

Did brentuximab vedotin's rise to the top ECHELON of Hodgkin therapeutics invalidate AETHERA results?

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High-dose therapy (HDT) with autologous hematopoietic cell transplantation (autoHCT) has been considered the standard-of-care for relapsed chemosensitive classical Hodgkin lymphoma (cHL), since the end of the last century.^{1,2} While this simple and time-tested modality can eradicate disease in the majority of patients undergoing this procedure, recurrent cHL remains the most common cause of treatment failure and death following autoHCT. Several prognostic factors (primary refractory disease, early relapse after frontline treatment, poor patient performance status, extranodal involvement, positron emission tomography-avid residual disease prior to autoHCT, etc.) have been known to predict the risk of relapse after HDT and autoHCT.³ However, pharmacological interventions to mitigate the risk of lymphoma relapse after autoHCT had remained elusive, until the clinical availability of brentuximab vedotin.

Brentuximab vedotin is an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule-disrupting agent, monomethyl auristatin E (MMAE). Brentuximab ve-

dotin derives its antitumor activity by binding the antibody-drug conjugate (ADC) to CD30-expressing cells, leading to internalization of the ADC-CD30 complex followed by proteolytic cleavage and release of MMAE. MMAE disrupts the microtubule network by binding to tubulin within the cell, thereby causing cell cycle arrest and apoptotic death of the cell.⁴ The key phase II registration study of brentuximab vedotin (1.8 mg/kg every 3 weeks) in relapsed/refractory cHL (n=102; overall response rate = 75%)⁵ eventually paved the path to the prospective, multicenter, phase III randomized AETHERA trial, in which 327 patients with cHL at increased risk of progression after autoHCT, who had been treated with a minimum of two prior systemic therapies and had achieved a complete or partial remission or had stable disease at the time of autoHCT, were randomized to receive brentuximab vedotin consolidation or placebo (every 3 weeks for up to 16 cycles) after HDT.⁶ Patients were eligible for the study if they met one of the following criteria: primary refractory disease following first-line therapy, first remission dur-

Table 1. Indications for brentuximab vedotin treatment of classical Hodgkin lymphoma approved by the United States Food and Drug Administration and the European Medicines Agency.

Indications for brentuximab vedotin treatment of cHL according to the FDA	
Previously untreated stage III/IV cHL	Adult patients with previously untreated stage III/IV cHL in combination with doxorubicin, vinblastine, and dacarbazine.
cHL post-autoHCT consolidation¹	Adult patients with cHL at high risk of relapse or progression as post autoHCT consolidation.
Relapsed/refractory cHL	Adult patients with cHL after failure of autoHSCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not auto-HSCT candidates.
Indications for brentuximab vedotin treatment of cHL according to the EMA	
Previously untreated stage III/IV cHL	Adult patients with previously untreated CD30 ⁺ stage IV cHL in combination with doxorubicin, vinblastine and dacarbazine.
cHL post-autoHCT consolidation[*]	Treatment of adult cHL patients at increased risk of relapse or progression following autoHCT.
Relapsed/refractory cHL	<ol style="list-style-type: none"> 1. following autoHCT, or 2. following at least two prior therapies when autoHCT or multi-agent chemotherapy is not a treatment option.

*Increased risk defined for the AETHERA trial as either primary refractory cHL, relapsed cHL with an initial remission duration of <12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy. cHL: classical Hodgkin lymphoma; FDA: Food and Drug Administration; EMA: European Medicines Agency; autoHCT: autologous hematopoietic stem cell transplantation.

ation of less than 12 months, or extranodal involvement at the start of salvage chemotherapy. After a median follow-up of 30 months, the estimated 2-year rate of progression-free survival by independent review was 63% (95% confidence interval [95% CI]: 55–70) in the brentuximab vedotin group and 51% (95% CI: 43–59) in the placebo group (hazard ratio = 0.57; 95% CI: 0.40–0.81). Overall survival was 88% at 2 years in both arms.

Of note, the AETHERA trial only enrolled cHL patients who had not previously received treatment with brentuximab vedotin. However, since publication of the results of AETHERA, brentuximab vedotin (at a dose of 1.2 mg/kg up to a maximum of 120 mg every 2 weeks in combination with doxorubicin, vinblastine, and dacarbazine) has become approved in the frontline setting based on the results of ECHELON1⁷ (Table 1) and is being increasingly used in pre-autoHCT salvage regimens.⁸ Accordingly, in current clinical practice, the proportion of brentuximab vedotin-naïve high-risk cHL patients undergoing autoHCT is declining. While international consensus guidelines suggest the use of post-autoHCT brentuximab vedotin maintenance in high-risk cHL patients with limited prior exposure to brentuximab vedotin (defined as approximately ≤4–6 cycles),⁹ these recommendations lack supportive evidence.

In a Letter to the Editor published in this issue of *Haematologica*, Marouf *et al.*¹⁰ report a retrospective nationwide French cohort (AMAHRELIS) study, examining the real-life outcome of cHL patients who received post-transplant brentuximab vedotin maintenance (n=115) during 2012–2017. Since brentuximab vedotin received European Commission approval in 2016,¹¹ it is not clear whether these patients were treated on local clinical trials or had access through compassionate use protocols. Compared to AETHERA, more patients in the AMAHRELIS cohort received escalated BEACOPP in first-line (16% vs. 37%), had a negative positron emission tomography scan prior to autoHCT (47% vs. 82%) and underwent more than one salvage therapies (43% vs. 51%). Ninety-five percent of patients in the AMAHRELIS cohort met the AETHERA definition of high-risk disease.

More importantly, 70% (n=81) of patients in the AMAHRELIS cohort had been exposure to brentuximab vedotin prior to autoHCT. The mean number of brentuximab vedotin doses administered after autoHCT was 11 (range, 3–18), without difference between patients who had and had not been previously exposed to brentuximab vedotin. Treatment-related events led to maintenance discontinuation in 10% of patients, which is surprising, since nearly a third of brentuximab vedotin-naïve AETHERA patients discontinued treatment due to adverse events.⁸ The 2-year progression-free survival of patients in AMAHRELIS was 75% and was not affected by pre-transplant exposure to brentuximab vedotin. These rates seem to be numerically higher than rates reported in the AETHERA study; a potential explanation for these improved outcomes is a higher proportion of patients with complete metabolic remission in the retrospective cohort prior to transplantation. With limitations of a retrospective cohort in mind, these results are noteworthy and provide much needed evidence supporting the use of brentuximab vedotin maintenance after autoHCT in cHL patients with prior exposure to this agent. In the recent past, nonrandomized data on post-transplant maintenance with checkpoint inhibitors have shown a high degree of disease control.¹² Whether checkpoint inhibitors are superior to brentuximab vedotin in the post-transplant maintenance space merits examination, especially when considering the recent results of the KEYNOTE-204 trial showing a progression-free survival benefit of pembrolizumab compared with brentuximab vedotin, in patients with cHL who have relapsed after autoHCT or are ineligible for autoHCT.¹³

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