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Short Communication

Allogeneic Hematopoietic Cell Transplantation: Treatment for Primary Mediastinal Large B cell Lymphoma

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ABOUT THE STUDY

The Herrera reported a multicenter retrospective data on outcomes after allogeneic Hematopoietic Cell Transplantation (allo-HCT) in Primary Mediastinal Large B Cell Lymphoma (PMBCL). PMBCL is a subtype of DLBCL with different morphological, immunohistochemical, genetic, and clinical features. While first-line therapy for PMBCL is currently excellent, outcomes are poor for patients with Relapsed and Refractory (R/R) disease and autologous or allogeneic hematopoietic cell transplantation is often considered. Before to 2019, the only published data on allo-HCT in R/R PMBCL was case reports or small case series, making this an important topic [1]. Furthermore, treatment options for PMBCL have changed in recent years as a result of increased use of the dose-adjusted R-EPOCH regimen, a shift away from involved field radiation [2,3], and recent reports demonstrating significant activity of PD-1 inhibitors [4,5] and Chimeric Antigen Receptor T Cell (CAR-T) therapy in heavily treated R/R PMBCL [6]. As a result, such as that reported by Herrera are particularly timely, as clinicians struggle to incorporate allo-HCT into this new treatment landscape.

First-line therapy for PMBCL has a high success rate, ranging from 70% to 93% depending on the regimen used [2,3]. However, once patients develop R/R PMBCL, the outcome becomes so much less. Historically, second-line platinum-based therapy with autologous Hematopoietic Cell Transplantation (auto-HCT) has been pursued for patients with R/R disease; involved-field radiation therapy is frequently integrated as well if it was not given during first-line therapy. Two retrospective studies have shown the patients with R/R PMBCL who undergo auto-HCT with chemo sensitive disease have a 64% to 70% Progression-Free Survival (PFS) at 4 to 5 years [7,8].

Unfortunately, second-line (salvage) therapy has a low response rate in PMBCL. Kuruvilla [9] observed that only 25% of patients achieved a Complete Response (CR) or Partial Response (PR) to second-line therapy. In that study, all PMBCL patients who developed R/R disease were included. Less than half of those who received second-line therapy eventually responded and went on to receive auto-HCT and the 2-year Overall Survival (OS) after the initial diagnosis of R/R disease was low, at 15% [9]. As a result, auto-HCT either fails to produce long-term remission or is invalid due to refractory disease in many R/R patients. As a result, allo-HCT is often considered for patients with R/R PMBCL, despite the reality that there is limited data on outcomes.

Herrera reports the findings of 28 patients with R/R PMBCL who underwent allo-HCT at five important US academic centers between 2000 and 2015. All patients had previously received rituximab, and 86% had previously received radiation. Only one of the 28 patients received DA-EPOCH-R as an induction regimen, and none had received a checkpoint inhibitor or CAR T cell therapy; however, 71% had progressed after previous auto-HCT. Before to allo-HCT, 21% of patients had refractory disease, with 75% in a PR and only 1 patient (4%) in a CR. Although the use of various conditioning regimens, all but 4 patients had reduced-intensity conditioning and 83% had a matched related or matched unrelated donor. The average duration of follow-up was 5 years. At 5 years, non-relapse mortality was 32%, and relapse was 33%. As a result, the 5-year PFS of 33% and the 5-year OS is 45%. PFS at 2 years was 50% (versus 0% in chemo refractory patients) and OS was 58%(versus 0% in chemo refractory patients) in patients with chemo sensitive disease before to allo-HCT. It is important to note that some patients with progressive or residual disease after allo-HCT responded to immunosuppressive reduction and/or donor lymphocyte infusion, suggesting a graft-versus-lymphoma effect in PMBCL.

The results by Herrera, et al. should be considered in combination with a recent study from the Japan Society for Hematopoietic Cell Transplantation registry published by Kondo [10] after a failed auto-HCT, 23 patients with R/R PMBCL underwent allo-HCT. The median patient age was 33 years, and PFS and OS at 3 years of 33% and 49%, respectively. Similar to Herrera, et al. notably, 6 of the 15 patients with refractory disease before to allo-HCT achieved a CR. The remission was lengthy in 3 of these patients. In contrast to Herrera, et al. this study suggests that long-term remission is possible in a small subset of

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patients with refractory PMBCL who undergo allo-HCT. However, there were some significant differences from the Herrera, et al. cohort. Different conditioning regimens were used (including 44% myeloablative), and alternative donors were used at a much higher rate (61%versus 18% by Herrera, et al). Kondo studies did not include regimens given before to allo-HCT.

It is possible that these differences account for the discrepancy in results between the two studies in individuals undergoing allo-HCT with refractory disease. Herrera results make an important contribution to the literature.

The results, as well as those of Kondo completely support the use of allo-HCT in patients with R/R PMBCL who have failed auto-HCT and obtained at least a PR before to allo-HCT. A Centre for International Blood and Marrow Transplant Research evaluating the outcomes of allo-HCT after a failed auto-HCT for the broader pathological entity of DLBCL also validates this procedure [11].

CONCLUSION

However, the results of Herrera suggest that allo-HCT is not beneficial for patients with truly refractory disease, and that such patients would be better served by alternative strategies such as PD-1 inhibitors (alone or in novel combinations), other checkpoint inhibitors, and/or CAR-T cell therapy. As more patients with R/R PMBCL undergo these alternative treatments in the future, an important future question will be the optimal sequencing of allo-HCT in relation to these new treatments.

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