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ORIGINAL ARTICLE

Successful reversal of severe liver function impairment with Brentuximab vedotin in multiply relapsed/refractory classical Hodgkin lymphoma

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Summary

Purpose: *To present our experience on the use of Brentuximab Vedotin (BV) in patients with relapsed/refractory classical Hodgkin Lymphoma (cHL) and severe liver function impairment with marked jaundice.*

Methods: *Two patients with relapsed/refractory cHL were evaluated. BV was administered in the presence of liver dysfunction and severe jaundice due to liver infiltration by cHL, as confirmed by PET-CT. Complete blood counts, biochemical profile, physical and imaging findings were reviewed to assess BV efficacy and tolerance.*

Results: *Case 1 had stage IVB, mixed cellularity cHL. Following ABVD chemotherapy, the patient experienced a relapse and responded to IGEV (ifosfamide, gemcitabine, vinorelbine, steroids) chemotherapy followed by autologous stem cell transplantation (ASCT). Thereafter, he experienced a second relapse with constitutional symptoms, severe jaundice and pancytopenia. Liver involvement was confirmed by PET-CT. Case 2 was admitted with a very late relapse of cHL. After a single cycle of gemcitabine-vinorelbine chemotherapy, which was not tolerated, the patient developed fever, anemia and jaundice, with laboratory findings indicating bone marrow and liver infiltration. The latter was confirmed by PET-CT. Both patients received BV monotherapy according to its formal indication at the reduced dose of 1.2 mg/kg due to severe liver impairment and experienced a rapid clinical and laboratory improvement. BV was well tolerated and offered a clinical benefit for approximately 4 months.*

Conclusions: *BV was safely administered to patients with relapsed/refractory cHL and severe liver function impairment with marked jaundice due to liver involvement, offering significant clinical improvement and reversal of liver abnormalities. BV may serve as a bridge to further salvage combination chemotherapy or a transplant procedure.*

Key words: *brentuximab vedotin, Hodgkin lymphoma, hyperbilirubinemia, liver function impairment*

Introduction

Although Hodgkin lymphoma (HL) is considered curable, with long-term relapse-free survival rates of 70-80% after first line conventional chemotherapy, a 20-30% of the patients relapse or have primary chemorefractory disease [1-3]; for most of these cases autologous stem cell transplantation (ASCT) is the standard of care. [4,5]. Brentuximab vedotin (BV) is an antibody-drug conjugate, directed against the surface of CD30, the hallmark of classical HL (cHL). BV is currently indicated for relapsed/refractory CD30+ HL in adults, either after ASCT failure or following ≥2 prior therapies when

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ASCT or multi-agent chemotherapy is not a treatment option; it is also indicated as consolidation for patients at high risk of relapse/progression after ASCT [6,7]. Recently, BV received FDA approval in combination with chemotherapy as first-line treatment of advanced cHL, while EMA approved BV in combination with doxorubicin, vinblastine and dacarbazine for the first-line treatment of stage IV cHL [7-9].

In the presence of impaired liver function the standard BV dose of 1.8 mg/kg should be reduced to 1.2 mg/kg and patients should be closely monitored for adverse events; however, there is virtually no accumulated experience in heavily jaundiced patients [10]. We present two cases with relapsed/refractory cHL, treated with BV in the presence of prohibitively high serum bilirubin levels due to liver involvement.

Methods

We retrospectively evaluated the data of two patients with relapsed/refractory cHL who were treated with BV in the presence of severe liver function impairment and marked jaundice. Conventional imaging and FDG PET-CT were used to confirm liver infiltration before treatment initiation. Complete blood counts, biochemical profile, physical and imaging assessments were applied before and during treatment and were reviewed to assess BV efficacy and tolerance. In addition to imaging and clinical examination, the course of serum bilirubin, hemoglobin, leukocyte and platelet counts and liver function tests were specifically used to assess safety of BV and efficacy in terms of disease control and clinical benefit.

Results

Case #1

A 39-year-old male presented on April 2013 with fever, a palpable right inguino-femoral mass and further infradiaphragmatic lymphadenopathy. Mixed cellularity cHL, stage IVB with bone marrow involvement was diagnosed. A total of 8 ABVD cycles were given following a negative interim PET/CT (PET-2) [11]. Conventional imaging and bone marrow biopsy demonstrated a complete remission (CR), but PET/CT still revealed low grade 18FDG uptake (SUVmax=3) in bilateral hilar and mediastinal lymph nodes. Lymphadenopathy progressed 7 months later and histologic examination confirmed cHL recurrence. The patient then responded to 3 cycles of IGEV consisting of ifosfamide, gemcitabine, vinorelbine and steroids and underwent ASCT. At that time BV for post-ASCT consolidation had not been established and approved. Three months after ASCT a PET/CT demonstrated abnormal 18FDG uptake (SUVmax=6) in multiple but sub-centimeter mediastinal and abdominal lymph nodes. Conventional imaging was still compatible with CR as previously reported [11]. In the absence of conventional radiographic progression and due to the difficulty of histologic confirmation of persistent disease, the patient was placed on close follow-up.

Four months later and seven months after ASCT, the patient developed fever and jaundice as well as anemia and thrombocytopenia. Although liver ultrasound and MRI, CTs and bone marrow biopsy were all within normal limits, PET/CT revealed 18FDG uptake (SUVmax=5.4) in multiple lymph nodes above and below the diaphragm, disseminated liver lesions (SUVmax=8) and multiple focal bone marrow lesions indicative of infiltration by HL. The patient rapidly developed marked hyperbilirubinemia (17.39 mg/dl) and severe blood count deterioration (hematocrit: 17.9%, WBC: 3.89 $\times 10^9$/L, platelets count: 11×10^9/L - Figure 1A and B). The patient's liver injury was classified as Child-Pugh B score (serum albumin 2.2 g/dl, INR 1.63, absence of ascites or encephalopathy), although this was disease and cytokine-related and there was no clinical suspicion of liver cirrhosis.

Due to the severe liver dysfunction only mechlorethamine or cis-platinum monotherapy were safe but predictably suboptimal options. BV was initiated according to its approved indications at that time (consolidation after ASCT and first-line therapy had not been approved yet) at a dose of 1.2mg/kg due to the extreme hyperbilirubinemia. Additionally, the patient received 40mg dexamethasone intravenously for 2 two-day courses. One week later, the bilirubin level was 4.41 mg/dl and platelet count 41×10^9/L. The patient developed grade 4 neutropenia and neutropenic fever requiring G-CSF and antibiotics. Three weeks later bilirubin level was 1.71 mg/dl. A second course of BV was administered at the full dose of 1.8mg/kg followed by a third cycle 3 weeks later, as bilirubin level and platelet count had completely normalized. The course of the laboratory findings during the entire treatment period is presented in Figure 1A and B and supplementary Table 1.

A new PET/CT following the 4th cycle of BV revealed high metabolic activity in multiple lymph nodes above and below the diaphragm and bone marrow foci. However, liver lesions had completely cleared and were not demonstrable by PET. BV was continued for one more cycle, while bilirubin and platelet levels were stable. Soon after the 5th cycle, the patient developed fever and night sweats, followed by anemia and thrombocytopenia. Due to obvious disease progression we

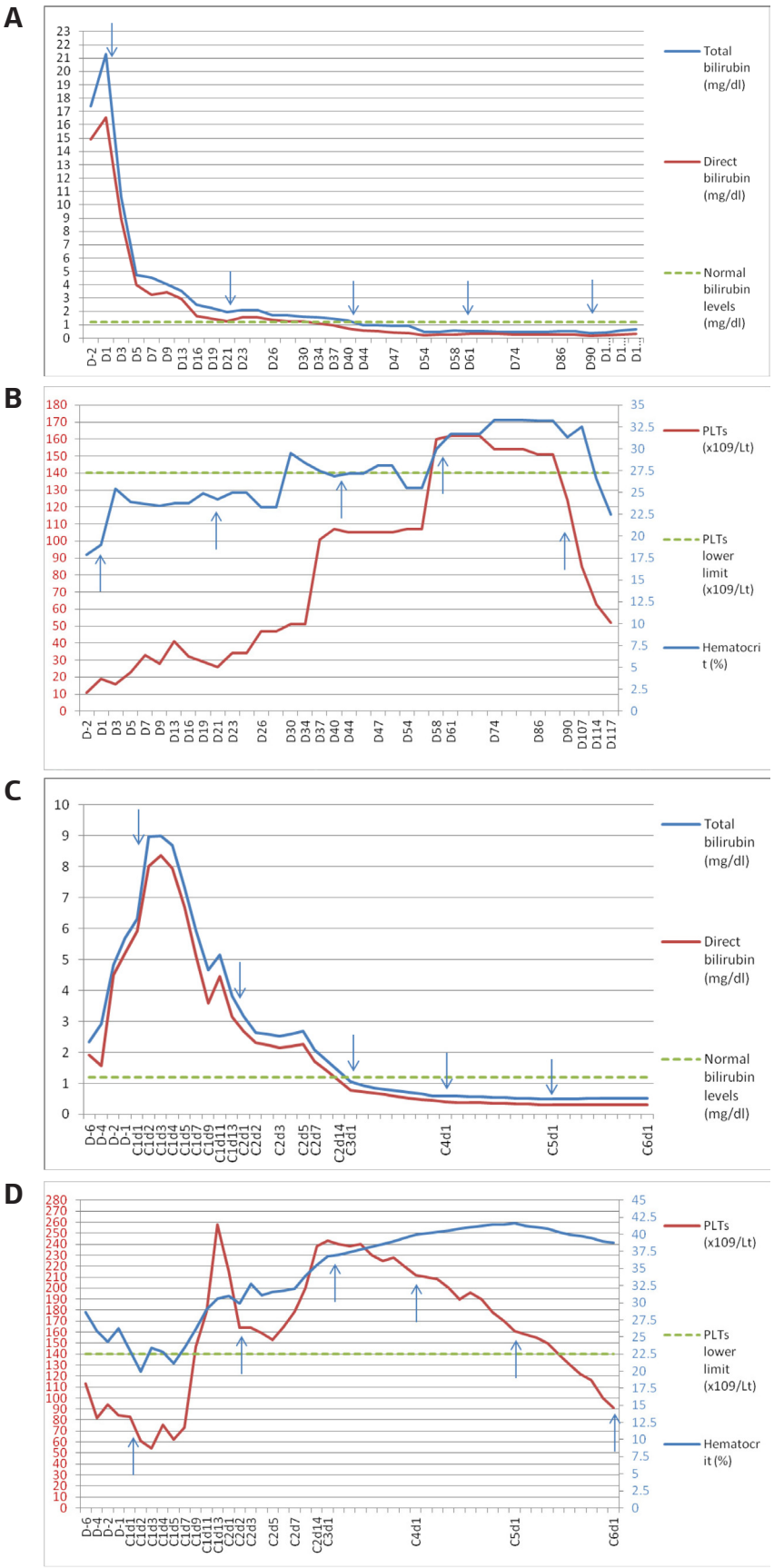

Figure 1. A: Course of total and direct bilirubin levels during BV treatment (case 1). **B:** Course of hematocrit (Hct) and platelet (Plt) levels during BV treatment (case 1). Hct level is lower than normal during treatment, but a marked increase can be seen as BV courses are given. We can also notice a significant decrease at the time of relapse. **C:** Course of total and direct bilirubin levels during BV treatment (case 2). **D:** Course of hematocrit (Hct) and platelet (Plts) levels during BV treatment (case 2). Blue arrows indicate dates of BV treatment

discontinued BV, but liver function tests remained normal (supplementary Table 1). PD-1 inhibitors were then considered.

Case #2

A 70-year-old male was admitted with relapsed cHL. In 1995 he had been diagnosed with clinical stage IIIA cHL with overlapping features between mixed cellularity and nodular sclerosis. He was treated with 1 cycle of MOPP/ABV hybrid followed by ABVDx5 due to a systemic allergic reaction to procarbazine, achieving CR.

At relapse, 20 years later, on June 2016, he had stage IVA mixed cellularity cHL, with disseminated lymphadenopathy, spleen and liver involvement. He received only 1 cycle of gemcitabine-vinorelbine due to a severe systemic allergic reaction and remained off-treatment for the next two months, experiencing an acute coronary event meanwhile. Two months later, the patient was admitted with prolonged fever and progressive anemia, thrombocytopenia and hyperbilirubinemia (maximum 8.99 mg/dl). PET/CT showed lymphadenopathy above and below the diaphragm (SUVmax=12.5), hypermetabolic lung, pleural, bone, spleen and liver (SUVmax=5.7) lesions; CT imaging was also positive. A bone marrow biopsy revealed limited infiltration by cHL. The patient was classified as Child-Pugh C score (serum albumin 2.23 g/dl, INR 1.55, absence of ascites, mild encephalopathy). This was again considered as disease- and cytokine-related and there was no clinical suspicion of liver cirrhosis.

At that point, the patient had severe liver impairment with jaundice (6.31 mg/dl) and deteriorating consciousness level. BV was commenced at 1.2 mg/kg. Bilirubin levels fell to 4.41 mg/dl and 3.17 mg/dl after 1 and 2 weeks respectively and a second cycle of 1.2 mg/kg BV was given. Two 4-day courses of 40mg dexamethasone i.v. were also concomitantly given. His clinical condition

Supplementary Table 1. Peripheral blood findings and liver function tests during BV treatment

	Hematocrit (%)	*WBC ($\times 10^9$/Lt)*	*PLTs ($\times 10^9$/Lt)*	*Total bilirubin (mg/dl)*	*Direct bilirubin (mg/dl)*	*Creatinine (mg/dl)*	*AST/ALT (U/L)*	*ALP/GGT (U/L)*	*CRP (mg/L)*
D-2	17.9	3.89	11	17.39	14.92	2.0	53/59	148/54	
C1d1	19.0	2.48	19	21.29	16.54	1.2	43/43	169/99	
C1d3	25.4	5.31	16	10.58	8.97	0.9	31/49	184/119	18.3
C1d5	23.9	5.38	23	4.74	4.01	0.7	45/99	181/226	7.87
C1d7	23.7	2.56	33	4.55	3.25	0.7	29/91		
C1d9	23.5	1.33	28	4.04	3.42	0.7	27/80	169/248	
C1d13	23.8	0.27	41	3.53	2.96	0.8	25/63	149/193	
C1d16	23.8	3.32	32	2.49	1.64	0.58	31/67	102/204	
C1d19	24.9	2.59	29	2.23	1.44	0.66	35/72	101/135	
C2d1	24.2	3.4	26	1.98	1.25	0.76	32/70	102/143	
C2d3	25	2.88	34	2.08	1.54	0.72	69/102	110/150	
C2d6	23.3	2.77	47	1.71	1.34	0.7	130/185	134/183	
C2d10	29.5	2.95	51	1.60	1.25	0.8	108/259	135/216	
C2d14	28.4	2.43	51	1.56	1.09	0.7	69/207	126/189	
C2d17	27.5	3.53	101	1.45	0.98	0.7	40/130	118/169	
C3d1	26.9	10.09	107	1.29	0.70	0.79	35/101	136/156	51.9
C3d5	27.2	4.96	105	0.96	0.57	0.7	40/79	115/116	
C3d8	28.1	5.41	105	0.92	0.41	0.6	57/104	111/120	9.8
C3d15	25.5	3.45	107	0.47	0.24	0.7	55/109	87/93	
C3d19	30	2.83	160	0.58	0.25	0.7	41/87	86/78	7.9
C4d1	31.7	6.58	162	0.50	0.30	0.7	40/76	108/84	
C4d14	33.3	3.59	154	0.48	0.26	0.6	39/96		40.4
C4d23	33.2	5.61	151	0.52	0.26	0.7			66.5
C5d1	31.3	5.84	124	0.35	0.18	0.76	20/37	113/76	
C5d18	32.5	1.28	85	0.41	0.21	0.8	11/16	98/45	99.6
C5d25	26.6	4.21	63	0.57	0.28	1.0	9/16	126/61	12.64
C5d28	22.5	4.37	52	0.67	0.31	0.86	9/14	139/76	

Bold typeface indicate the dates of BV infusion

Supplementary Table 2. Peripheral blood findings and liver function tests during BV treatment

	Hematocrit (%)	*WBC (×10⁹/Lt)*	*PLTs (×10⁹/Lt)*	*Total bilirubin (mg/dl)*	*Direct bilirubin (mg/dl)*	*Creatinine (mg/dl)*	*AST/ALT (U/L)*	*ALP/GGT (U/L)*	*CRP (mg/L)*
D-6	28.6	7.29	113	2.33	1.91	0.78	63/122		
D-4	25.9	6.26	82	2.91	1.56	1.00	93/130	649/280	196
D-2	24.3	6.39	94	4.83	4.49	0.91	128/234	964/347	
D-1	26.3	7.73	84	5.68	5.20	0.99	64/201	892/301	
C1d1	23.0	6.14	83	6.31	5.93	1.02	65/149	704/226	200
C1d2	20.0	4.35	61	8.96	8.01	1.18	175/224		
C1d3	23.4	5.88	54	8.99	8.36	0.85	110/205	658/217	
C1d4	22.8	7.35	76	8.68	7.95	0.68	106/192	743/307	104
C1d5	21.1	5.67	62	7.32	6.70	0.60	69/176	695/358	
C1d7	23.4	9.30	73	5.92	5.11	0.50	24/84	670/484	48.3
C1d9	26.2	9.00	147	4.66	3.60	0.37	50/66	807/679	
C1d11	29.0	9.14	179	5.16	4.46	0.45	49/61	707/582	68.8
C1d13	30.6	16.71	258	3.83	3.16	0.37	35/65	628/405	33.8
C2d1	31.0	12.10	215	3.17	2.69	0.38	32/63	593/497	
C2d2	29.9	9.26	164	2.63	2.32	0.37	31/59	536/543	8.91
C2d3	32.8	9.65	164	2.52	2.14	0.44	31/60		
C2d5	31.6	7.54	153	2.68	2.26	0.42	31/58	489/518	22.4
C2d7	32.1	7.53	179	2.07	1.71	0.46	20/45	447/388	15.6
C2d14	35.5	10.77	238	1.41	1.10	0.46	22/26	273/222	<3.17
C3d1	36.8	10.03	243	1.05	0.77	0.53	25/26	207/128	
C4d1	40.0	7.68	212	0.58		0.52	55/51	195/92	
C5d1	41.6	5.13	161	0.50		0.56	28/25	196/66	40.8
C6d1	38.8	9.03	91	0.53		0.49	30/29	181/83	

Bold typeface indicate the dates of BV infusion

and laboratory findings gradually improved and he was discharged with a bilirubin level of 2 mg/dl, hemoglobin 10.9 g/dl and normal platelet count (Figure 1C and D and supplementary Table 2).

Clinical status and laboratory findings improved; the patient underwent 4 further full dose cycles of BV (1.8mg/kg) without steroids. Just before the 7th BV cycle, he was admitted with dyspnea and fever. Abdominal and thoracic CT scans demonstrated stable liver lesions, bilateral pleural effusion and features compatible with interstitial lung disease. BV treatment was discontinued and the patient was transferred to the Lung Disease Department of another hospital, where he succumbed to septic shock, based on information obtained during oral communication with the treating physicians.

Discussion

Both patients reported here had advanced-stage cHL and had been treated with conventional chemotherapy regimens used in HL. After relapse, salvage chemotherapy was followed by high-dose therapy and ASCT in the first patient, while the second patient was older and too fragile for an ASCT, as well as intolerant to salvage chemotherapy. Subsequently, both developed progressive disease with severe jaundice, anemia and thrombocytopenia. PET/CT confirmed liver involvement in both cases and the prognosis was indeed poor [12]. Since well-established chemotherapy regimens had already been used and severe jaundice did not permit further treatment with combination chemotherapy regimens, we decided to treat both of them with BV monotherapy.

After ASCT failure in cHL, response rates vary but can be up to 75% with a median progression-free and overall survival of 9.3 and 40.5 months respectively [13,14]. These results have been obtained in real-life settings as well and BV may indeed prolong survival in cHL patients failing ASCT [7,15-18]. In both these patients serum bilirubin levels were extremely high, and, because of this, BV was initially administered at the decreased dose of 1.2 mg/kg (maximum 120 mg/dose), as recommended by the manufacturer for hepatic impairment. After the first dose -in combination with a short-term i.v. dexamethasone course- serum bilirubin levels

dropped dramatically and platelet counts increased. However, in patient #1, this was followed by severe neutropenia and fever, which could have been a bystander effect of BV due to the extensive bone marrow involvement [4,13,16,17]. Once bilirubin levels normalized, BV was given at the conventional dose of 1.8 mg/kg for all subsequent cycles. Hematocrit and platelet levels normalized after the second cycle and bilirubin remained normal. Despite dramatic clinical improvement, the clinical benefit was transient lasting for no more than 5 to 6 BV cycles (~4 months). However, despite the development of progressive disease, bilirubin remained normal and PET/CT demonstrated complete remission of liver disease in patient #1. The second patient was stabilized and remained in a good clinical condition after 6 cycles. Serum bilirubin remained normal throughout BV treatment, but unfortunately, he succumbed to an infectious complication.

In the cases described here, BV provided an effective reversal of liver function impairment and a progression-free survival of approximately 4 months in clinical situations where combination chemotherapy was not an option. Its use in the presence of severe jaundice could be considered successful and the drug was very well tolerated. To our knowledge, there is one published case describing BV use in a jaundiced patient with relapsed/refractory HL; bilirubin levels were lower at the time of relapse and the response was much shorter because of fatal septic shock [18]. Recently, the successful use of BV in jaundiced patients was confirmed in a series of 5 previously untreated patients with HL and liver impairment. BV was given as first-line treatment in order to normalize their liver function and permit further treatment with ABVD [19]. In addition, Zhao et al published a phase 1 open label evaluation of pharmacokinetics of BV in patients with CD30+ hematological malignancies and liver or renal impairment. Seven patients with liver impairment were enrolled, 1 with a Child-Pugh A score, 5 with a Child-Pugh B score and 1 with a Child-Pugh C score. Five out of 7 patients died after 1 cycle of BV while the two remaining patients continued treatment. Lymphoma was noted to contribute to liver dysfunction in 5 of these patients. Most of the patients died had an ECOG 3 status and substantial comorbidities [20]. Although the duration of clinical benefit was rather limited, our experience was clearly more favorable than the above named reports.

Our findings suggest that BV can be safely used in severely jaundiced patients with multiply relapsed/refractory cHL in an attempt to improve severely compromised liver function and bridge cytotoxic salvage combination chemotherapy or even further transplant procedures that are precluded due to liver impairment.

Conflict of interests

The authors declare no conflict of interests.

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