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 the dilemma of 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. 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. Venous thrombosis may be controlled by anticoagulation and may respond to thrombolysis, 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, 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, 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), 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; 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, and that syngeneic transplantation without conditioning has been followed by relapse.

Therefore, it may be appropriate to consider the optimal conditioning regimen carefully. Ringdén et al. 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. 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 and they do not have a growth advantage in mouse models. If there is always bone marrow failure in PNH, 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 and by others.

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

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 – with the actuarial survival curve after allo-BMT from the IBMTR (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...
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.