Published in final edited form as:

Leuk Lymphoma. 2015 ; 56(8): 2235–2236. doi:10.3109/10428194.2015.1036260.

Defining Vulnerability in Allogeneic Transplants is More Complicated than the Two Numerical Digits of Age

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Keywords

Hematopoietic cell transplantation; graft-versus-host disease; non-relapse mortality aging; comorbidities; HCT-CI

In this issue of *Leukemia & Lymphoma*, colleagues from the graft-versus-host disease (GVHD) Working Group of Japan Society for Hematopoietic Cell Transplantation (HCT) reported the results of a registry-database-based retrospective analysis of the prognostic impact of increasing age on non-relapse mortality (NRM) following acute GVHD in a large cohort of patients (n=2682)[1]. Patients were diagnosed with various hematological malignancies and were treated with their first allogeneic HCT over a period of 5 years. Median age was 48 (range: 20-82) years. The 2-year cumulative incidence of NRM increased steadily with increasing age within five distinctive age groups so that patients aged 60 years had almost twice the NRM incidence (40.4%) compared to those with 20–29 years of age (20.7%). Two-year overall survival (OS, $p<0.001$), but not relapse ($p=0.727$), significantly differed between age groups. In multivariate models adjusted for a number of baseline patient characteristics, excluding comorbidity burden, patients aged 50–59 and 60 years had a nearly two-fold increase in risks of post-GVHD NRM compared to those aged 20–29 years. The association between age 50 years and post-GVHD NRM was stronger following grade II versus grades III-IV acute GVHD[1].

The two major points of this paper are the diverse impact of age 50 years compared to younger adults on risks of post-GVHD NRM and the more pronounced impact of age after grade II versus higher grades of acute GVHD. With lack of an accompanying evidence-based explanation for this age association, the authors refer us to earlier results from the same group showing that patients aged 50 years tended to have worse response to systemic steroids compared to those aged 18-49 years[2]. Clearly, lack of response to systemic steroids could explain, at least in part, the association between increasing age and post-GVHD NRM. Is older age to be blamed for lack of response to systemic steroids? Are there

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Disclosures: The author declares no competing financial interests.

other possible explanations for the association between aging and post-GVHD NRM? Should older patients be treated differently for acute GVHD?

Lack of adequate response to systemic steroids could be, in part, the result of inadequate delivery of steroid doses or insufficient duration of therapy; both could in some cases be triggered by physician bias against the ability of older patients to tolerate a full course of therapy. Alternatively, older patients are the ones that are more frequently challenged with high comorbidity burden[3,4]. About a decade ago, the impact of organ dysfunctions on NRM following allogeneic HCT was defined[5] and then further characterized by development and validation of the HCT-specific comorbidity index (HCT-CI)[6]. Patients with higher comorbidity scores were shown to experience higher risks for developing acute GVHD as well as higher risks for post-GVHD mortality[7]. Recently, The impact of age on NRM was quantified to be modest and to be the equivalent of a single comorbidity with a weight of 1 within the HCT-CI[8]. This finding would still apply on post-GVHD NRM since the impact of age was assessed on all events of NRM over time. The combined comorbidity/age index[8] represents a better way to evaluate patient vulnerability to acute GVHD. Other health limitations were also shown to impact mortality following HCT[9-11]. Therefore, we cannot really blame age per se for the intolerance to a full course of steroid therapy. Age is probably a surrogate measure of increased comorbidities, impaired physical performance, and other geriatric health limitations, as well as physician bias. Likewise, patients with multiple health limitations are more prone to develop complications to GVHD therapy that subsequently will also lead to increased NRM.

Given the previous points, there is really no reason to specifically treat older patients differently for acute GVHD. We need to adequately identify medically infirm and frail patients before HCT as candidates for trials exploring novel GVHD prophylaxis and treatment approaches that can be better tolerated without reducing efficacy. Recent results advocate for using lower doses of steroids to treat acute GVHD[12]. Whether this approach can improve post-GVHD NRM among vulnerable patients is still to be seen.

Finally, development of acute GVHD was shown to have an additive prognostic effect to comorbidities on subsequent mortality[7]. It is also well known that grades III-IV acute GVHD are associated with higher mortality rates compared to grade II. Therefore, development of grades III-IV acute GVHD is likely to blunt the effect of age on post-GVHD NRM as observed in the Japanese study.

Older patients might suffer from impaired health status and/or physician bias and both might limit adequate treatment of their acute GVHD or result in increased treatment-related morbidities. A novel study to design a composite health model incorporating the most relevant items of the HCT-CI, Karnofsky performance status, geriatric assessment tools, as well as molecular biomarkers[13] is underway [14]. Until then, comorbidities and physical health should be accounted for when evaluating associations between age and post-HCT outcomes. This is critical in order to avoid denying adequate therapy from fit older patients but also to avoid the treating young medically infirm patients with harmful aggressive therapy.

Acknowledgments

This work was supported by Grant No. HL088021 from the National Institutes of Health; by Research Scholar Grant No. RSG-13-084-01-CPHPS from the American Cancer Society; and by Patient-Centered Outcome Research Institute Contract No. CE-1304-7451. The author is grateful to Bonnie Larson and Helen Crawford for manuscript preparation.

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