ADAMTS13. But this phenomenon cannot be explained directly through facilitated cleavage by the presence of platelets and the loss of large VWF multimers. The results were when platelet transfusions were given simultaneously. This story illustrates the link between giant platelet syndromes and VWD2B, a link which is progressively being established but is not yet really understood.

The binding of abnormal VWF to the platelet surface is an important factor in explaining the appearance of platelet aggregates and the loss of large VWF multimers through facilitated cleavage by ADAMTS13. But this phenomenon cannot directly explain the presence of giant platelets in the circulation.

Another lesson from the report by Jackson et al is the absolute need to investigate RIPA and VWF in patients with unexplained congenital macrothrombocytopenia, with or without spontaneous agglutination. The analysis of exon 28 of the VWF gene should also be considered because, in some cases, the affinity of the remaining mutated VWF for GPIbα is so high that the observed ratio between VWF:Ag and VWF:RCo can be normal. The second very important point for the saga of VWF and thrombocytopenia is to focus on the origin of the abnormal platelets; the authors raise questions about the implication of a specific mutation for the observed phenotype. The figures show an identical phenotype for a French patient with the same mutation, showing that MPS indeed occurs elsewhere. The search for modifier genes explaining the heterogeneity in VWD2B is for the future.

Another key question concerns the role of VWF during megakaryocytogenesis. How does the abnormal VWF in the bone marrow affect platelet production? Are joined platelets really agglutinated after they have been produced or are they incompletely separated during megakaryocytogenesis? The saga of VWD2B is not closed and new episodes are required.

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Comment on Bruno et al, page 3375, and Rotta et al, page 3383

Reduction-intensity allogeneic transplantation for myeloma: reality bites

A. Keith Stewart MAYO CLINIC

Like a second marriage, the continued pursuit of safe and effective allogeneic stem cell transplantation for myeloma appears to be a triumph of hope over experience. In this issue of Blood, Bruno et al1 and Rotta et al2 (along with a previous article by Rosinol et al3) describe the long-term outcomes of patients treated with NMT therapy for MM.

In the 3 papers, the results are consistent: 11% to 18% of patients died as a result of the procedure within 5 years (the majority within the first 2 years), 50% to 78% have extensive chronic graft-versus-host disease (GVHD), one-third are still on immunosuppressive drugs at 5 years, donor lymphocyte infusions are ineffective at relapse, progression-free, overall survival is statistically the same as for tandem autologous stem cell transplantation (AST), and little evidence for a real plateau is seen in survival.4 To quote directly from Rotta et al, “long-term disease control and GVHD remain key issues” —indeed!

Three randomized trials are now published comparing nonmyeloablative allogeneic transplantation (NMT) with tandem AST showing either worse (in high-risk patients)5 or no improvement in outcomes,6 with the third such trial suggesting an advantage to NMT.7 Because the randomized trial data are conflicting, the results of a major ongoing Bone Marrow Transplant Clinical Trial Network study are eagerly anticipated and will hopefully provide definitive answers. Until then, NMT should, in this author’s opinion, no longer be offered as front-line therapy to multiple myeloma (MM) patients outside of a clinical trial.

In support of this contention, and with the dangers of cross-comparison and selection bias acknowledged, it is instructive to examine the results of large contemporaneous tandem AST trials involving more than 1000 patients that reported 60% to 65% 5-year survivals3,4,7 and to compare these results with the AST-NMT trials reported in this issue, which report 5-year survivals of 64% to 66%. It is argued by allogeneic proponents that the advantages of NMT only become apparent with long-term follow-up when a plateau in survival develops. But it must be remembered in this context that 33% of tandem AST MM patients also survive 10 years, even in the absence of any allogeneic cell therapy and before bortezomib, thalidomide, and lenalidomide were widely available.8 Furthermore, with the advent of new drugs, there is little doubt that survival in MM is continuing to improve rapidly.

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Although long-term results in the era of proteasome inhibitors and immunomodulatory drugs are not yet available, early indicators are that patients are living longer and in better health than before. As examples, recent studies show 90% of patients alive at 3 years following lenalidomide and dexamethasone induction and 87% of tandem AST patients with maintenance thalidomide alive at 4 years.

The results are even more compelling when genetic risk is factored in. For low-risk patients (absence of t(4;14), normal chromosome 13 and 17, and low beta-2 microglobulin) treated by conventional chemotherapy followed by tandem AST, 75% are alive at 5 years. In a second study, two-thirds of patients without cytogenetic abnormalities treated with tandem transplantation and thalidomide have remained alive at 7 years. Importantly, this latter population represents a majority of all myeloma patients treated and is from an era before all modern drugs were widely accessible. In this context and until proven otherwise, it is hard to accept an NMT treatment-related mortality (TRM) rate of 10% to 15% within 2 years and 18% within 5 years, a figure all the more compelling coming from one of the world’s most experienced transplant centers. It would be a surprise if many informed patients would accept such odds today.

It could be argued that a high treatment-related mortality is acceptable in patients at very high risk for early progression and death from disease. Unfortunately, the only randomized trial in this population, however, actually showed NMT to be inferior to tandem AST. Paradoxically, those who may actually benefit from NMT are those with good prognosis disease who can today reasonably expect to live 8 to 10 years on average from diagnosis, even without the hardship and risks associated with GVHD and infection.

Given all of the above, prudence suggests that NMT only be conducted in the context of a controlled clinical trial and assigned only to the highest-risk patient population, for whom other therapies are still clearly insufficient. Finally, consent forms for NMT must clearly document the 11% to 18% nonrelapse mortality and 50% to 74% chronic GVHD, as reported here.

Despite the early promise of NMT, it is perhaps time to learn from collective experience and retire the quixotic quest for safer and more effective NMT for now, lest history continues to repeat itself.

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