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The Bottom Line

Comment: Is There a Role for Allogenic Hematopoietic Cell Transplantation in Primary Mediastinal Large B Cell Lymphoma?

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In this issue of *Biology of Blood and Marrow Transplantation*, Herrera et al [1] report a multicenter retrospective series looking at outcomes after allogeneic hematopoietic cell transplantation (allo-HCT) in primary mediastinal large B cell lymphoma (PMBCL). PMBCL is a subtype of diffuse large B cell lymphoma (DLBCL) with distinct pathological, immunohistochemical, genetic, and clinical features. While outcomes with first-line therapy for PMBCL are now excellent, for patients with relapsed and refractory (R/R) disease, outcomes are unfavorable, and autologous or allogeneic hematopoietic cell transplantation is often considered. Before 2019, the only published data on allo-HCT in R/R PMBCL was limited to case reports or small case series, making this an important topic. In addition, treatment options for PMBCL have changed in recent years, owing to increased use of the dose-adjusted R-EPOCH regimen, movement away from the use of involved field radiation [2,3], and recent reports showing significant activity of PD-1 inhibitors [4,5] and chimeric antigen receptor T cell (CAR-T) therapy [6] in heavily treated R/R PMBCL. As a result, data such as that reported by Herrera et al are particularly timely, as clinicians struggle to incorporate allo-HCT into this new treatment landscape.

First-line therapy of PMBCL has a high rate of success, in the 70% to 93% range depending on the regimen used [2,3]. However, once patients develop R/R PMBCL, outcomes become much less favorable. Historically, for patients with R/R disease, second-line platinum-based therapy with autologous hematopoietic cell transplantation (auto-HCT) is pursued; involved-field radiation therapy is often incorporated as well if it was not given during first-line therapy. Two retrospective studies have shown a 64% to 70% progression-free survival (PFS) at 4 to 5 years for patients with R/R PMBCL who undergo auto-HCT with chemosensitive disease [7,8].

Unfortunately, PMBCL has a relatively low response to second-line (salvage) therapy. According to a study reported by Kuruvilla et al [9], only 25% of patients achieved a complete response (CR) or partial response (PR) to second-line therapy. In that study, of all the patients with PMBCL who developed R/R disease, less than one-half ultimately achieved a response to second-line therapy and went on to receive auto-HCT, and the 2-year overall survival (OS) after the initial diagnosis of R/R disease was discouragingly low, at 15% [9]. Therefore, for many R/R patients, auto-HCT either fails to produce long-term remission or is not a suitable option due to refractory disease. As a result, allo-HCT is often considered for patients with R/R PMBCL, although there are very little data available regarding outcomes.

Herrera et al report the outcomes of a cohort of 28 patients with R/R PMBCL who underwent allo-HCT at 4 large US academic centers between 2000 and 2015. All patients had previous rituximab exposure, and 86% had previous radiation exposure. As a reflection of the era, only 1 of the 28 patients received DA-EPOCH-R as an induction regimen, and none of the patients had received a checkpoint inhibitor or CAR T cell therapy; however, 71% had progressed after a previous auto-HCT. Before allo-HCT, 21% had refractory disease, with 75% in a PR and only 1 patient (4%) in CR. Although various conditioning regimens were used, all but 4 patients underwent reduced-intensity conditioning, and 83% had a matched related or matched unrelated donor. The median duration of follow-up was 5 years. At 5 years, the nonrelapse mortality was 32% and the rate of relapse was 33%. This resulted in a 5-year PFS of 33% and 5-year OS of 45%. Among the patients with chemosensitive disease before allo-HCT, the PFS at 2 years was 50% (versus 0% in chemorefractory patients), and the 2-year OS was 58% (versus 0% in chemorefractory patients). Of note, some patients with progressive or residual disease after allo-HCT responded to reduction in immune suppression and/or donor lymphocyte infusion, providing evidence of a graft-versus-lymphoma effect in PMBCL.

The results reported by Herrera et al should considered along with a very recent study from the Japan Society for Hematopoietic Cell Transplantation registry published by Kondo et al [10], in which 23 patients with R/R PMBCL underwent allo-HCT after a failed auto-HCT. The median patient age was

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33 years, and 3-year PFS and OS were 33% and 49%, respectively, very similar to the results of Herrera et al. Notably, of the 15 patients with refractory disease before allo-HCT, 6 achieved a CR after allo-HCT. In 3 of these patients, the remission was durable. That study, in contrast to the study by Herrera et al, suggests that long-term remission is possible in a small subset of patients with refractory PMBCL who undergo allo-HCT. However, there were some important differences from the cohort studied by Herrera et al. In particular, different conditioning regimens were used (including 44% myeloablative), and a much higher rate of alternative donors was used (61%, versus 18% by Herrera et al). Regimens given before allo-HCT were not captured in the study of Kondo et al. It is possible that these differences may account for the discrepancy in the 2 studies in terms of outcome among patients undergoing allo-HCT with refractory disease.

The results of Herrera et al are an important contribution to the literature. The study, along with the recent results from Kondo et al, certainly justify the use of allo-HCT in patients with R/R PMBCL who have failed auto-HCT and who achieve at least a PR before allo-HCT. This practice is also supported by a Center for International Blood and Marrow Transplant Research study evaluating the outcomes of allo-HCT after a failed auto-HCT for the broader pathological entity of DLBCL [11]. However, for patients with truly refractory disease, the results reported by Herrera et al would suggest that allo-HCT is not beneficial, and that such patients generally would be better served with alternative strategies such as PD-1 inhibitors (alone or in novel combinations), other checkpoint inhibitors, and/or CAR-T cell therapy. Moving forward, more patients with R/R PMBCL will be undergoing these alternative treatments, so an important future question will relate to the optimal sequencing of allo-HCT relative to these new treatments.

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