

## Stem cell transplant for lymphoma - never too late?

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In this issue, using the Center for International Blood and Marrow Transplant Research (CIBMTR) registry, Mei *et al.*<sup>1</sup> provide a retrospective outcomes analysis of 285 patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who underwent autologous hematopoietic cell transplantation (autoHCT) after achieving complete (CR) or partial response (PR) to their *third or higher line* of chemotherapy. Sixty three percent of patients had primary refractory disease or relapsed within 1 year of initial diagnosis. For perspective, during the same interval 577 patients with R/R DLBCL in the registry underwent autoHCT after second line therapy. Patients in the registry with detailed data including prior lines of therapy comprise approximately 8-10% of all patients in the CIBMTR registry, which in other analyses have been representative of the entire dataset (personal communication with corresponding author). Mei *et al.* report 5-year overall survival (OS) and progression-free survival (PFS) for the study population of 51% and 38%. As expected, patients in CR at the time of transplant had better OS and PFS, but a substantial minority of patients with PR also benefited from autoHCT, with a 5-year PFS of 34%. Relapses in patients with a PR occurred early, with a near plateau in the relapse/progression curve after 1 year. In contrast, patients in CR had a significantly lower 1-year risk of relapse but a continuous risk of relapse for at least 4 years after autoHCT, resulting in a non-significant difference in the 5-year risk of relapse between the two groups (CR 45% vs. PR 54%,  $P=0.14$ ).

Importantly, while nearly half of all patients were without relapse at 5 years, the 5-year PFS of 38% reflects a 5-year non-relapse mortality of 12%. After lymphoma, the second most common cause of death was second malignancy, in 10% of the study cohort during the entire follow-up period.

How does this retrospective registry analysis inform our decision whether to pursue autoHCT for a given patient with R/R DLBCL? Primarily, it confirms that patients with chemosensitive disease can achieve long-term remissions after autoHCT, including those who have early failure of frontline immunochemotherapy, those who achieve less than a CR to salvage chemotherapy, and those who have been treated with more than one line of salvage chemotherapy. Consistent with prior reports, Mei *et al.* found that, while patients in CR have a better PFS than those in PR, approximately a third of PR patients remain alive and progression-free after autoHCT. Their results mirror another CIBMTR analysis<sup>2</sup> that reported 5-year PFS of 41% for patients with R/R DLBCL who had PET-positive PR prior to autoHCT. Even patients with primary refractory disease or early relapse have a 40-50% chance of durable PFS after autoHCT, if they respond to salvage therapy.<sup>3,4,5</sup>

Unfortunately, many patients with R/R DLBCL do not achieve a CR or PR to one or more lines of salvage

chemotherapy. In the prospective, randomized CORAL study,<sup>4</sup> 63% of all patients, 51% of patients previously treated with rituximab, and 46% of patients with primary refractory disease or early relapse achieved CR or PR to R-ICE or R-DHAP. Of the patients who did not respond to the study-assigned salvage regimen, only 32% responded to subsequent therapy and underwent a stem cell transplant.<sup>6</sup> In two randomized studies of anti-CD19 chimeric antigen receptor T-cell therapy (CAR-T) *versus* standard of care in patients with early failure of frontline immunochemotherapy, the response rates to standard second line therapies were 50%<sup>7</sup> and 43%.<sup>8</sup> Clearly, inadequate response to second- or third-line therapy is a significant barrier to use of autoHCT in many patients with R/R DLBCL. New agents with encouraging activity in R/R DLBCL, including bispecific T-cell engagers<sup>9</sup> and antibody-drug conjugates,<sup>10</sup> may improve the number of patients who achieve PR or CR to second- or third-line therapy making autoHCT an option for more patients. However, whether response to novel therapies with unique mechanisms of action will predict response to autoHCT is unknown and will be extremely challenging to study.

While CAR-T is the obvious choice for patients who do not respond to standard second- or third-line regimens, the choice between autoHCT and CAR-T can be difficult for patients with chemosensitive R/R DLBCL. The potential approval of CAR-T in the second line will increase the challenge of weighing the relative benefits of autoHCT *versus* CAR-T for a given patient. Now more than 4 years after approval of the first CAR-T for R/R DLBCL, significant hurdles remain, including complicated and delayed insurance approvals, limitations on manufacturing slots, and the potential for progressive disease and worsening performance status during the “waiting period”. Rigorous cost-benefit analysis of CAR-T *versus* autoHCT for patients with chemosensitive disease in second and third line would be informative. Additionally, late effects of CAR-T and autoHCT need to be compared and considered in the treatment decision. Post-CAR-T complications, especially prolonged cytopenias and infections, can be more challenging than post-autoHCT in a significant minority of patients, and, as Mei’s study demonstrates, second malignancies are a concerning cause of non-relapse mortality post-autoHCT.

Although we have ample data on the tolerability and efficacy of CAR-T following relapse after autoHCT, there is no data on autoHCT following CAR-T cell failure. In the current use of CAR-T for chemorefractory disease or relapse after autoHCT, patients would not be candidates for autoHCT after CAR-T. However, if approvals are forthcoming for CAR-T as second-line therapy, understanding the feasibility and efficacy of autoHCT after CAR-T would help inform the decision of sequencing these therapies in patients responding to second- or third-

line chemotherapy. In the meantime, the retrospective studies by Mei *et al.* and others provide important benchmarks of outcomes following autoHCT, suggesting that autoHCT remains a reasonable option for the patients with chemosensitive R/R DLBCL, even in later lines of therapy. For those patients, CAR-T can be held in reserve in case of relapse after transplant.

### Disclosures

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### Contributions

AC and NLB contributed equally to the writing of this editorial.

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