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Hematologic Malignancies

Brentuximab Vedotin in Transplant-Naïve Relapsed/Refractory Hodgkin Lymphoma: Experience in 30 Patients

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

Key Words. Hodgkin lymphoma • Brentuximab vedotin • Salvage treatment • Transplant • Positron emission tomography

Abstract

Background. Hodgkin lymphoma (HL) is characterized by the presence of CD30-positive Hodgkin Reed-Sternberg cells. Approximately 30%–40% of patients with advanced disease are refractory to frontline therapy or will relapse after first-line treatment. The standard management of these patients is salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplant (ASCT). The best prognostic factor is the status of disease before ASCT; in particular, the normalization of positron emission tomography (PET) scan. Brentuximab vedotin (BV) has shown a high overall response rate in refractory/relapsed HL after ASCT, whereas few data are available regarding its role before ASCT.

Patients and Methods. A multicenter, retrospective, observational study was conducted. The primary endpoint of the study was the effectiveness of BV as single agent in patients with relapsed/refractory, ASCT-naïve HL, determined by the conversion of PET status from positive to negative; secondary endpoints were safety, capacity to proceed to ASCT, survival, and progression-free status.

Results. Thirty patients with relapsed/refractory HL- and PET-positive disease after conventional chemotherapy salvage treatments were treated with a median of 4 cycles of BV. Normalization of PET findings (Deauville score $\leq$2) occurred in 9 of 30 patients (30%). Those nine patients proceeded to ASCT.

Conclusion. These data suggest that BV can normalize PET status in a subset of HL patients refractory to conventional chemotherapy salvage treatments, such as ifosfamide-containing regimens, cytarabine- and platinum-containing regimens, prior to ASCT.

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Implications for Practice: Administration of brentuximab vedotin has resulted in a high overall response rate in refractory/relapsed Hodgkin lymphoma after autologous stem cell transplant, whereas few data are available regarding its role before transplant. The data suggest that brentuximab vedotin can normalize positron emission tomography results in a subset of patients refractory to conventional salvage treatments prior to transplant. Experience indicates that patients previously regarded as not ideal candidates for transplantation may be able to undergo further cytoreductive therapy using brentuximab vedotin.

Introduction

Approximately 30%–40% of patients with advanced Hodgkin lymphoma (HL) disease are refractory to frontline therapy or will relapse after first-line treatment [1, 2]. The standard treatment for patients with HL who are unresponsive to frontline therapy or relapse after primary treatment consists of salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) [3–6]. Fifty percent of these patients achieve a long-term progression-free survival (PFS). However, the outcomes are poorer in those with primary chemorefractory disease, especially when associated with extranodal or bulky disease [7, 8]. In this setting, long-term overall survival approaches only 25%.

The goal of pretransplant therapy is to achieve a complete remission prior to transplantation. Failure to accomplish this is associated with a poor outcome [9–13]. Namely, the quality of response to salvage chemotherapy remains one of the strongest predictors for long-term survival in patients with relapsed/refractory HL undergoing ASCT. Several studies showed that chemoresistance or suboptimal response to pretransplant salvage chemotherapy

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represents the major adverse prognostic factors affecting PFS [5, 6, 9–13].

While clinical studies were unable to demonstrate any clear advantage among the commonly used pretransplant salvage regimens, a common finding in most series was that chemosensitivity and quality of remission status at transplant were critical [14].

The critical prognostic role of disease "size" and "activity" before transplantation in the ASCT setting has been highlighted by applying modern imaging techniques to the ASCT setting. Several studies have shown that findings on positron emission tomography (PET) imaging performed after salvage chemotherapy and before ASCT, are a critical predictor of outcome in patients with relapsed/refractory (R/R) HL [15–18]. On the basis of these data, it is reasonable to consider patients with a PET-positive scan at transplantation as an unfavorable group to receive further treatment to improve their outcome.

Given that PET-negative status is advisable before ASCT, brentuximab vedotin (BV) may represent an optimal therapeutic option as a bridge to ASCT in HL patients achieving a suboptimal response after salvage treatment [19]. It has a rapid activity (three or four courses), including efficacy in inducing PET negativity in relapsed/refractory HL with a mild toxicity profile [20–25]. In this regard, limited data exist on the use of BV as a salvage therapy prior to ASCT [26–28]. Herein, we report an Italian, multicenter, retrospective experience with BV in 30 ASCT-naïve patients with heavily pretreated R/R HL.

Patients and Methods

An observational, multicenter, retrospective study was conducted to analyze outcome and toxicity data of patients managed in a nontrial setting. The study was approved by our institutional board (Azienda Ospedaliera di Bologna, Policlinico S. Orsola-Malpighi, coordinating center) and by all involved ethical committees. All participants gave written informed consent in accordance with the Declaration of Helsinki. A shared database was used after the approval of all the authors and variables were strictly defined to avoid bias in reporting data.

From December 2011 to January 2014, a total of 7 Italian centers used BV in HL patients who failed the last salvage therapy and were ineligible for ASCT due to a persistence of the disease. All patients had histologically confirmed $CD30^+$ disease; all patients were relapsed/refractory to frontline therapy (a doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD] regimen) and were also refractory to the salvage therapy, such as ifosfamide-containing regimens, cytarabine- and platinum-containing regimens, or a bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen. All patients underwent pre-BV assessments including physical examination, routine hematology and biochemistry testing, as well as PET/CT imaging prior to therapy. They received BV following the conventional chemotherapy salvage treatment (ifosfamide-containing regimen, cytarabine- and platinum-containing regimen, or BEACOPP regimen) and underwent follow-up functional imaging with PET scan after four cycles. Patients received a 30-minute infusion of BV at the dosage of 1.8 mg/kg of body weight every 3 weeks.

The primary endpoint of this retrospective study was the conversion of PET scan findings to negative status; secondary endpoints were safety, capacity to proceed to ASCT, survival, and progression-free status. Deauville criteria were used to evaluate PET status: Scores of 1 and 2 were regarded as PET negative [29]. Further evaluations related to the therapeutic response were assessed according to the revised response criteria for malignant lymphoma [30]. Safety and tolerability were evaluated by recording incidence, severity, and type of any adverse event according to US National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 [31].

Results

Thirty patients with primary refractory or relapsed HL treated with BV prior to high-dose chemotherapy and ASCT were included in this retrospective analysis. The baseline characteristics are summarized in Table 1. The mean $\pm$ SD age at diagnosis was 30.9 $\pm$ 12.8 years, and the number of patients with stage III and IV disease at diagnosis was 17 (57%). Twenty-one patients (70%) had primary refractory disease and 9 (30%) patients had relapsed disease after a median of 10 months after the first-line therapeutic approach. All patients received ABVD as first-line therapy. The median number of regimens received prior to BV was 3 (range, 2–11) and, particularly, the first salvage therapy was an ifosfamide-containing regimen in 17 patients, cytarabine- and platinum-containing regimen in 9 patients, and the BEACOPP regimen in the remaining 4 patients.

All patients underwent stem cell collection following chemomobilization with the conventional chemotherapy salvage treatments. In terms of clinical response, HL in all patients was refractory to the conventional chemotherapy salvage treatments (all patients had PET-positive disease at the time that BV was initiated).

A median of 4 (range: 2–8) cycles of BV was administered at a standard dose of 1.8 mg/kg intravenously every 3 weeks over 30 minutes on an outpatient basis. Only 1 patient developed a documented grade 3 peripheral sensorial neuropathy that required BV dose reduction to 1.2 mg/kg from the third cycle; hematologic side effects of BV were represented by grade 1/2 neutropenia in 4 patients, and grade 1/2 anemia in 3 patients. Four patients achieved only one BV course because of lymphoma progression.

Considering all the patients in an intention-to-treat analysis, the overall response rate was 40% (12 of 30 patients). According to the PET evaluation after 4 cycles of BV, 9 (30%) obtained a complete response (CR) and 3 patients (10%) achieved a partial response (PR). All nine patients who converted to PET negativity proceeded directly to consolidative ASCT. The median time between last dose of BV and ASCT in this group was 48 days (range: 32–60 days). Of the 17 patients whose HL remained refractory after BV, 4 went on to receive additional salvage therapy, 5 proceeded directly to ASCT, and the remaining 8 patients received palliative treatment. In each of these four patients who received additional, post-BV salvage therapy, persistent PET-positive disease was present at the time of ASCT, except in one patient who obtained PR status with bendamustine.

Among the 9 patients who underwent ASCT after achieving CR status after BV, 8 (80%) were documented in continuous CR with a median follow-up after ASCT of 18 months; on the contrary, among 5 BV nonresponder patients who proceeded to ASCT, only 1 obtained a CR after the transplant.

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Table 1. Patients' demographics and disease characteristics ($n = 30$)

Characteristic	Data
Age, years, mean ± SD, median	30.9 ± 12.8, 27
Sex, male/female, *n*	13/17
Stage, *n* (%)	
II	13 (43.3)
III–IV	17 (56.7)
Primary refractory disease, *n* (%)	21 (70.0)
Regimens prior to BV, median no.	3 (range, 2–11)
First salvage treatment, *n*	
Ifosfamide-containing regimen	17
Cytarabine- and platinum-containing regimen	9
BEACOPP regimen	4
BV cycles, median no.	4 (range, 2–8)

Abbreviations: BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; BV, brentuximab vedotin.

Discussion

Chemosensitivity and remission status are critical for long-term outcomes of ASCT. In particular, compelling evidence indicates that the effectiveness of high-dose therapy in improving long-term survival of patients with R/R HL is mainly influenced by the presence of active disease before ASCT. When the first salvage treatment does not achieve a disease response, patients should be regarded as not ideal candidates to receive ASCT. These patients should be considered for further cytoreductive therapy using a third line of treatment before proceeding to ASCT. Ideally, this treatment should rely on the early use of biologically targeted agents, with a potentially higher capacity of achieving PET negativity and without significant overlapping toxicities with the previous therapies. Given that PET-negative status is advisable before ASCT, any novel treatment with low toxicity represents a major advance.

Our data suggest that BV can normalize PET results in a subset of refractory HL patients after conventional chemotherapy salvage treatments such as an ifosfamide-containing regimen, cytarabine- and platinum-containing regimen, or BEACOPP regimen, and prior to ASCT. BV may be considered potentially more effective as a second-line salvage treatment for those patients who did not obtain any response following such conventional chemotherapy salvage treatments. We obtained a 30% PET normalization rate (9 of 30 patients) in this group of HL patients with poor prognosis; these 9 PET-negative patients underwent ASCT and 8 of them are in continuous CR with a median follow-up of 18 months.

BV may represent an optimal therapeutic candidate and displays a number of features favoring its use as a bridge to ASCT in HL patients achieving a suboptimal response to salvage treatment [19, 32]. First, it has a toxicity profile that does not overlap with most agents used in conditioning regimens. Second, it has a documented ability to induce PET negativity in patients with refractory disease [20]. Third, it induces clinical responses quite rapidly (i.e., within the first three or four cycles in most responders), allowing a timely application of ASCT [10].

In this regard, a recently published phase II study evaluated the efficacy and safety of single-agent BV for 2 cycles prior to ASCT in 46 patients with R/R HL [26]. In this study, 27% of the patients attained PET normalization after BV alone and all but 1 proceeded to ASCT. In addition, Chen et al. reported a consecutive series of 36 patients with R/R HL who received BV as first salvage after an ABVD regimen; 13 of the 36 patients (36%) achieved PET normalization [33]. Finally, Onishi et al. tested BV in patients with R/R HL who were refractory to platinum-based salvage chemotherapy prior to ASCT [28]. They showed that treatment with BV converted 47% of platinum-refractory patients (7 of 15) to a PET-negative status.

Conclusion

It is very likely that in patients attaining suboptimal cytoreduction after conventional salvage chemotherapy, the use of BV may be a safer and efficient strategy to achieve good disease control before ASCT. On the basis of these data, when the first salvage conventional chemotherapy treatment does not achieve a disease response, patients should be regarded as not ideal candidates for ASCT. However, further cytoreductive therapy using another line of treatment may be an option before proceeding to transplant. This role could be played by BV, with a potentially higher capacity of achieving PET negativity and without significant overlapping toxicities with the previous chemotherapies.

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Disclosures

Antonello Pinto: Takeda (RF). The other authors indicated no financial relationships.

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