Unrelated Hematopoietic Cell Transplantation in Aplastic Anemia
There Is More to a Successful Outcome Than Meets the Eye

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Aplastic anemia is a condition in which the hematopoietic stem cells fail to function adequately leading to peripheral pancytopenia. When the cytopenia is severe, patients require intensive support with blood products and broad spectrum antibiotics, and without definitive treatment, most will eventually die of infections or bleeding. Over the past 4 decades, however, these once uniformly fatal conditions have been transformed into potentially highly curable ones.

Matched related hematopoietic cell transplantation (HCT) is now the standard curative modality for acquired severe aplastic anemia.
(SAA) in patients younger than 40 years, with excellent long-term, relapse-free survival; favorable results have also been reported in matched related HCT in patients older than 40 years. Similarly, matched related HCT is curative for Blackfan-Diamond anemia, with long-term survival rates approaching 90%. In Fanconi anemia, however, the underlying genomic instability of the Fanconi anemia cells represented a stumbling block with the use of conventional myeloablative preparatory regimens, but this was soon surmounted by the use of very low dose cyclophosphamide and more recently fludarabine with excellent long-term survival.1,2

For patients with acquired aplastic anemia with no suitable matched related donor and for those older than 40 years not considered sufficiently fit to undergo HCT, immune suppressive therapy with antithymocyte globulin (ATG) and cyclosporine is a valid alternative. This approach is, however, associated with substantial relapses. On failure of immune suppressive therapy and in patients with hereditary aplastic anemia who lack a matched related donor, unrelated donor HCT represents one of the best alternatives.1

The results of unrelated donor HCT have in general been less rewarding, but major strides have been made in this field. Following a conditioning regimen of fludarabine, cyclophosphamide, and ATG, with or without low-dose radiation, 5-year survival as high as 75% has been reported in patients with acquired SAA, and the use of the same regimen as described significantly improved survival in older patients. Even the effect of mismatching seemed to diminish in face of the recently used conditioning regimens.2

In hereditary anemias, however, the results of unrelated HCT vary widely according to the specific underlying disease. While excellent results have been reported in patients with Blackfan-Diamond anemia, the results of such an approach in patients with Fanconi anemia have been remarkably inferior.3

Therefore, and despite the remarkable progress made in the field of unrelated HCT, it has become obvious that refining the HLA typing, manipulating the conditioning regimen, and improving the GVHD prophylaxis and treatment represent only the tip of the iceberg and that additional factors on the cellular level in the donor and recipient may play an important role in determining the outcome of HCT.

The ultimate goal of translational medicine is to convert new knowledge and techniques generated by advances in basic sciences into new approaches for prevention, diagnosis, and treatment of disease and ultimately improve health. Translating the current understanding of dysfunctional, short telomeres, and defective telomerasises into diagnostic and prognostic tools in the different fields of medicine depicts this goal at its best.4

Telomeres are repeated nucleotide sequences that cap the ends of chromosomes and protect them from damage. They are shortened at each mitotic division of normal cells. Telomere shortening is one common pathway underlying bone marrow failure in constitutional and acquired aplastic anemias.

Gadalla et al examined the association between leukocyte telomere length and outcomes in matched unrelated HCT in patients with aplastic anemia, and, in findings conforming to already published data, patients in this study had significantly mean shorter leukocyte telomere lengths than their healthy donors. More importantly, shorter pretransplant leukocyte telomere length in the recipients was not associated with lower survival after HCT, in sharp contrast to data on patients with SAA treated with immune suppressive therapy in which shorter telomere length was associated with increased risk of relapse, clonal evolution, and lower survival.5 Therefore, this finding should help the clinicians to better select the right candidates for upfront, unrelated HCT.

Yet the salient finding of the trial by Gadalla et al is that longer donor leukocyte telomere length was associated with a significantly higher probability of post-HCT overall survival, independent of donor age. This finding could help further fine-tune the process of choosing the optimal donor for patients with SAA. The fact that the results were not altered by the aplastic anemia subtype (acquired vs inherited) makes this finding more germane in hereditary anemias like FA, in which the results of unrelated HCT have remained far from optimal.

Surprisingly, however, better survival could not be attributed to faster engraftment, lower incidence of acute or chronic graft-vs-host disease, or even to lower incidence of graft failure in recipients of the longer donor telomere grafts. Furthermore, the authors did not find a statistically significant difference in reported mortality causes by donor leukocyte telomere length.

How then? No conclusive explanation is offered by the authors, but telomeres seem to be intricately associated with human health. They have become valuable prognostic biomarkers in many clinical settings; shorter telomere length seems to portend worse prognoses in many malignant neoplasms and has been associated with increased risk of early death in the general population.

These results are inspiring and represent an additional building block toward a better understanding of the different factors influencing the outcome of HCT. More work is needed, however. Larger cohorts, longer follow-up, and trials in older populations and in other disease categories are warranted to further delineate the role of telomeres in dictating the final transplant outcome.

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REFERENCES