

AUTOLOGOUS TRANSPLANT IN LYMPHOMAS IN THE CURRENT ERA OF IMMUNOTHERAPY

Autologous stem cell transplant (ASCT) is the treatment of choice for aggressive, relapsed/refractory non-Hodgkin's and Hodgkin's lymphomas (HLs).^[1,2] In patients aged <65 years, 40–45% achieve cure with this form of treatment. The duration of remission post-transplant depends on the histological subtype, prior treatment and the response to salvage therapy. In Pakistan, the common lymphomas for which patients receive treatment include diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, follicular lymphoma and HL.^[3] Of these, ASCT is commonly performed for DLBCL and HL in the second complete remission.^[4]

Based on the opinion that ASCT can potentially cure 50% of patients who relapse but is chemosensitive, this procedure was performed in a cohort of patients who partially responded to chemotherapy. Philip *et al.*, in 1998,^[5] reported that 76% of the patients remained disease free with a 6-year survival of 75% post-ASCT. The Non-HL Cooperative Study in 1993 showed a 5-year disease-free survival of 36% ($n = 21$ patients).^[6] This translated as a potential cure of approximately one in three patients with partial remission after ASCT. Hamadani *et al.*, in 2014,^[7] reported important outcomes on $n = 516$ DLBCL patients with respect to Rituximab-based therapies and ASCT. The observations included as follows: (a) Patients receiving Rituximab-based therapy and experiencing late relapse (>1 year after treatment) have excellent response to ASCT; (b) in patients with early relapse (within 1 year of treatment with Rituximab-based regimens), ASCT can confer durable disease control and (c) in patients who have refractory disease but respond to salvage therapies, ASCT is the only potentially curative treatment option; however, a fourth observation included that a subset of patients relapsed within 6–9 months of transplant. This led to the inference of maintenance Rituximab. Gisselbrecht *et al.*, in 2012,^[8] after performing ASCT and randomly assigning patients to two groups of cohort ($n = 122$ patients who received

Rituximab and $n = 120$ patients who did not receive Rituximab) concluded that there was no difference between the maintenance group and control group and did not recommend maintenance post-transplant. A study was done by Zhang *et al.*^[9] demonstrated that ASCT in combination with Rituximab *in vivo* purging followed by maintenance Rituximab prolongs progression-free survival and overall survival. However, this was a cohort of $n = 12$ young patients with DLBCL. Therefore, the current recommendation for relapsed/refractory DLBCL remains to be ASCT in transplant-eligible patients with no role of maintenance Rituximab.

Most patients with HL achieve long-term remission with chemo or radiotherapy. However, 10–30% of patients progress or relapse depending on the stage. ASCT can cure 50% of these patients. In the remaining 50%, treatment of HL remains to be a challenge.^[10,11] The use of brentuximab vedotin (anti-CD30) in early Phase I trials did not demonstrate any clinical significance.^[12,13] Phase II trials, however, demonstrated satisfactory results. The German Hodgkin Study Group showed an overall response rate (ORR) of 60% in $n = 45$, heavily pre-treated patients.^[14] Due to this increased ORR and tolerable safety profile of the drug, Food and Drug Administration granted an accelerated approval for the treatment of HL in patients who relapse after ASCT or in patients ineligible for transplant. The National Comprehensive Cancer Network guideline includes brentuximab for the same. Brentuximab has also been used as a bridge to ASCT in patients who fail standard and salvage treatments.^[15]

Moving forward, to further improve outcomes after ASCT in relapsed/refractory lymphomas, efforts need to be focused on evaluating novel consolidation or maintenance strategies, possibly with agents not used in induction/salvage therapies. The current standard of care remains to be high-dose chemotherapy followed by ASCT and immunotherapies cannot be used as an alternative to transplant.

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