Consolidation therapy in Hodgkin lymphoma

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Modern treatments for newly diagnosed Hodgkin lymphoma (HL) have led to impressive survival of ≥80%. Despite the fact that the majority of patients are cured of HL with first-line therapy, a proportion of patients are refractory to such treatment or relapse after achieving a first remission; the survival for that group is poor, at only ~50%. High-dose therapy and autologous stem cell transplantation (ASCT) is the standard of care for such patients,1,2 but despite this aggressive therapy, as many as 50% of patients will relapse thereafter and eventually die of their lymphoma. Because HL patients who undergo ASCT are generally young and fit, their survival is dictated by lymphoma control and not typically by treatment toxicity, and recent attempts have been made to increase the amount of therapy for relapsed/refractory HL by including post-ASCT consolidation therapy. Consolidation involves relatively intensive and limited-duration therapy designed to further diminish the number of lymphoma cells and improve the likelihood of completely eradicating the disease.

**CLINICAL TRIALS**

Only 2 randomized controlled trials of consolidation therapy post-ASCT for HL have been reported, with a single recent study (the AETHERA trial) demonstrating improved progression-free survival (PFS) with consolidation therapy with brentuximab vedotin.3 This study enrolled patients with relapsed or refractory HL deemed to be at high risk of recurrence post-ASCT: primary refractory disease, relapse ≤12 months from initial therapy and/or extranodal disease at relapse. Brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to a microtubule-disrupting agent, monomethyl auristatin E, and has demonstrated efficacy in relapsed and refractory HL patients,4 making it an ideal agent for consolidation therapy in this population. The AETHERA study demonstrated a clinically meaningful improvement in 24-month PFS of 63% compared to 51% for placebo (p=0.0013) at the expense of a significant increase in peripheral sensory neuropathy (56% of patients, grade 3 in 10%) and neutropenia (35%, grade 3 in 29%). In a followup report, it was noted that 65% of patients followed for neuropathy had complete resolution of complaints and 23% had “some improvement.”

Another study initiated around the same time as AETHERA was a double-blind, placebo-controlled, randomized prospective study of panobinostat consolidation therapy for 1 year post-ASCT in high-risk patients with relapsed HL.5 Unfortunately, the study was prematurely closed due to failure of accrual, with only ~10% of the desired total population enrolled. The study demonstrated safety in using panobinostat early after ASCT in HL patients, but could make no conclusions on efficacy. The efficacy data for panobinostat in relapsed HL were not as promising as the data with brentuximab vedotin, which was likely the cause for low patient and physician interest in this study.

**PRACTICE CHANGES**

The results of the AETHERA trial have influenced practice in many transplant centres to include consolidation therapy with brentuximab vedotin post-ASCT in high-risk HL patients. However, some questions remain. In the AETHERA study, crossover was allowed and 85% of patients in the placebo group who progressed were later treated with brentuximab vedotin. The trial did not, therefore, demonstrate an overall survival (OS) advantage. It has been argued that consolidation therapy may delay a relapse that could otherwise have been treated with brentuximab vedotin, with the same resultant OS. Although brentuximab vedotin is generally well tolerated, a third of patients in the consolidation group discontinued therapy because of toxicity (mostly neuropathy). Cost and toxicity are important considerations.

**LINGERING QUESTIONS**

There is definitely a population of patients who are destined to relapse post-ASCT and who could benefit from post-ASCT consolidation therapy. The difficulty facing physicians is the lack of clarity about how best to risk-stratify such patients. The placebo-treated group in the AETHERA study had a PFS of 51% at 24 months, which suggests that the population was not significantly more high-risk than the general post-ASCT HL population. The definition of high-risk disease would likely have been improved by the use of positron emission tomography (PET) scanning, which has demonstrated very high sensitivity in HL, even in relapsed disease.3 Additionally, a study to determine prognostic factors that included data from 5 collaborative groups with transplant centres was able to further risk-stratify patients by time from initial therapy to relapse, with patients relapsing less than 6 months after completing chemotherapy being especially high-risk.7 Thus, while consolidation therapy in the AETHERA study led to a clinically important improvement in PFS in relapsed/refractory HL patients, the lack of OS advantage compared to patients treated only when relapse occurred makes it clear that better risk stratification is needed to guide decision-making around which patients will benefit from consolidation therapy post-ASCT.

**References**


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