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Long-Term Responders After Brentuximab Vedotin: Single-Center Experience on Relapsed and Refractory Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Brentuximab vedotin • Long-term response • Real life • Hodgkin lymphoma • Systemic anaplastic large cell lymphoma

ABSTRACT

Background. Brentuximab vedotin (BV) has shown high overall response rate in refractory/relapsed Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL) with reported long-term response duration in clinical trials, but few data are available regarding its role in long-term outcomes in real life.

Patients and Methods. A single-center observational study was conducted on patients treated with BV in daily clinical practice to evaluate the long-term effectiveness of BV in HL and sALCL patients and to check whether clinical trial results are confirmed in a real-life context.

Results. The best response rate in the treated 53 patients (43 HL and 10 sALCL) was 69.8% (with 46.5% complete response [CR]) in HL and 100% (80% CR) for sALCL, respectively. With a median patient follow-up of 36.8 months, the estimated median duration of response was 31.5 months for HL and 17.8 for sALCL, respectively. At the latest available follow-up, 75% of patients were still in response, with 43% without any consolidation. Toxicity was primarily neurological and it was rarely so serious to require dose reduction or interruption. In addition, it always reversed completely after the end of treatment.

Conclusion. Our data showed that 51% of patients treated with BV can be regarded as "long-term responders." Among these cases, for all patients who underwent stem cell transplantation immediately after BV, the procedure was consolidative. For patients who have remained in continuous CR without any consolidation after therapy, BV can induce prolonged disease control. ***The Oncologist*** 2016;21:1–6

Implications for Practice: Brentuximab vedotin (BV) has shown a high overall response rate in refractory/relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma, with reported long-term response duration in clinical trials, whereas few data are available regarding its role in long-term outcomes in real life. The data reported in this study suggest that BV can induce the same results in daily clinical practice. The data showed that 51% of patients treated with BV can be regarded as "long-term responders." Among these cases, BV can induce prolonged disease control in patients who have remained in continuous complete response without any consolidation after the drug.

INTRODUCTION

Nowadays, the standard treatment for patients with Hodgkin lymphoma (HL) who are unresponsive to upfront therapy or who relapse after primary treatment consists of salvage chemotherapy (aimed at harvesting autologous stem cells from peripheral blood) followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) [1, 2]. Approximately 40%–65% of patients with systemic anaplastic large cell lymphoma (sALCL) develop recurrent disease after front-line therapy [3]. At relapse, the disease is historically resistant to conventional multiagent chemotherapy regimens, and there is no established standard of care. High-dose therapy and ASCT may result in long-term remission in 30%–40% of patients, but the benefit is limited to patients with chemotherapy-sensitive disease [4–8].

Given that most patients with relapsed and refractory HL or sALCL are scheduled to undergo a highly toxic high-dose chemotherapy regimen, any strategy aimed at achieving a minimal disease status, and at specifically obtaining a positron emission tomography (PET)-negative status before ASCT without severe toxicity, would represent a major advance in the overall management of these patients. Furthermore, although ASCT has yielded a long-term progression-free

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survival (PFS) in 50%–60% of patients with chemosensitive relapse, the outcomes remain poor among those with primary chemorefractory disease, where long-term survival rarely exceeds 15%–17% [1]. In fact, disease recurrence still remains the principal cause of ASCT failure, and early disease progression after transplant (i.e., within 6 months from high-dose conditioning) emerges as the most important predictor of unfavorable outcome. No standard treatment options exist for patients showing disease relapse after ASCT or for patients not eligible for ASCT. In fact, although allogeneic stem cell transplantation may induce a long-term PFS in a fraction of patients, only a few are candidates for this procedure, mainly as a result of unsatisfactory pretransplant cytoreduction and substantial risk of morbidity due to the heavy load of previous therapies. Therefore, the optimization of the outcomes obtained with high-dose regimens and ASCT still remains a current strategic priority to offer the best likelihood of cure for the largest fraction of patients with refractory and relapsing disease.

Brentuximab vedotin (BV) antibody-drug conjugates (ADC) targeting CD30 may represent the optimal candidate among the newly developed agents for the treatment of HL and sALCL [9]. In fact, sALCL and the malignant Hodgkin's Reed-Sternberg cells of classical HL are both characterized by the expression of CD30. Several studies have shown the efficacy of BV in patients with HL and sALCL. In particular, in a pivotal phase 2 study in patients with relapsed or refractory HL after ASCT, 75% of patients achieved an objective response and 34% of patients achieved a complete response (CR) [10]. A second phase 2 study was performed among patients with sALCL and 50 patients (86%) achieved an objective response, 57% of whom had a complete remission [11]. This high response rate is important not only in pretreated patients showing a historically poor prognosis, but also in first-line relapsed or refractory patients because a complete remission before the transplant procedure is one of the strongest predictors for long-term survival [12–14]. BV can represent an optimal therapeutic option as a bridge to an autologous or allogenic transplant program in patients achieving a suboptimal response after salvage treatment [15–18]. Recent updates of the two pivotal studies have shown that BV can induce complete lasting remission, either without additional consolidation therapies, in both HL and sALCL pretreated cases suggesting that BV may be curative for some patients [19, 20].

After accelerated approval by US Food and Drug Administration, eligible patients in Italy were granted early access through a Named Patient Program (NPP). After the closure of NPP, since 2012, BV was available in Italy for patients with relapsed HL and sALCL, based on a local disposition of the Italian Drug Agency (AIFA) issued according to a national law (law no. 648/96: "Medicinal products that are provided free of charge on the national health service"): a boundary zone in the passage from clinical trials to marketing and free use phases where patients can be treated in any case. On the basis of the data available in literature, we reviewed our clinical database to evaluate the long-term effectiveness of BV in HL and sALCL patients and to check if clinical trial results are confirmed in a real-life context.

Patients and Methods

An observational retrospective study was conducted among patients with HL or sALCL treated with BV at our institute outside of clinical trials, based on a local disposition that AIFA issued according to a national law (law no. 648/96). The patient list was extracted from the electronic database of our institute. The study was approved by our institutional board and by our ethical committee and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Patients were consecutively enrolled to avoid selection bias, and all patients provided written informed consent to collect retrospectively their data. We obtained a special permission (for scientific purpose) from our ethical committee to collect data even for patients who were deceased or lost to follow-up.

Fifty-three patients were treated with BV in our institute: 43 with a diagnosis of HL and 10 with sALCL. All patients had histologically confirmed $CD30^+$ disease. All patients underwent pre-BV assessments including physical examination, routine hematology, and biochemistry testing, as well as PET/computed tomography (CT) imaging before therapy. Response to treatment was assessed every four cycles with PET/CT and at the end of treatment. Patients who discontinued treatment without disease progression and who did not receive further therapy were restaged per standard of care every 6 months for the first 3 years and annually thereafter. The determination of tumor response was based on the revised response criteria for malignant lymphoma and on the Lugano classification [21, 22]. In patients with bone-marrow involvement at baseline, a biopsy was carried out at the end of the whole treatment to confirm response.

Patients received a 30-minute infusion of BV at a dose of 1.8 mg/kg every 3 weeks for a maximum of 16 cycles. Dose reduction to 1.2 mg/kg was recommended in case of grade 3 toxicity. The treatment was interrupted in case of grade 4 toxicity. Safety and tolerability were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

The primary endpoint was the best response achieved anytime during BV therapy. Secondary endpoints were the overall response rate (ORR, sum of CR and partial response [PR] rates) at the end of treatment, duration of response, survival, and the incidence and severity of any adverse event occurring during BV therapy. Effectiveness was also evaluated through the occurrence of long-term responders (LTRs), defined as patients who have response (CR o PR) duration $\geq$ 12 months. "Primary refractory disease" is defined as no CR or relapse after 6 months of frontline therapy.

Overall survival (OS) was calculated from start of BV treatment to the date of death due to any cause and was censored at the last date the patient was known to be alive. Disease free survival (DFS) was calculated for CR patients from the start of treatment to the date of relapse or death due to lymphoma or acute toxicity of treatment. Response duration was calculated from the first objective tumor response (CR or PR) to first documentation of progression or death, whereas PFS was calculated from the start of treatment to relapse or death [21]. For these analyses, patients were censored at their last assessment that documented the absence of progressive

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disease if they were given another treatment before documentation of progression except for stem cell transplantation (SCT), autologous or allogeneic, as the first therapy after discontinuing BV (consolidative transplant). Further considerations were made between patients who achieved response and then either did or did not undergo consolidative SCT. Safety population included all patients who received at least one dose of BV.

No formal sample size estimation and power calculation were made for this observational retrospective study. We reported our single-center experience as explorative study to conduct subsequently a larger Italian national study on the use of BV in everyday clinical practice. All other time-to-event endpoints included in the study have been estimated with the Kaplan-Meier method. All analyses were performed using STATA (version 11.1; College Station, TX, USA, http://www.stata.com/).

Results

Patients

Patient demographics and characteristics at baseline (i.e., immediately before BV administration) are summarized in Table 1. Briefly, the 43 HL patients were 27 males (62.7%) and 16 females, with a median age at treatment of 33.4 years (range, 18.2–79.4 years). Four patients had >60 years at baseline. Median time from diagnosis to BV therapy was 25.9 months. There were 19 (44.2%) stage IV cases, with 6 bulky diseases and 4 (9.3%) bone-marrow involvements. Systemic symptoms were present in the 39.5% of cases. Thirty-two (74.4%) patients were refractory to most recent therapy, whereas 29 (67.4%) were refractory to the first line treatment. Median number of prior treatments was 3 (range, 2–7), comprising prior ASCT (60.5%) and prior radiotherapy (30.2%).

The 10 sALCL patients were 6 males (60%) and 4 females, with a median age at treatment of 52.6 years (range, 41.9–77.6 years). Four patients had >60 years at baseline. Nine patients were anaplastic lymphoma kinase negative (ALK-). Median time from diagnosis to BV therapy was 27.9 months. There were 6 (60%) stage IV cases, with 1 bulky disease and 2 (20%) bone-marrow involvements. Systemic symptoms were present in the 10% of cases. Four (40%) patients were refractory to most recent therapy, whereas 6 (60%) were refractory to the first line treatment. Median number of prior treatment was 3 (range, 2–10), comprising prior ASCT (40%) and prior radiotherapy (30%).

Response to Treatment

In the HL population, median times to the first objective response and to CR were 12.3 weeks (i.e., the time of the first response assessment after the cycle 4 infusion). Overall best responses to BV were 20 (46.5%) CRs, 10 (23.3%) PRs, 4 (9.3%) stable diseases (SDs), and 9 (20.9%) progressive diseases (PDs), leading to an ORR of 69.8%. The four older patients had no response (Table 2).

The ORR at the end of treatment to BV was 53.4% (44.2% CR, 9.3% PR). Eight patients with PRs after cycle 4 converted to CRs after an additional 4 infusions. Seventeen patients stopped therapy due to PD. The median number of cycles administered was 8 (range, 4–16).

Table 1. Patient demographics and characteristics at baseline

Characteristic	HL ($n = 43$)	sALCL ($n = 10$)
Median age, years (range)	33.4 (18.2–79.4)	52.6 (41.9–77.6)
Median time from diagnosis: BV, months (range)	25.9 (9.0–411.6)	27.9 (5.6–205.0)
Male, *n* (%)	27 (62.7)	6 (60.0)
Stage, *n* (%)		
I/II	18 (41.9)	1 (10.0)
III	6 (13.9)	3 (30.0)
IV	19 (44.2)	6 (60.0)
ECOG performance status, *n* (%)		
0	26 (60.5)	8 (80.0)
1	17 (39.5)	2 (20.0)
Bulky disease, *n* (%)	6 (13.9)	1 (10.0)
Extranodal sites, *n* (%)	8 (18.6)	6 (60.0)
Bone marrow involvement, *n* (%)	4 (9.3)	2 (20.0)
Systemic symptoms, *n* (%)	17 (39.5)	1 (10.0)
ALK, *n* (%)	—	9 (90.0)
Refractory to most recent therapy, *n* (%)	32 (74.4)	4 (40.0)
Refractory to first line therapy, *n* (%)	29 (67.4)	6 (60.0)
Median number of previous therapies (range)	3 (2–7)	3 (2–10)
Prior autologous stem cell transplant, *n* (%)	26 (60.5)	4 (40.0)
Prior radiotherapy, *n* (%)	13 (30.2)	3 (30.0)

Abbreviations: —, not applicable; ALK, anaplastic lymphoma kinase BV, brentuximab vedotin; ECOG, Eastern Cooperative Oncology Group; HL, Hodgkin lymphoma; sALCL, systemic anaplastic large cell lymphoma.

After discontinuing therapy with BV, 27 patients received subsequent treatments, which included both single-agent and multiagent regimens, standard and experimental agents, and consolidative SCT. Ten patients received a consolidative SCT (six received a consolidative auto-SCT and four received a consolidative allo-SCT).

Best ORR for sALCL was 100% (eight CRs and two PRs) and at the end of treatment was 90% (eight CRs and one PR): one PR converted to CR and one CR patient relapsed during BV therapy. All four older patients achieved CR. The median number of cycles administered was 9 (range, 4–16). After treatment discontinuation, one patient underwent CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), one patient received an experimental therapy, and three patients had consolidative SCT (one auto-SCT and two allo-SCT).

Safety

All patients received at least 4 doses of BV with a median of 8 cycles of BV (range, 4–16). In general, the treatment was well tolerated and the toxicity profile was very similar to the previously published data. Dose reduction (to 1.2 mg/kg) due to grade 3/4 toxicity was necessary in only 3 patients (all for peripheral neuropathy). Globally, the neurological toxicity was observed in

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Table 2. Pattern of response and survival in the whole sample ($N = 53$)

Feature	HL ($n = 43$)	sALCL ($n = 10$)
Best response		
CR, *n* (%)	20 (46.5)	8 (80.0)
PR, *n* (%)	10 (23.3)	2 (20.0)
SD, *n* (%)	4 (9.3)	—
PD, *n* (%)	9 (20.9)	—
ORR, %	30 (69.8)	10 (100)
Response at EOT		
CR, *n* (%)	19 (44.2)	8 (80.0)
PR, *n* (%)	4 (9.3)	1 (10.0)
SD, *n* (%)	2 (4.7)	—
PD, *n* (%)	18 (41.9)	1 (10.0)
ORR, %	23 (53.4)	9 (90.0)
Median duration of response (CR+PR), months (range)	31.5 (4.0-56.1)	17.8 (6.8-28.8)
Median duration of response (CR), months (range)	31.5 (4.0-56.1)	17.8 (6.8-28.8)
3-year OS, %	74.6	100
Median, months	NR	NR
3-year PFS, %	36.7	61.7
Median, months	10.2	NR
3-year DFS, %	74.6	58.3
Median, months	NR	NR
CCR, *n* (%)	15 (75.0)	6 (75.0)
With SCT consolidation	6 (39.0)	3 (37.5)
Without SCT consolidation	9 (45.0)	3 (37.5)
LTR, *n* (%)	19 (63.3)	8 (80.0)
Relapsed	2	1
With SCT consolidation	8	3 (50.0)
Without SCT consolidation	11	5 (30.0)
Median follow-up, months	36.8	26.4

Abbreviations: CCR, continuous complete response; CR, complete response; DFS, disease free survival; EOT, end of treatment; HL, Hodgkin lymphoma; LTR, long-term responder; NR, not reached; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant; SD, stable disease.

22 (41.5%) patients: peripheral sensory neuropathy grade 1/2 was documented in 17 patients and grade 3/4 was reported in 5 patients (in 2 of these patients, there was also a grade 4 peripheral motor neuropathy and treatment was interrupted). No significant hematological or infectious toxicities occurred. No treatment-related death or hospitalization was registered. No long-term toxicity occurred during the follow-up period.

Long-Term Outcomes

Patients have been followed for a median of 36.8 months (range, 2.5–63.8 months) from their first dose of BV. The estimated median duration of response for patients who achieved at least PR was 31.5 months for HL and 17.8 for sALCL, respectively. The same median duration of response for the CR patients, both HL and sALCL, occurred (Table 2).

In the HL subset, at the last follow-up, 15/20 (75%) patients were still in response, 6 with SCT consolidation and 9 without SCT consolidation, leading to a 3-year DFS of 74.6%. Three-year PFS was 36.7 and OS was 74.6%, with 9 deaths (7 due to lymphoma and 2 due to other causes).

We observed 19 LTRs (2 PRs and 17 CRs); 3 of them relapsed (before receiving any consolidation) and 16 (2 PRs and 14 CRs) are still in response. Among these 16, 8 CRs had no SCT consolidation, with a median duration of response of 38.6 months. They were 4 females and 4 males, with a baseline average age of 42 years (range, 22.5–58.1). No difference in patients characteristics was found between them and all the other treated patients, except for the median time from diagnosis and first BV infusion (18.4 months in LTRs vs. 30.5 months in the other cases) and the disease stage (LTRs were 75% stage II, whereas among other patients, we found only 37% of stage II cases).

In the sALCL subset, at the last follow-up, 6/8 (75%) patients are still in response, 3 with SCT consolidation and 3 without SCT consolidation, with a 3-year DFS of 58.3%. Three-year PFS was 61.7 and OS was 100%, because no patient died.

We observed eight LTRs (one PR and seven CRs); one of them relapsed (before receiving any consolidation) and seven (one PR and six CRs) are still in response. Among these seven, four (one PR and three CRs) had no SCT consolidation, with a median duration of response of 18.3 months. These 4 LTRs are 3 males aged >60 years at baseline and 1 female aged 54 years. No difference in any patients characteristic was found between them and all the other treated cases, except for median age at treatment.

Discussion

HL and sALCL patients with multiple relapses are mostly in a palliative situation, and novel drugs for this patient group are needed. Furthermore, novel less toxic but equally effective second-line salvage approaches are required as therapy-related late sequelae represent a relevant cause of morbidity and mortality in lymphoma survivors. In patients with an available donor, allogeneic SCT may also be considered and, thus, it is essential to find a drug inducing a minimal disease status. With numerous treatment options available, we advocate for a tailored therapeutic approach for relapsed patients guided by patient-specific characteristics including age, comorbidities, sites of disease, previous chemosensitivity, and goals of treatment (long-term disease control vs. consolidative SCT).

Excellent response rates in heavily pretreated patients were observed both in HL and sALCL with the ADC BV directed against CD30 [23]. Recent pivotal study updates indicated long-term responses for a subset of patients and favorable outcomes even among older adults [19, 20, 24, 25]. Since 2012, BV has been available in Italy for patients with relapsed HL and sALCL, based on a local disposition of AIFA issued according to a national law (law no. 648/96) and its use is becoming widespread.

We reviewed our database to evaluate our real-life experiences with BV, as the assessment of drugs during daily clinical practice may reveal evidence of additional side effects or change in efficacy. The best ORR in the treated 53 patients

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(43 HL and 10 sALCL) was 69.8% (with 46.5% CR) in HL and 100% (80% CR) for sALCL, respectively, in line with the 2 pivotal studies and previous reports on patients treated in NPP [10–12, 15, 17, 26]. Nine patients converted from PR, per the first assessment, to CR at the second restaging, and the median response duration is greater than 12 months for both diseases. A large retrospective study on the French BV NPP reported lower duration of response, but the median follow-up was shorter, and patients who had received BV after allogeneic SCT were enrolled [27].

We observed 8 older adult patients (≥60 years) treated with BV. The four HL patients did not respond, whereas the four sALCL patients achieved CR (three of them are in continuous complete response [CCR] after a median time of response duration of 18.3 months). These observations are contrasting, but the sample is too exiguous to draw conclusions, and further investigations are needed in the subset of older adults.

With regard to safety, we confirm the data set forthcoming in literature [13]. Toxicity was primarily neurological and rarely so serious as to require treatment reduction or interruption; furthermore, neurological toxicity always reversed completely after the end of treatment. No long-term toxicity was assessed during the follow-up period, even in patients later subjected to transplant consolidation.

Conclusion

With a median patient follow-up of approximately 3.5 years, this study confirms the safety and the high effectiveness of BV, which can be considered a very active treatment in patients with relapsed/refractory HL or sALCL. This treatment not only reaches a high ORR, but it is also well tolerated in heavily pretreated patients. The complete response induced by BV can represent a "bridge" to auto-SCT or allo-SCT. No patients showed any difficulty after BV treatment both with regard to mobilization and harvest autologous stem cells or increased toxicity during autologous or allogenic transplantation. Thus, in addition to its established activity in relapsed and refractory Hodgkin lymphoma and sALCL, BV displays a number of features favoring its use as a bridge to transplantation in patients with active disease who achieve a suboptimal response to salvage treatment. In fact, it induces clinical responses quite rapidly (i.e., within the first four cycles in most responders), thus permitting the timely application of the transplantation phase. Furthermore, BV displays a favorable toxicity profile, without overlapping toxicities, with most of the agents employed in high-dose conditioning regimens, and it has a documented ability to induce PET-negativity in patients with advanced disease. For all responder patients who underwent SCT, this procedure was found to be actually consolidative for response.

In addition, our data showed that 51% of patients can be regarded as "long-term responders," with 24/53 (45.3%) of them still in CR. Among these cases, BV can induce prolonged disease control in patients who have remained in CCR without any consolidation after drug. Although we do not have statistically significant prognostic factors to predict treatment response or its duration, our data appear to show a greater efficacy in the early stage and when BV treatment is carried out early in the progression of the disease. On the basis of these results, a large Italian national observational study was designed and is ongoing to evaluate further the effectiveness and the safety of BV in daily clinical practice and to identify prognostic factors and statistically significant differences in patients' characteristics, if any, between subgroups defined as per type and duration of response.

Author Contributions

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Disclosures

The authors indicated no financial relationships.

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