddle: what do aplastic anemia, paroxysmal nocturnal hemoglobinuria and "hypoplastic" leukemia have in common? Blood 1967; 30:251-4.
8. Luzzatto L, Bessler M, Rotoli B. Somatic mutations in paroxysmal nocturnal hemoglobinuria: A blessing in disguise? Cell 1997; 88:1-4.
9. Nafa K, Bessler M, Deeg HJ, Luzzatto L. New somatic mutation in the PIG-A gene emerges at relapse of paroxysmal nocturnal hemoglobinuria. Blood 1998; 92:3422-7.
10. Ringden, O, Remberger M, Ruutu T, et al. Increased risk of chronic graft-versus-host disease, obstructive bronchiolitis, and alopecia with busulfan versus total body irradiation: long-term results of a randomized trial in allogeneic marrow recipients with leukemia. Nordic Bone Marrow Transplantation Group. Blood 1999; 93:2196-201.
11. Araten DJ, Nafa K, Pakdeesuwan K, Luzzatto L. Clonal populations of hematopoietic cells with paroxysmal nocturnal hemoglobinuria genotype and phenotype are present in normal individuals. Proc Natl Acad Sci USA 1999; 96:5209-14.
12. Murakami Y, Kinoshita T, Maeda Y, Nakano T, Kosaka H, Takeda J. Different roles of glycosylphosphatidylinositol in various hematopoietic cells as revealed by model mice of paroxysmal nocturnal hemoglobinuria. Blood 1999; 94:2963.
13. Tremml G, Dominguez C, Rosti V, et al. Increased sensitivity to complement and a decreased red cell life span in mice mosaic for a non-functional Pig-A gene. Blood 1999; 94:2945.
14. Bacigalupo A. Bone marrow transplantation for severe aplastic anemia from HLA identical siblings. Haematologica 1999; 84:2-4.
15. Storb R, Etzioni R, Anasetti C, et al. Cyclophosphamide combined with antithymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. Blood 1994; 84:941-9.
16. Curtis RE, Rowlings PA, Deeg HJ, et al. Solid cancers after bone marrow transplantation. N Engl J Med 1997; 336:897-904.
17. Antin JH, Ginsburg D, Smith BR, Nathan DG, Orkin SH, Rappeport JM. Bone marrow transplantation for paroxysmal nocturnal hemoglobunuria: eradication of the PNH clone and documentation of complete lymphohematopoietic engraftment. Blood 1985; 6: 1247-50.
18. Kawahara K, Witherspoon RP, Storb R. Marrow transplantation for paroxysmal nocturnal hemoglobinuria. Am J Hematol 1992; 39:283-8.