

Brentuximab vedotin consolidation therapy after autologous stem-cell transplantation in patients with high-risk Hodgkin lymphoma: Multicenter retrospective study

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Abstract

The AETHERA trial reported an increased progression-free survival (PFS) when Brentuximab Vedotin (BV) was used as maintenance therapy in high-risk Hodgkin's Lymphoma (HL) after autologous stem cell transplantation (ASCT). Thus, we aimed to determine the impact and safety of BV as maintenance after ASCT in real-world patients. Seventy-five patients with relapsed/refractory HL started on BV consolidation therapy after ASCT due to high risk of relapse, between January 2016 and July 2019, from 25 institutions, were included in the study. The median follow-up time was 26 months. The most common high-risk features were primary refractory or relapsed disease < 12 months (n = 61), lack of CR to the last salvage regimen (n = 51), and having had at least two salvage regimens (n = 29). At the time of analysis, 42 patients completed consolidation courses, and BV was discontinued in 33 patients. Fifty patients had an ongoing response (CR in 41, PR in six, and SD in three patients), 25 had progressed. Ten died in the follow-up, eight with progressive disease and two due to infection while in CR. The 2-years PFS and OS rates were 67.75% (95% CI:0.55–0.77) and 87.61% (95% CI:0.76–0.94), respectively. Seventeen patients (23%) received BV in the pre-ASCT treatment lines, and there was no survival difference between the BV naïve and BV exposed groups. The most common adverse events were neutropenia (27%) and peripheral neuropathy (21%). Sixteen patients (21.3%) experienced grade 3 or 4 toxicity. BV was discontinued due to AE in 12 patients. Consolidation with BV after ASCT can achieve a 2-year PFS of 67.75% (95% CI: 0.55–0.75) with an acceptable toxicity profile.

Background & Objective

The standard of care for patients with relapsed/refractory (R/R) Hodgkin Lymphoma (HL) is high dose chemotherapy with autologous stem cell support (ASCT), which offers a cure rate of up to 50%.¹ Recently, the outcome of relapsed/refractory HL improved dramatically with the advent of novel targeted drugs, such as brentuximab vedotin (BV). In the randomized phase 3 AETHERA trial, early consolidation with BV following ASCT resulted in a superior progression-free survival (PFS) in patients who were at high risk of relapse or progression after ASCT compared to placebo.² We aimed to assess the efficacy and safety of BV consolidation therapy following ASCT in patients with high-risk HL, including BV pre-treated cases, in a real-life context.

Materials & Methods

Twenty-five Turkish institutions participated in this multi-center, retrospective study. Patients (≥ 18 years old) with histologically confirmed HL, who had undergone ASCT have been included in our evaluation. Eligible patients had at least one of the following risk factors for progression: 1) primary refractory HL (defined as progression during or failure to achieve a complete remission after frontline therapy) or relapse < 12 months, 2) extranodal disease at relapse, 3) B symptoms at relapse, 4) ≥ two prior salvage therapies, 5) partial response (PR) or stable disease (SD) to most recent salvage therapy.

There was no restriction for BV-use in the pre-ASCT setting. Post-ASCT disease status was checked at a mean of 3 months. BV consolidation was initiated within 6 months of ASCT and administered at a dose of 1.8 mg/kg intravenous infusion over 30 min every 3 weeks in an outpatient setting. Physicians aimed to complete a total of 16 cycles, including pre-ASCT BV administrations.

Results

Patients

Patients' baseline characteristics, initial treatment strategies, and treatment responses are summarized in Table 1. The most common high-risk features were primary refractory or relapsed disease < 12 months (n=61), lack of CR to the last salvage regimen (n=51), and having had at least two salvage regimens (n=29).

Table 1. Baseline characteristics	n=75
Age (years)	31 (18-65)
Male / Female	42 / 33
Median follow-up	26 months
Frontline therapy	
ABVD	73
Other	2
Pre-ASCT radiotherapy	18 (24%)
Number of previous salvage therapies	
1	46 (61.3%)
≥ 2	29 (38.7%)
Disease status after frontline therapy	
Refractory	26(34.6%)
Relapse < 12 months	35 (46.7%)
Relapse ≥ 12months	14 (18.7%)
Pre-consolidation ECOG performance status	
0	61 (81.33%)
1	14 (18.67%)
B symptoms before auto-SCT	16 (21.3%)
Extranodal involvement at pre-ASCT relapse	15 (20%)
BV response pre-ASCT (n=17)	
Complete remission	11 (64.7%)
Partial remission	6 (35.3%)
Pre-ASCT PET status	
Negative	31 (43%)
Positive	41 (57%)
ASCT conditioning regimen	
BEAM	63
CBV	3
Other	9
Response after ASCT	
Complete remission	55 (73.3%)
Partial remission	15 (20%)
Stable disease	5 (6.7%)

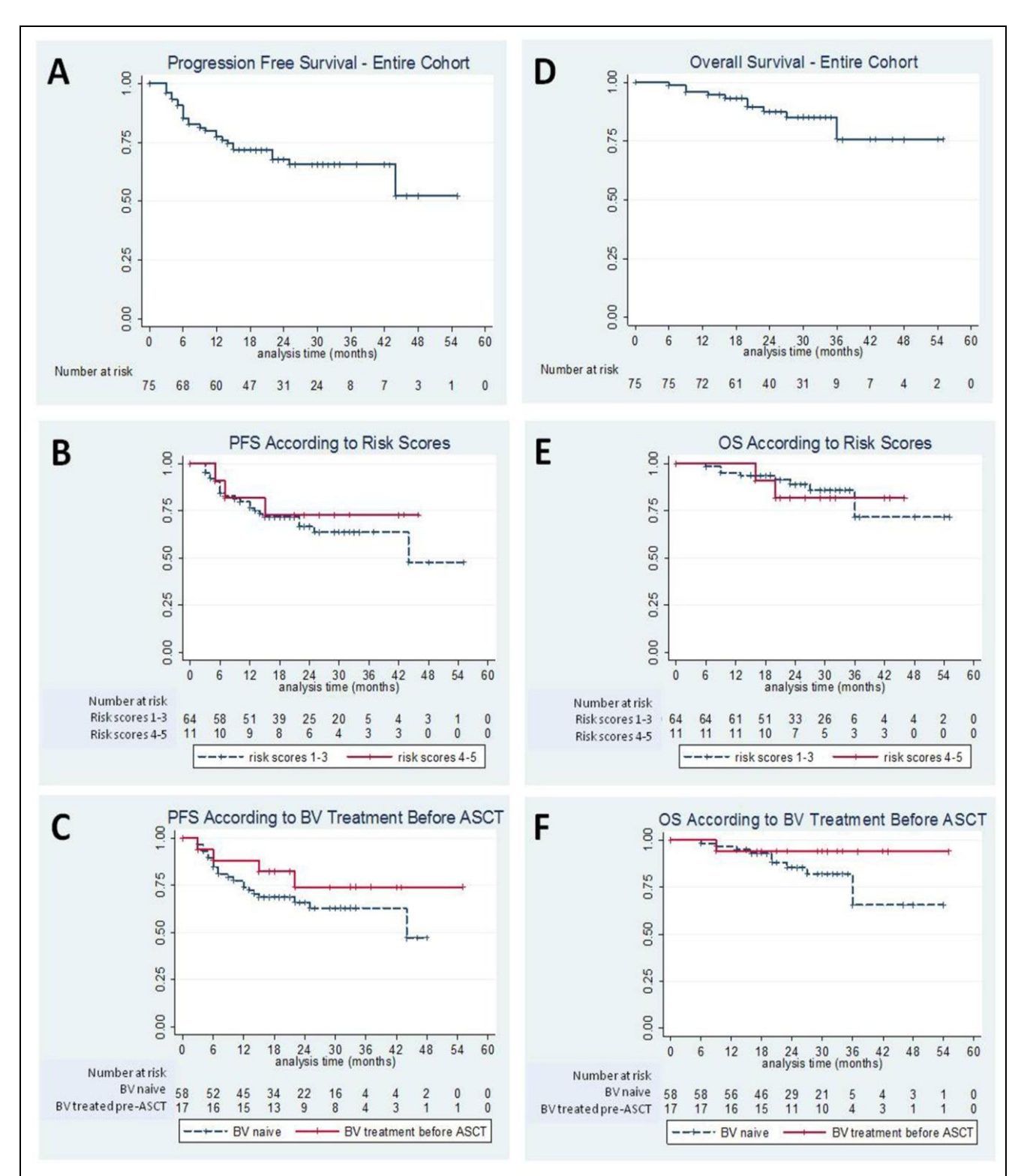
Response to treatment

At the time of analysis, 42 patients completed BV consolidation courses,. BV was discontinued in 33 patients. The reason for discontinuation of BV were PD (n=15), adverse events (n=12), patient's (n=3) and physician's (n=2) decision, and death due to sepsis (n=1). At the time of analysis, 50 patients had an ongoing response (CR in 41, PR in six, and SD in three). Twenty-five patients (14 in CR, nine in PR, and two with SD in post-ASCT evaluation) had PD (n=16 under- and n=9 following-consolidation). Among 17 patients who received BV before ASCT, thirteen continued their response under BV consolidation. Remaining four cases had PD at 3rd, 6th, 15th and 22nd months.

SURVIVAL - PFS

The 2-year PFS rate was 67.75% (95% CI: 0.55–0.75) (Figure 1A). Patients with 1–3 risk factors had similar PFS compared to patients with 4–5 risk factors (Figure 1B; p = 0.58).

There was no difference in 2-year PFS rates between BV naïve and BV pre-treated groups (66.04% [95% CI: 0.52-0.77] and 74.12% [95% CI: 0.44-0.90], respectively; p=0.32) (Figure 1C).



Safety

Fifty-eight adverse events (AEs) were reported in 36 of the 75 patients (48%). Sixteen patients (21.3%) experienced grade 3 or 4 toxicity. BV was discontinued due to AEs in 12 (16%) patients [neuropathy (n=9; grade 2 in one, grade 3 in seven, and grade 4 in one case), pulmonary toxicity (n=1), neutropenia and infection (n=2)] One patient who experienced grade 3 anaphylaxis could continue on BV consolidation following desensitization therapy (Table 2).

One patient died due to sepsis secondary to pneumonia while on BV consolidation; his primary physician reported that he had poor engraftment after ASCT and that the death was not associated with the agent..

Patients who required early cessation of BV consolidation

BV was discontinued in 17 patients. They received a median of eight cycles (range:3–15). Among patients who completed the consolidation (n=42), six cases experienced disease progression, whereas two of 17 patients whose consolidation had to be prematurely discontinued had progressive disease. The 2-year PFS rates were 87.62% (95% CI: 0.69–0.95) and 81.45% (95% CI 0.52–0.93) in the completed and discontinued groups, respectively (p=0.74). The OS rates for the completed and discontinued groups were 100% and 94.12% (95% CI: 0.65–0.99), respectively (p=0.46).

Discussion

Considering 2-years PFS was 67.75% (95% CI: 0.55–0.75) in our cohort, the present data support the efficacy of post-ASCT BV consolidation in HL patients at risk of relapse or progression. Compared to the results reported in the AETHERA trial, the numerically superior PFS in our study might be due to the inclusion of patients with the chemosensitive disease (primary refractory patients constituted 60% of the cohort in the AETHERA trial, 34.6% in our study), and the fewer patients with B symptoms (28% in the AETHERA trial, 21.3% in our cohort) and extranodal disease (33% in the AETHERA trial, 20% in our cohort). The relapse rate in our cohort was 33.33% at a median follow-up of 26 months, and was 20% within 12 months after initiation of BV consolidation. Given the relatively decreased 2-years relapse rate in our cohort, it is suggested that post-ASCT BV consolidation treatment might reduce early relapses or progressions, by deferring the first 1–2 years period associated with the highest risk of relapse or progressions after transplantation in HL. In the recently presented poster of the AMAHRELIS trial³, the 2-year PFS and OS were reported to be 75.3% (95% CI:0.68–0.84) and 96.4% (95% CI:0.91–1.0), respectively. The PFS rates were higher compared to our results. The best response after the salvage therapy was CR in 90% and PR in 7% of cases. The highly chemosensitive disease cohort might be the main cause of the improved PFS rates. In our cohort, 17 patients who received BV before ASCT were included. This subgroup also continued to experience survival benefit with BV consolidation after ASCT, similar to BV-naïve patients. A consensus panel of ASBMT, CIBMTR, and EBMT on maintenance therapies after ASCT has recommended BV in patients with prior limited BV exposure (≤ 4–6 cycles), who meet the AETHERA criteria, and who are not resistant to or intolerant of BV.⁴ Patients should be followed closely for adverse events, and dose modification or discontinuation of BV consolidation should be cautiously evaluated in case of severe polyneuropathy. In conclusion, BV consolidation after ASCT in patients with high-risk HL in a real-life setting seems to be a reasonable therapeutic option, especially given the increased possibility of cure and decreased subsequent application of highly toxic approaches.