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Original

A targeted salvage therapy with Brentuximab vedotin in heavily treated refractory or relapsed pediatric Hodgkin lymphoma patients before and after stem cell transplantation

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Hodgkin's lymphoma (HL) is highly curable disease in its early stages, but in advanced stages, it presents a dilemma when it becomes refractory or relapses after several rounds of chemotherapy. Brentuximab vedotin (BV) is an antibody–drug conjugate that targets the tumor necrosis receptor family protein member CD30 positive malignancies via an anti-CD30 monoclonal antibody linked to monomethyl auristatin-E. In adult and pediatric studies, it has been shown to be an effective salvage therapy for primary refractory HL or relapse after autologous stem cell transplant (ASCT).

Between July 2012 and August 2017, we administered BV (1.8 mg/m^2 every three weeks; 12 cycles totally) with doxorubucin, vinblastin, dacarbazine (AVD), rituximab + ifosfamide + carboplatin + etoposide (RICE), or bendamustine combination treatment in pediatric HL patients, who were previosuly treated for refractory or relapsed advanced stage HL before (seven patients) or after (one patient) ASCT in our center. After eight BV courses, one patient was able to undergo match unrelated donor (MUD) SCT. Another seven pediatric HL patients, who were not able to go into remission with any other classical HL chemotherapy protocols, received 4–6 courses of BV-AVD and/or RICE/bendamustine. All were able to undergo ASCT after negative positron emission tomography (PET) imaging results. After ASCT, we switched to BV as consolidation therapy until a total of 12 cycles was completed. Patients went into remission after a median 34 (range: 12–42) months from the start of BV treatment. BV is an encouraging, well- tolerated, and effective targeted therapy especially when combined with AVD or when alternated with another targeted therapy combination, including RICE, when needed.

Key words: Hodgkin lymphoma, brentuximab vedotin.

Current treatment modalities can cure up to 95% of patients with the classical Hodgkin's lymphoma (HL); however, the treatment becomes a big dilemma when the HL is refractory, or relapsed disease has reached advanced stage of chemotherapy courses causing approximately 5%–10% of patients to require further treatment options. However, brentuximab (BV) is an anti-CD30 antibody conjugated via protease-cleavable linker to the

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potent anti-microtubule agent monomethyl auristatin-E (MMAE). Following binding to CD30, BV vedotin is rapidly internalized and transported to lysosomes where MMAE is released and binds to tubulin, leading to cell cycle arrest and apoptosis. BV has been approved for the treatment of relapse refractory disease or consolidation after autologous transplantation in HL.[1-4] Despite BV's efficacy, there is still a scarcity of studies that focus on Hodgkin's lymphoma (HL) in children. Typically, it has been observed in Phase I/II-level studies that BV may serve as a frontline agent for high-risk pediatric HL patients.[5] With reference to children with relapsed–refractory (RR)/HL, the primary goal is to enable autologous or allogeneic stem cell transplantation after achieving salvage chemotherapy induced remission with fewer side effects in these patients. In this study, we report the experience of using high-dose chemotherapy with autologous stem cell transplantation (ASCT), which remains the current standard of treatment for young patients with HL who are in the first relapse period or in those who are refractory to first-line treatment. We used BV in combination with doxorubucin, vinblastin, dacarbazine (AVD), bendamustine, or rituximab + ifosfamide + carboplatin + etoposide (RICE) in eight RR/HL pediatric patients. The use of BV provided a bridge until it was time for SCT.

Material and Methods

We retrospectively evaluated our BV experience in patients diagnosed with HL between 2012 and 2017. In our clinic, BV has been used for pediatric HL patients who underwent early relapse or were refractory to primary treatment or relapsed after ASCT since 2012. Early relapse was considered as occuring between three and 12 months after the end of therapy. AVD with bleomycin (AVBD) was used as standard therapy for initial treatment, whereas BV combined AVD , RICE, or bendamustine was used as second-line therapy after relapse in HL patients. However, our first experince with BV as a targeted treatment was in the first patient who relapsed after ASCT because BV was not available at that time for refractory or relapse disease in our country. Since the first patient's pathological study showed CD20 positivity, while the others had been CD20 negative, we were able to use antiCD20 treatment only in this patient. Thus, BV was used on eight pediatric patients who relapsed just after chemotherapy or ASCT or were refractory to the treatment and whose tumor tissues were CD30 positive. A 1.8 mg/kg dose of BV was administered at intervals of three weeks with an infusion period longer than 30 min before and after SCT for at least 12 cycles as consolidation therapy. For BV's safety and suitability, the National Cancer Institute (NCI) Common Toxicology Criteria were taken into consideration before each BV cycle (23). Common adverse effects of BV, such as nausea, vomiting, fatigue, myalgia, constipation, and / or itching were recorded, and side effects related to BV were recorded. Any adverse effects, which would limit the use of BV, such as chronic kidney failure, seizures, demyelinating neuropathy, or myelosuppression were evaluated prior to drug use. Patients' responses to chemotherapy before and after BV were determined by physical examinations, laboratory analyses, and radiologic imaging (ultrasonography, computed tomography, and positron emission tomography [PET]). Clinical, radiological, and nuclear medicine evaluation (PET) were obtained after every two cycles of chemoterapy. The primary refractory disease was assessed as relapse or failure to achieve complete remission during the first three months of first- line treatment. The study was reviewed and approved by an Ethics Committee (IRB:03-113-13). The authors report no conflicts of interest and any financial relationship.

Results

The median age of the eight participating patients' was 14 (6–18) years. The ratio of males to females was 7/1. Histopathological diagnoses of patients consisted of two findings: (1) mixed celluler (n=6) and (2) nodular sclerosis (n=2). Five patients were determined to have stage IVB, and three patients had stage IIIB. Three patients received chemotherapy in combination with BV for the primary refractory disease. Moreover, three patients with early relapse and two patients with relapsed HL after ASCT received chemotherapy in combination with BV. Except for the first patient, the

number of BV administrations was between 4 and 6 cycles in most of the patients before they underwent ASCT. After transplantation and in order to resume control of the disease, we continued BV up to 12 cycles. In this way, four of our patients went into remission after the second BV course. Moreover, three and one patient(s) went into remission after the fourth and eigth BV course, respectively. One patient, who received BV after his disease relapsed 12 months after ASCT (conditioning regimen containing total body irradiation [TBI] and melphalan), was the first pediatric patient who received BV in our center and country. He was in remission with negative PET result after six courses of BV-RICE (due to his CD20 positivity in tumor tissues) and two courses of BV-bendamustine. After eight BV courses, he was able to undergo match unrelated donor (MUD)-SCT. Donor leukocyte infusion (DLI) was administered to the patient who relapsed again 12 months after MUD. Following the DLI, he developed skin and gastrointestinal graft versus host disease (GIS- GVHD). Moreover, two more courses of BV in conjunction with bendamustine were administered to the patient after the DLI. PET-based involvement in one patient, who received two additional courses of BV and bendamustine in total after DLI, completely disappeared. We decreased the dosage from 1.8 to 1.2 mg/kg after 10 BV cycles and stopped BV on the 12th application because of neurotoxicity. The patient was still attending follow-ups with remission at the 36th month after BV treatment initiation. The second patient underwent ASCT because of refractory disease following the pre-emptive TBI and melphalan regimen. Moreover, BV treatment of eight cycles, which had been initiated before the transplant, was resumed during follow-up. This patient died from lymphoproliferative disease secondary to EBV in the 12th month after BV initiation. The third patient, who relapsed nine months after autologous transplantation, received BV and bendamustine in combination with the aim of remission before undergoing ASCT. However, remission obtained after six cycles caused the disease to relapse again, and the patient died from refractory disease. The other five RR/HL patients underwent ASCT following BV in combination with AVD. The patients were followed while in remission for 42, 40, 32, 32, and 24 months from BV treatment initiation, respectively (Table I). Fatigue was the most common side effect, and because of neurotoxicity, the BV dose had to be reduced in one patient.

Discussion

The cure rate of HL in pediatric patients is >95%, owing to recent advances in treatment options.[6] However, early relapse or treatment of primary refractory disease is still an important problem. With the associated risks of secondary cancer and cardiopulmonary toxicity, new modalities for minimizing toxicity in these patients are targeted similarly. Nuclear factor (NF)-kB and CD30 are also being identified as potential biomarkers in HL patients, suggesting that anti-CD30 could be used as a targeted treatment agent.[7,8]

In Locatelli's[5] study, BV was shown to be effective in pediatric patients with poor prognostic HL. BV has manageable toxicity and is associated with clinically meaningful responses in pediatric patients with relapsed or refractory HL. The use of BV enabled the investigators to provide a bridge to SCT for some patients.[9]

In this context, it has been shown that targeted treatment agents, such as CD30, are important for treating early relapsed or refractory HL cases before transplantation in order to achieve remission after the transplant. This shows that the use of valuable targeted treatment agents is important as a consolidation treatment for treatment of early relapsed or refractory cases of HL patients. In this group of patients, a salvage (rescue) and high-dose chemotherapy regimen followed by ASCT constitutes the standard treatment approach. Nevertheless, under these circumstances, 50% of patients experienced relapse and a certain decline in the quality of life during follow-up. The aim is to have a consolidation treatment that will prevent the relapse of the disease following ASCT.[10-14]

Two randomized trials showed a significant improvement in progression-free survival after ASCT, and several large studies have shown that this procedure can provide a cure in roughly 50% of the patients undergoing ASCT.

Table I. Summary of Patients Treated with Brentuximab.

Patient no	Age (Year)/ Sex	Histopathology	Stage	Disease condition after primary treatment	Relaps time	Pre-BV PET	Number of CT combined with BV before and after ASCT	Post-BV PET	HDT	Last Status
1	17/M	MC	IVB	Relapse after auto-SCT	First relapse 6 months later end of the initial CT Second relapse 12 months later auto-SCT	Positive	6 BV+RICE 2BV+B 4 BV	Negative	ASCT MEL+TBI MUD Allo	In remission on the 36th month of starting BV treatment
2	10/M	MC	IVB	Primary Refractory	On the 2th month of initial CT	Positive	4 BV+AVD 8 BV	Negative	ASCT MEL+TBI	Exitus on the 12th month of starting of BV treatment
3	18/M	NS	IVB	Relapse after auto-SCT	9 months later auto-SCT	Positive	6 BV+B 6 BV	Negative	ASCT BEAM	Exitus on the 39th month of starting of BV treatment
4	15/M	NS	IVB	Primary Refractory	On the 2th month of initial CT	Positive	4 BV+AVD 8 BV	Negative	ASCT BEAM	In remission on 42th month of starting BV treatment
5	6/M	MC	IIIB	Primary Refractory	On the 2th month of initial CT	Positive	4 BV+AVD 8 BV	Negative	ASCT BEAM	In remission on 40th month of starting BV treatment
6	16/F	MC	IIIB	Early relapse	8 months later en d of the initial CT	Positive	4 BV+AVD 8 BV	Negative	ASCT BEAM	In remission 32th month of starting BV treatment
7	7/M	MC	IIIB	Early relapse	6 months later end of the initial CT	Positive	4 BV+AVD 8 BV	Negative	ASCT BEAM	In remission 32th month of starting BV treatment
8	13/M	MC	IVB	Early relapse	9 months later end of the initial CT	Positive	6 BV+AVD 6 BV	Negative	ASCT BEAM	In remission 24th month of starting of BV treatment

CT: Chemotherapy, HDT: High dose chemotherapy before transplantation, MEL, melphalan,TBI: total body irradiation, MUD: Match unrelated donor, MC:mix cellular, NS: nodular sclerosis

Various treatment strategies for improving outcomes after ASCT have been investigated, including PET-adapted approaches, intensification of the conditioning regimen, radiation before and after transplantation, and consolidation therapy after transplantation.[5] Early consolidation with BV after ASCT-related improvements in progression free survival showed substantial efficacy in patients, including an objective response rate of 75% and complete remission rate of 34% in a pivotal phase 2 study of patients with CD30-positive HL in whom high-dose therapy and ASCT had been ineffective; longer-term follow-up showed a median overall survival of 40.5 months. As a targeted therapy with a low frequency of severe hematological toxic effects, use of BV might provide a unique opportunity to deliver pre-emptive therapy after ASCT.[9,12,15]

This study is quite promising as it reflects the first experience with BV in children with advanced stage RR/HL cases and positive results with respect to the use of BV, especially in early relapsed or refractory HL. In our study, six patients with early relapsed or primary refractory disease that have been treated with BV combined with AVD were able to go into remission. All of the six patients were able to undergo ASCT. The other two patients relapsed after ASCT. They were successfully treated with BV. After that successful treatment was accomplished, bridging BV therapy in one of them allowed him to undergo ASCT. He has survived so far, but unfortunately the second one died after the sixth BV cycle due to relapse/refractory disease. The outcome of the results of our single-center retrospective study demonstarted that BV is being considered as a safe agent in primary refractory and relapsed pediatric HL cases who are able to undergo ASCT. In the literature concerning adult cases, we have not encountered any adverse effects, such as chronic kidney failure, seizures, demyelinating neuropathy, and/or myelosuppression, that have been reported in association with BV and could limit BV's use.[16,17] Common adverse BV-associated effects are nausea, vomiting, fatigue, myalgia, constipation, and/or itching. However, the most common side effect observed in this study was fatigue. Neuropathy was associated with BV use were encountered in the first patient who underwent long-term chemotherapy and transplantation. Because of BV-induced neurotoxicity, we decreased the dosage from 1.8 to 1.2 mg/kg. Since neurotoxicity was progressing, we stopped the BV treatment at the followup. As there is limited data on its use in children, an administration plan has been proposed based on the adult literature (1.8 mg/kg at intervals of three weeks).[16,18] Recently, a study supporting our practice was published by Flerlage et al.[19] who reported that BV administration to children is safe at a dose of 1.8 mg/kg at intervals of three weeks. However, we still have to be careful about neurotoxicity, especially during repeated BV cycles. It was observed that PET involvement disappeared, and remission was clinically and radiologically achieved in five patients after the fourth course of BV, in two patients after the second BV course, and in one patient after the eigth BV course. As rapid remission is induced by BV, we believe that BV is an effective drug for relapsed and primary refractory patients.[16,17] It is also effective for controlling the disease before transplantation and maintaining disease-free control after transplantation. Other studies similarly report that good outcomes are obtained in controlling of disease with BV administration.[20-22] We adminsistered BV after transplantation for maintainance of therapy in all patients, and they are still in remission with the exception of two patients. We observed that it had a positive effect on the improvement of one of our patient's GVHD symptoms after alloSCT. In the literature, it has been reported that BV has a positive role in the elimination of alloreactive CD30 + donor T cells, thereby, contributing to the improvement of GVHD symptoms.[23] It is true that outcomes and experience from additional studies, which would reveal the positive and negative effects of BV and include many more pediatric patients, are needed. We still believe that our results will guide clinicians on BV's use since there are a lack of studies regarding BV's use in pediatric patients. In conclusion, BV is a safe salvage treatment agent with limited adverse effects for pediatric patients with refractory or relapsed advanced-stage HL before and after SCT.

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