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. However, there are many other factors that contribute to the outcome of HCT. Here, we discuss some of these factors that are not immediately obvious and may have a significant impact on the success of HCT.

Association Between Donor Leukocyte Telomere Length and Survival After Unrelated Allogeneic Hematopoietic Cell Transplantation for Severe Aplastic Anemia

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IMPORTANCE Telomeres protect chromosome ends and are markers of cellular aging and replicative capacity.

OBJECTIVE To evaluate the association between recipient and donor pretransplant leukocyte telomere length with outcomes after unrelated donor allogeneic hematopoietic cell transplantation (HCT) for patients with severe aplastic anemia.

DESIGN, PARTICIPANTS, AND SETTING The study included 330 patients (235 acquired, 85 Fanconi anemia, and 10 Diamond-Blackfan anemia) and their unrelated donors who had pre-HCT blood samples and clinical and outcome data available at the Center for International Blood and Marrow Transplant Research. Patients underwent HCT between 1989 and 2007 in 84 centers and were followed-up to March 2013.

EXPOSURES Recipient and donor pre-HCT leukocyte telomere length classified into long (third tertile) and short (first and second tertiles combined) based on donor telomere length distribution.

MAIN OUTCOMES AND MEASURES Overall survival, neutrophil recovery, and acute and chronic graft-vs-host disease, as ascertained by transplant centers through regular patient follow-up.

RESULTS Longer donor leukocyte telomere length was associated with higher survival probability (5-year overall survival, 56%; number at risk, 57; cumulative deaths, 50) than shorter donor leukocyte telomere length (5-year overall survival, 40%; number at risk, 71; cumulative deaths, 128; \( P = .009 \)). The association remained statistically significant after adjusting for donor age, disease subtype, Karnofsky performance score, graft type, HLA matching, prior aplastic anemia therapy, race/ethnicity, and calendar year of transplant (hazard ratio [HR], 0.61; 95% CI, 0.44-0.86). Similar results were noted in analyses stratified on severe aplastic anemia subtype, recipient age, HLA matching, calendar year of transplant, and conditioning regimen. There was no association between donor telomere length and neutrophil engraftment at 28 days (cumulative incidence, 86% vs 85%; HR, 0.94; 95% CI, 0.73-1.22), acute graft-vs-host disease grades III-IV at 100 days (cumulative incidence, 22% vs 28%; HR, 0.77; 95% CI, 0.48-1.23), or chronic graft-vs-host disease at 1-year (cumulative incidence, 28% vs 30%; HR, 0.81; 95% CI, 0.53-1.24) for long vs short, respectively. Pretransplant leukocyte telomere length in the recipients was not associated with posttransplant survival (HR, 0.91; 95% CI, 0.64-1.30).

CONCLUSIONS AND RELEVANCE Longer donor leukocyte telomere length was associated with increased 5-year survival in patients who received HCT for severe aplastic anemia. Patient leukocyte telomere length was not associated with survival. The results of this observational study suggest that donor leukocyte telomere length may have a role in long-term posttransplant survival.
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. 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.

ARTICLE INFORMATION
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Conflict of Interest Disclosures: None reported.

Additional Contributions: The author thanks Kareem Ayas, BA, for assistance in the linguistic editing of the manuscript; he received no compensation for his assistance.

REFERENCES