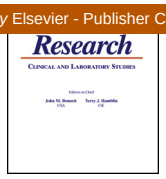
Leukemia Research 44 (2016) 25–31

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres



Treatment of CD30-positive systemic mastocytosis with brentuximab vedotin☆

Uma Borate[a,*], Amitkumar Mehta[b], Vishnu Reddy[c], Michaela Tsai[d], Neil Josephson[e], Ian Schnadig[f]

[a] Oregon Health & Science University, Mail Code L586, Division of Hematology and Medical Oncology, 3181 SW Sam Jackson Park Road, Portland, OR 97239 USA
[b] University of Alabama at Birmingham, Department of Medicine, Division of Hematology and Oncology, 1720 2nd Avenue South, NP2540, Birmingham, AL 35294, USA
[c] University of Alabama at Birmingham, Department of Pathology, Division of Laboratory Medicine, 619 19th Street South, WP, P230A, Birmingham, AL 35249, USA
[d] Minneapolis Clinic, 910 E 26th Street, Suite 200, Minneapolis, MN 55404, USA
[e] Seattle Genetics, Inc., 21823 30th Drive SE, Bothell, WA 98021, USA
[f] Compass Oncology, US Oncology Research 19260 SW 65th Avenue, Suite 435, Tualatin, OR 97062, USA

ARTICLE INFO

Article history:
Received 21 October 2015
Received in revised form 25 January 2016
Accepted 25 February 2016
Available online 27 February 2016

Keywords:
Mast cells
Immunoconjugates
Monomethyl auristatin E
Clinical trial
Hematologic neoplasms
Brentuximab vedotin

ABSTRACT

Systemic mastocytosis is a myeloproliferative neoplasm with varying presentation that is caused by infiltration of neoplastic mast cells into extracutaneous tissues. Cytoreductive therapy is used to control organ dysfunction in aggressive systemic mastocytosis and is sometimes needed for control of severe refractory symptoms in patients with indolent disease. However, current standard cytoreductive agents are limited by their suboptimal degree and duration of response and associated significant toxicities, highlighting the need for novel treatments for systemic mastocytosis. Recent studies have identified CD30 as a therapeutic target in systemic mastocytosis, as CD30 is expressed on a majority of neoplastic mast cells. In this case series, the clinical outcomes of 4 patients with aggressive or indolent systemic mastocytosis treated with the anti-CD30 antibody-drug conjugate brentuximab vedotin are reported. Two patients showed evidence of a response to treatment with a reduction in disease burden, 1 of which has demonstrated a durable response with ongoing benefit for more than 3 years. Treatment with brentuximab vedotin was well-tolerated with side effects that were effectively managed by dose modifications. The results presented suggest that brentuximab vedotin is active in systemic mastocytosis and can induce durable responses with a manageable toxicity profile.

1. Introduction

Systemic mastocytosis (SM) is a myeloproliferative neoplasm caused by clonally proliferating mast cells that infiltrate into extracutaneous tissues. The bone marrow (BM) is almost always involved, though the spleen, liver, skeletal system, lymph nodes, and gastrointestinal tract are also commonly affected [1]. Patients with aggressive systemic mastocytosis (ASM) exhibit organ dysfunction due to mast cell involvement and have a significantly reduced median survival (approximately 41 months) when compared with age-matched controls and patients with indolent SM (approximately 198 months) [2–4]. In ASM, cytoreductive therapy is used to control symptoms and complications of mast cell infiltration [2,3,5]. Patients with indolent SM do not show end organ damage but are frequently affected by symptoms due to mast cell mediator release. Approaches to management include avoidance of symptom triggers and the use of antimediator drugs such as H1 and H2 histamine receptor antagonists, antileukotriene agents, and cromolyn sodium. However, in some individuals with indolent SM, severe symptoms cannot be adequately controlled by this approach and cytoreductive therapy is required [6].

Abbreviations: 2-CdA, 2-chlorodeoxyadenosine; ADC, antibody-drug conjugate; ALCL, anaplastic large cell lymphoma; ANC, absolute neutrophil count; ASM, aggressive systemic mastocytosis; BM, bone marrow; CT, computed tomography; ECNM, European Competence Network on Mastocytosis; G-CSF, granulocyte colony stimulating factor; Hct, hematocrit; Hgb, hemoglobin; HL, Hodgkin's lymphoma; IFN-α, interferon-α; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; MMAE, monomethyl auristatin E; ORR, objective response rate; PCR, polymerase chain reaction; PLT, platelet count; Q1W, weekly for 3 weeks of a 4 week cycle; Q3W, every 3 weeks; Q6W, every 6 weeks; SM, systemic mastocytosis; TWC, total white count.

☆ Clinical Trial Registration Number: NCT01461538.

* Corresponding author. Tel.: +1 503 418 2294; fax: +1 503 494 3257.
E-mail address: borate@ohsu.edu (U. Borate).

http://dx.doi.org/10.1016/j.leukres.2016.02.010
0145-2126/

Interferon-alpha (IFN-α) and 2-chlorodeoxyadenosine (2-CdA) are the most commonly used cytoreductive treatments for SM [5,7]. In multiple small case series, overall response rates of approximately 50% have been reported with each of these agents, though durable remissions are uncommon [7–16]. Cytoreductive therapy is also associated with frequent side effects. For IFN-α these include constitutional symptoms, depression, and thrombocytopenia, while the most significant side effects of 2-CdA treatment are frequent marrow suppression and CD4 depletion [8,17]. Although the vast majority of SM cases are associated with the *KIT*D816 V mutation, for the few patients without this mutation imatinib mesylate can be an effective therapy [1,18].

The recent detection of CD30 expression on a majority of neoplastic mast cells has identified a new potential therapeutic target in SM [19–21]. Brentuximab vedotin (ADCETRIS®) is an anti-CD30 antibody-drug conjugate (ADC) consisting of the chimeric IgG_1 antibody cAC10, specific to human CD30, covalently attached to the microtubule-disrupting agent monomethyl auristatin E (MMAE) by a protease-cleavable linker. The anticancer activity of brentuximab vedotin is due to the binding of the ADC to CD30-expressing cells, followed by internalization of the ADC-CD30 complex, and the release of MMAE via proteolytic cleavage within the cell. Binding of MMAE to tubulin disrupts the microtubule network within the cell, inducing cell cycle arrest and apoptotic death of the cell [22].

Two pivotal phase 2 studies have demonstrated the efficacy and safety of brentuximab vedotin administered every 3 weeks (Q3W) as a single agent for treating relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL), malignancies known to express high levels of CD30. The objective response rate (ORR) for HL patients was 75%, with approximately one-third of patients achieving a complete remission [23]. ALCL patients had an ORR of 86%, with over 50% of patients achieving a complete remission [24]. In both studies, brentuximab vedotin was generally well-tolerated with manageable side effects.

In this case series, 4 patients with CD30-positive systemic mastocytosis were identified and treated with brentuximab vedotin. Two of the 4 patients showed evidence of a response to treatment with a reduction of disease burden. The clinical outcomes of these 4 patients are described here.

2. Methods

A phase 2, open-label study with a primary objective of evaluating the antitumor activity of brentuximab vedotin in patients with CD30-positive nonlymphomatous malignancies (NCT01461538) was sponsored by Seattle Genetics, Inc. (see Supplemental information). Patients with CD30-positive nonlymphomatous malignancies who failed, refused, or were deemed ineligible for standard therapy were identified through a companion screening protocol that employed immunohistochemical staining of tissue biopsy samples with an anti-BerH2 antibody or flow cytometric analysis of BM samples with an anti-BerH8 antibody. Three dosing regimens of brentuximab vedotin were evaluated in this study. Enrolled patients with all eligible pathologies received a starting dose of either 1.8 mg/kg Q3W or, following an amendment to the protocol to increase the starting dose level, 2.4 mg/kg brentuximab vedotin Q3W. An additional amendment then allowed for enrollment of some patients with acute leukemia or myelodysplastic syndrome to be treated with a starting dose of 1.2 mg/kg brentuximab vedotin on Days 1, 8, and 15 of each 4-week cycle (Q1W).

Monitoring for unacceptable toxicities was conducted and safety data were reviewed; dose modifications were dependent upon the type and severity of the toxicity. If unacceptable toxicities were observed, patients initially treated at a dose of 2.4 mg/kg Q3W could have their dose decreased to 1.8 mg/kg Q3W and patients initially treated at a dose of 1.8 mg/kg could have their dose decreased to 1.2 mg/kg Q3W. Dose delays of up to 3 weeks were also permitted for patients who received 1.8 mg/kg or 2.4 mg/kg brentuximab vedotin Q3W. For patients treated with 1.2 mg/kg brentuximab vedotin on Days 1, 8, and 15 of each cycle who experienced unacceptable toxicity, dosing could be delayed for up to 2 weeks and/or could be decreased to 1.0 mg/kg Q1W.

A total of 83 patients with CD30-positive disease, including 4 patients with CD30-positive SM, were treated during this study. All enrolled patients were identified as CD30-positive on a companion screening study. In the screening study, BM specimens from 8 patients with mast cell disease (6 with SM, 1 with mast cell leukemia, and 1 with chronic mast cell leukemia) were evaluated by flow cytometry and/or immunohistochemistry; 7 patients were shown to have CD30-positive disease. Systemic mastocytosis patients were enrolled into the brentuximab vedotin 1.8 mg/kg and 2.4 mg/kg Q3W dosing cohorts, though one patient (case 4) received a starting dose of 1.2 mg/kg Q3W due to renal insufficiency at baseline. Brentuximab vedotin was administered to SM patients via intravenous infusion over a period of 30 min on Day 1 of each 21-day cycle. Response assessments in SM patients were performed at Cycles 2 and 4, and every 4 cycles thereafter while patients were receiving treatment, and included a complete blood count with differential and a BM biopsy. The overall mast cell burden and CD30-positive mast cell burden were evaluated by immunohistochemical staining of the BM biopsy samples. Adverse events were recorded from Day 1 pre-dose through the end of study visit, or 30 days after the last study treatment, whichever was later. Patients with clinical benefit or better were eligible to continue treatment with brentuximab vedotin until disease progression, unacceptable toxicity, or study closure.

The screening and treatment studies were conducted at investigational sites following approval by an Investigational Review Board in accordance with the Declaration of Helsinki. All patients provided informed consent prior to administration of any study treatment.

3. Results

Of the 83 patients overall that were enrolled and treated in this study, 55 patients (66%) completed the study per protocol whereas 28 patients (34%) discontinued the study early. Reasons for study discontinuation included death (28%), study termination by the sponsor (4%), and patient withdrawal of consent (2%).

This study was designed to evaluate patients with a broad range of nonlymphomatous lesions. Therefore, the clinical data collected were not coordinated with standard SM response criteria. As such, chart reviews for the 4 patients with SM presented here were performed by the investigators in order to collect relevant clinical data that were not recorded in the original study database.

The first consensus response criteria for SM were published by Valent et al. in 2007 [25] and were based upon previously proposed SM response criteria [26], with minor modifications, to assess the efficacy of various treatments [7,27]. During the course of the present study, updated consensus response criteria for ASM were published by a joint committee of experts from the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and the European Competence Network on Mastocytosis (ECNM) [3,28]. The case reports presented herein give consideration to the established response criteria at the time of study onset and the more recently developed response criteria.

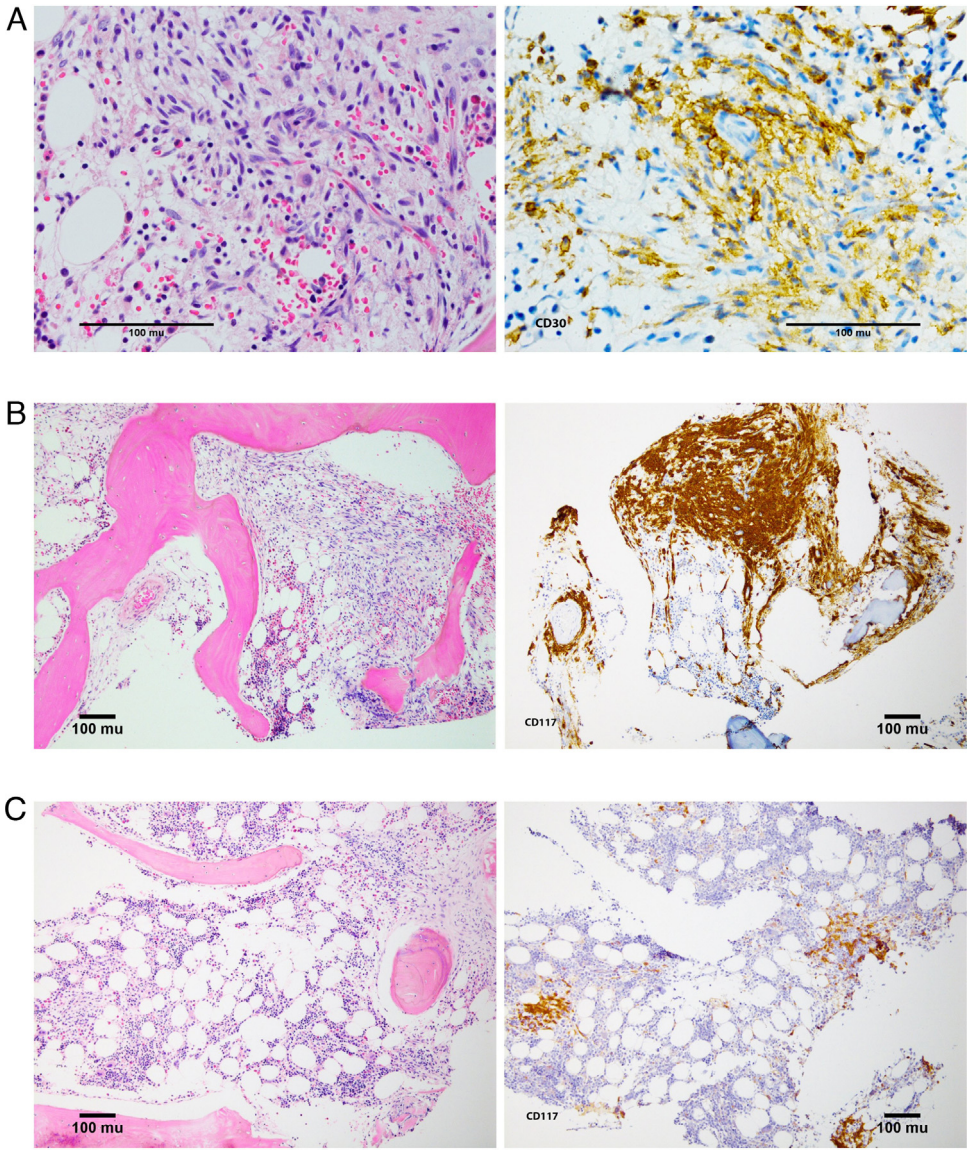


Fig. 1. Pre- and post-treatment bone marrow biopsy results in a patient with aggressive systemic mastocytosis. (A) Pre-treatment bone marrow biopsy (40× in both panels) from the patient in case 1 showing extensive infiltration of spindle mast cells with interspersed small areas of normal hematopoietic elements (hematoxylin and eosin stains [H&E], left panel). The majority of mast cells showed variable CD30 expression by immunohistochemistry (right panel). (B) Pre-treatment bone marrow biopsy (10× in both panels) from the patient in case 1 reveals mostly mast cell infiltrates with small pockets of normal marrow (H&E, left panel). CD117 staining of the biopsy shows strong expression in spindle mast cells (right panel). (C) Post-treatment biopsy (10× in both panels) after 8 cycles of brentuximab vedotin treatment in the patient in case 1 shows reduction of mast cell mass and return of normal marrow elements (H&E, left panel). CD117 staining of the same biopsy demonstrates a considerably decreased number of scattered focal areas of mast cells when compared with the pre-treatment biopsy (right panel).

3.1. Case 1

A 62-year-old male with a past medical history of diabetes mellitus, rheumatoid arthritis, and coronary artery disease developed sudden vision loss, secondary to a pseudomonas corneal infection. At initial diagnosis, the patient was found to have new onset pancytopenia with an absolute neutrophil count (ANC) of 0. His total white count (TWC) was 1.0×10^9/L, hemoglobin (Hgb) 109 g/L, hematocrit (Hct) 0.31, and platelet count (PLT) 192×10^9/L. His serum tryptase level was elevated at 276 ng/mL (normal 2–10 ng/mL). A BM biopsy revealed variable cellularity with several fibrotic areas containing spindle cells, which stained intensely positive for CD30 and tryptase. Overall, 35% of BM cells were neoplastic mast cells with 70% of the mast cells demonstrating CD30 expression (Fig. 1A). Reticulin staining demonstrated 1+ BM fibrosis and the BM was positive for the *KIT*D816 V mutation by polymerase chain reaction (PCR). Based on these findings, the patient was diagnosed with ASM. He received 2 cycles of 2-CdA 4 weeks apart with a minimal response and was hospitalized for symptomatic anemia requiring transfusion of packed red blood cells.

A baseline BM biopsy at study enrollment demonstrated a mast cell burden that had increased to 50% of BM cells (Fig. 1B). His neutropenia responded to treatment with pegylated granulocyte colony stimulating factor (G-CSF) (Fig. 2).

After 4 doses of brentuximab vedotin at 1.8 mg/kg Q3W, the patient developed Grade 2 peripheral neuropathy and dosing was delayed for 5 weeks until his symptoms improved to Grade 1. At that time he was restarted on a reduced dose of brentuximab vedotin (1.2 mg/kg Q3W). A BM biopsy following Cycle 8 of brentuximab vedotin demonstrated a significant reduction in the degree of marrow infiltration by CD117-positive mast cells, and the return of normal hematopoietic elements (Fig. 1B and C). The patient con-

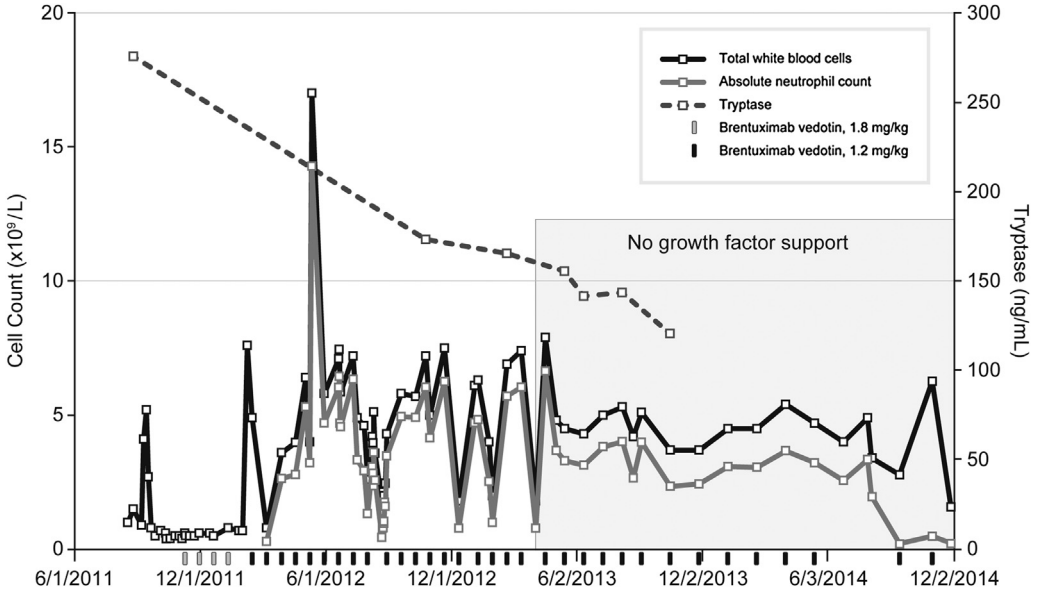


Fig. 2. Response to brentuximab vedotin in a patient with aggressive systemic mastocytosis. Total white cell count, absolute neutrophil count, tryptase levels, and growth factor support over time in the patient in case 1 with aggressive systemic mastocytosis who was treated with brentuximab vedotin.

Table 1
Patient Response to Treatment with Brentuximab Vedotin.

Case	*KIT*D816 V Mutation Status	Pre-treatment IHC Mast Cell Findings	Response According to Valent et al. Criteria	Response According to IWG-MRT/ECNM Criteria	Cycles of Brentuximab Vedotin Received	Patient Still on Brentuximab Vedotin Treatment
Case 1	Positive	Tryptase: positive Reticulin: 1+ CD117: positive CD30: positive (70%)	Major Response with Incomplete Remission	Partial Remission	44	Yes
Case 2	Positive	Tryptase:positive CD117: positive CD30: positive (30–40%)	No response	Stable Disease	8	No
Case 3	Negative	Tryptase:positive CD117: positive CD2: positive CD25: positive CD30: positive (15%)	Major Regression of systemic mediator-related symptoms	N/A	11	No
Case 4	Unknown	Tryptase:positive CD30: positive (50%)	No Response	No Response	3	No

Abbreviations: ECNM = European Competence Network on Mastocytosis; IHC = immunohistochemistry; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; N/A = not applicable.

tinued treatment with pegylated G-CSF through Cycle 23, after which his ANC has remained normal without growth factor support (Fig. 2). Serial BM biopsies performed every 4 cycles demonstrated stable reduction of BM mast cell involvement to 20% from Cycle 12 through Cycle 24. An increase in BM mast cell burden to 35% was noted at Cycle 28 but on the following biopsy at Cycle 32, it had decreased to 8%. Serum tryptase levels dropped on treatment (Fig. 2), reaching a final on-study value of 120 ng/mL at Cycle 29. Due to persistent Grade 1 neuropathy after Cycle 30, the dose interval of brentuximab vedotin 1.2 mg/kg was increased to every 6 weeks (Q6W). Even with this change in dosing, the patient's ANC remained stable. Based on these findings, the patient was determined to have a Major Response with Incomplete Remission according to the criteria of Valent et al. [25] and a Partial Remission using the IWG-MRT/ECNM criteria (Table 1) [28].

The patient received a total of 39 cycles of brentuximab vedotin during the course of the study and he continued treatment with brentuximab vedotin on a Q6W schedule after study closure. Thus far, the patient has completed 44 cycles of brentuximab vedotin over the course of 44 months. His most recent peripheral blood counts were TWC of 5.0×10^9/L, ANC 3.5×10^9/L, Hgb of 135 g/L, and PLT of 133×10^9/L. Additionally, his tryptase level dropped further to 109 ng/mL when last measured following study closure. With the exception of the described peripheral neuropathy, the patient has tolerated treatment with brentuximab vedotin well.

3.2. Case 2

A 79-year-old male with a history of hypertension, hyperlipidemia, coronary artery disease, and obstructive sleep apnea syndrome was referred for new onset pancytopenia associated with fatigue and generalized weakness. His blood counts on presentation showed a TWC of 2.8×10^9/L with an ANC of 1.1×10^9/L, and his Hgb was 108 g/L, Hct was 0.31, and PLT was 225×10^9/L. A

BM biopsy revealed a hypercellular marrow with 40% infiltrating and strongly CD117- and tryptase-positive spindle shaped mast cells. Approximately 30–40% of these mast cells stained positive for CD30. There was also significant paratrabecular fibrosis and reduction of normal trilineage hematopoiesis. His serum tryptase level was 224 ng/mL. A computed tomography (CT) scan of his abdomen and pelvis demonstrated splenomegaly of 15.5 cm with diffuse, patchy, sclerotic disease involving the pelvis, sacrum, spine, and ribs. Based on these findings, he was diagnosed with ASM. Subsequent BM testing was positive for the *KIT*D816 V mutation.

At the time of enrollment, approximately 5 months after his initial diagnosis, a baseline study BM biopsy showed 75% mast cells, his leukopenia and neutropenia persisted, and his Hgb and Hct remained low. After 2 cycles of brentuximab vedotin 1.8 mg/kg Q3W, his blood counts did not change significantly from baseline levels and a repeat BM biopsy showed modest improvement, with the percentage of mast cells decreased to 40%. An increase in normal hematopoietic elements and stable reticulin staining were also observed. After 2 additional infusions of brentuximab vedotin 1.8 mg/kg Q3W, the patient's BM biopsy showed 55% of marrow cells to be mast cells. Based on the IWG-MRT/ECNM response criteria, the patient had Stable Disease (Table 1) [28].

After a total of 7 cycles of brentuximab vedotin, the patient developed Grade 2 sensory and motor peripheral neuropathy causing delay of further treatment for 6 weeks until the neuropathy improved to Grade 1. He received 1 additional infusion of brentuximab vedotin at a reduced dose of 1.2 mg/kg. A repeat BM biopsy after Cycle 8 demonstrated no evidence of cytoreduction with a BM mast cell burden of 48% and the serum tryptase level was 252 ng/mL. No additional cycles of brentuximab vedotin were administered and 1 month later the patient was removed from the study due to clinical progression based on investigator assessment.

3.3. Case 3

A 34-year-old otherwise healthy female with a 6-year history of a waxing and waning pruritic urticarial rash and a 20-year history of loose stools developed markedly worsening gastrointestinal symptoms including fecal urgency, nausea, and abdominal discomfort. At initial presentation, she had Grade 3 diarrhea with watery stools 4–8 times daily that significantly interfered with her activities of daily living. She underwent colonoscopy and the entire colonic mucosa appeared grossly normal. Random biopsies were obtained from throughout the examined colon, revealing a dense mast cell infiltrate throughout the lamina propria, staining positive for CD117. Aberrant expression of CD2 and CD25 by mast cells was also noted. Her blood counts were normal: TWC 5.5×10^9/L, Hgb 119 g/L, Hct 0.36, and PLT 308×10^9/L. Her serum tryptase was elevated at 42 ng/mL. Her BM biopsy showed a normocellular marrow with trilineage hematopoiesis. There was a dense mast cell infiltrate (8%) with greater than 25% of the mast cells exhibiting spindle or atypical morphology. By immunohistochemistry, the mast cell infiltrate was tryptase-, CD117-, CD2-, and CD25-positive. There was paratrabecular fibrosis and osteosclerosis associated with the mast cell infiltrates. The BM was tested for the *KIT*D816 V mutation by PCR amplification and bi-directional sequencing and no mutation was identified. Abdominal ultrasound showed no evidence of hepatosplenomegaly and a complete bone survey showed no evidence of osteosclerotic lesions. Based on these findings, the patient was diagnosed with indolent SM. She received treatment with complete histamine blockade, cromolyn sodium, and leukotriene receptor antagonists with no improvement in her Grade 3 diarrhea or urticarial rash.

To qualify for the study, an additional BM biopsy and aspirate were performed which demonstrated a baseline marrow mast cell burden of 8% by immunohistochemistry, of which 15% stained positive for CD30. By flow cytometry, 37% of marrow mast cells on an aspirate sample expressed CD30. After 3 cycles of brentuximab vedotin 2.4 mg/kg Q3W, her diarrhea improved to Grade 1 with 1 or 2 bowel movements daily and her urticarial rash resolved completely. After 3 cycles of treatment, a repeat marrow biopsy sample showed a total mast cell burden of 16%, an increase that was felt by the local hematopathologist to be due to sampling bias. A subsequent BM biopsy obtained after 7 cycles of treatment showed 4% marrow mast cells. No significant changes in her serum tryptase levels were noted. The patient developed an intermittent Grade 1 peripheral neuropathy after Cycle 2 that increased to Grade 2 after Cycle 7. Treatment was withheld for 6 weeks and was resumed at an attenuated dose of 1.2 mg/kg Q3W after her neuropathy symptoms improved to Grade 1. She was considered to have a Major Regression of systemic mediator-related symptoms according to the criteria of Valent et al. (Table 1) [25]. The IWG-MRT/ECNM criteria do not address responses in indolent SM. She discontinued treatment after 11 cycles of brentuximab vedotin due to plans to conceive a child. A BM biopsy obtained after Cycle 11 showed 8% mast cells and her serum tryptase remained stable. At the time of this report, the patient has been off of therapy for approximately 52 weeks; her Grade 1 diarrhea symptoms remain unchanged and her peripheral neuropathy was resolved.

3.4. Case 4

A 77-year-old male with a history of type 2 diabetes mellitus, coronary artery disease, hypertension, chronic kidney disease, hyperlipidemia, degenerative joint disease, cholelithiasis, and benign prostatic hypertrophy presented with diarrhea, anemia, symptomatic splenomegaly and ascites as demonstrated by CT, as well as lytic and blastic bony lesions evident upon skeletal survey. A work-up including a BM biopsy revealed hypercellularity with 40% of BM cells identified as malignant tryptase-positive mast cells; 50% of the BM mast cells expressed CD30. The *KIT*D816 V mutation status of the patient is unknown. At baseline, the patient's TWC was 8.5×10^9/L, Hgb was 97 g/L, PLT was 252×10^9/L, and ANC was 2.0×10^9/L. Other notable findings included reduced albumin (24 g/L) which was concerning for potential SM gut involvement. The patient also had chronic renal insufficiency with a stable creatinine clearance of 28 mL/min.

The patient was treated with brentuximab vedotin at a reduced dose of 1.2 mg/kg Q3W due to his underlying renal insufficiency. After Cycle 2, a response assessment demonstrated progression of his anemia with Hgb of 79 g/L, though his TWC, neutrophil, and PLT all remained stable. A BM biopsy demonstrated persistent hypercellularity with 30% mast cells.

The patient began to experience symptomatic deterioration 2 days after the Cycle 3 Day 1 administration of brentuximab vedotin. At that point, his diarrhea worsened to Grade 3 and was accompanied by Grade 3 vomiting and Grade 3 dehydration, though all symptoms were considered unrelated to brentuximab vedotin treatment. At the same time, the patient developed Grade 2 aspiration pneumonia that progressed to Grade 4 sepsis, both of which were considered unrelated to treatment with brentuximab vedotin. One month after the Cycle 3 Day 1 dose of brentuximab vedotin, the patient died of progressive disease.

4. Discussion

Recent studies of the immunological and molecular phenotype of mast cells from patients with SM have led to improvements in the diagnosis and classification of this disease. Currently, cytoreductive therapy is indicated for SM patients with aggressive disease or for individuals with indolent disease and severe mediator-release

symptoms that are not adequately controlled with a combination of antihistamines, antileukotriene agents, and cromolyn sodium [6]. However, the treatment of SM with conventional therapies (IFN-α and 2-CdA) is associated with significant side effects and short-lived responses [7–17], demonstrating the need for novel therapies with longer durations of response that are also well-tolerated.

CD30 is a transmembrane glycoprotein belonging to the tumor necrosis factor superfamily that is generally expressed only on activated or proliferating B and T cells and is absent or expressed at very low levels in normal tissues [29]. Activation of CD30 by its ligand, CD30L, can have pleiotropic effects which depend on the cells on which it is expressed [30]. Expression of CD30 has been demonstrated in malignancies involving tissues of both lymphoid and nonlymphoid origin, including HL [31], mesenchymal tumors [32], and acute myelogenous leukemia [33]. Additionally, recent work has demonstrated that CD30 is frequently expressed on neoplastic mast cells [34]. In a study by Sotlar et al., CD30 expression was detected by immunohistochemistry in marrow mast cells from 11 of 13 (85%) patients with advanced disease (including smoldering SM, ASM, and mast cell leukemia). In contrast, CD30 expression was detected in only 12/45 (27%) of patients with indolent disease [20]. However, in a subsequent study by Morgado et al. that employed flow cytometry to detect CD30, high rates of CD30 expression were detected in marrow mast cells in both aggressive (8/8, 100%) and indolent (98/123, 80%) disease [19]. Together, these studies suggest that CD30 is a viable therapeutic target for patients with SM, particularly ASM.

The current consensus response criteria for ASM suggest that the BM mast cell burden is best quantified using morphologic analysis and immunohistochemical methods on the core BM biopsy [28]. However, multiparameter flow cytometry is the preferred method of immunophenotyping of several aberrantly expressed surface markers present in SM as it allows for the sensitive detection of these markers and quantitative evaluation of antigen expression in large numbers of mast cells, even if these mast cells are present at low frequencies within individual samples [35]. Based on flow cytometry results from a subset of ASM and indolent SM BM samples that were also stained by immunohistochemistry, flow cytometry appears to be a more sensitive method for detecting CD30 than immunohistochemistry [19]. Multiparameter flow cytometry has also proven useful in the classification of several subtypes of SM based on surface antigen expression and these distinct immunophenotypes were associated with both the genetic markers of SM and its clinical behavior [36].

Brentuximab vedotin is an anti-CD30 ADC that delivers the microtubule-disrupting agent MMAE to CD30-expressing cells and has been shown to be a highly active agent in the treatment of CD30 expressing lymphomas [22–24]. Though this case series is the first report to explore the clinical activity of brentuximab vedotin in the treatment of SM, a recent publication has demonstrated that brentuximab vedotin has anti-neoplastic activity in vitro against CD30-expressing transformed human mast cell lines and patient derived primary neoplastic mast cells [37]. In the current case series, 4 patients with SM were treated with brentuximab vedotin (Table 1) at starting doses of 1.2-2.4 mg/kg Q3W. Two patients (1 with ASM and 1 with indolent SM) showed evidence of a response to treatment with a reduction of disease burden, and 1 patient with ASM is still receiving brentuximab vedotin treatment after study closure, with ongoing clinical benefit.

In the patient with ASM in case 1, the response to brentuximab vedotin has been durable and the treatment has been well-tolerated. At this point, the patient has been on treatment for 44 months and has maintained normal peripheral blood counts without growth factor support for over a year. He did experience a peripheral neuropathy that necessitated lowering the brentuximab dose to 1.2 mg/kg and increasing the intervals between infusions to 6 weeks, after which his neuropathy has remained at Grade 1.

The patient in case 3 had symptomatic indolent SM that was poorly controlled with standard therapy. On treatment with brentuximab vedotin, she experienced Major Regression of her systemic mediator-related symptoms under the consensus criteria of Valent et al. [25]. Due to Grade 2 neuropathy, treatment was withheld and was resumed at 1.2 mg/kg Q3W after her neuropathy symptoms improved to Grade 1. She discontinued treatment after Cycle 11, with plans to conceive a child. Now off therapy for approximately 52 weeks, her tryptase level remains stable, her Grade 1 diarrhea is unchanged, and her peripheral neuropathy has resolved.

Two additional study patients with SM were treated with brentuximab vedotin. One had a high burden of disease affecting his BM and spleen and achieved a best response of Stable Disease for 6 months while undergoing treatment with brentuximab vedotin at 1.8 mg/kg Q3W. However, this patient required a dose delay and reduction to 1.2 mg/kg Q3W due to peripheral sensory and motor neuropathies. Shortly after the dose reduction, the patient was removed from the study due to progressive disease, suggesting that this lower dose of brentuximab vedotin was not enough to control his disease. The other patient presented with advanced disease, but did not show evidence of therapeutic benefit with clinical progression after 3 cycles of treatment with brentuximab vedotin. This patient was treated with a reduced starting dose of brentuximab vedotin at 1.2 mg/kg Q3W due to underlying renal insufficiency; however, it is unclear whether his lack of response to treatment was due to this lowered dosage. Though brentuximab vedotin is highly effective in treating both relapsed HL and systemic ALCL, malignancies defined by their expression of CD30, not all patients respond to treatment and resistance can develop in patients who initially respond. Mechanisms of resistance to brentuximab vedotin have been studied in HL and ALCL cell lines and primary patient samples [38,39]. Studies in these cell lines suggest that downregulation of CD30 expression is associated with the development of resistance to brentuximab vedotin. However, results in both cell lines and clinical samples show a more consistent association with the development of resistance to brentuximab vedotin and an increased expression of multidrug resistance efflux pumps, which may increase the transport of brentuximab vedotin out of the target cells [38].

5. Conclusions

This small case series provides evidence that brentuximab vedotin is an active and well-tolerated agent in the treatment of SM with side effects that are effectively managed by dose modifications. There are a limited number of cytoreductive agents that are effective in this rare yet debilitating disease. These results show brentuximab vedotin to be a promising treatment option in the management of both aggressive and refractory symptomatic indolent SM that deserves to be studied more extensively. Larger studies are needed to better define response rates to treatment with brentuximab vedotin and to explore the efficacy and tolerability of different dosing schedules. Furthermore, efforts to understand the mechanisms of resistance to brentuximab vedotin in mast cells and to characterize biomarkers that predict responses will be important in defining the role of brentuximab vedotin in the clinical management of SM.

Acknowledgements

Seattle Genetics, Inc. funded this study and was responsible for the design of the study. Along with the investigators, Seattle Genetics, Inc. aided in the collection, analysis, and interpretation of data;

the writing of this report; and the decision to submit the report for publication.

U. Borate, A. Mehta, V. Reddy, M. Tsai, N. Josephson, and I. Schnadig analyzed and interpreted patient data and were major contributors in preparation of the manuscript. All authors read and approved the final manuscript. Manuscript preparation assistance was provided by Chantelle Rein-Smith of Whitsell Innovations, Inc. (sponsored by Seattle Genetics, Inc.).

Seattle Genetics, Inc. has provided research funding to U. Borate, A. Mehta, V. Reddy, M. Tsai, and I. Schnadig via their respective institutions. U. Borate is a consultant for Genoptix and is on the speakers bureaus of Novartis International AG and Alexion Pharmaceuticals, Inc. N. Josephson is an employee of, and has equity ownership in, Seattle Genetics, Inc.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2016.02.010.

References

[1] A. Vega-Ruiz, J.E. Cortes, M. Sever, T. Manshouri, A. Quintas-Cardama, R. Luthra, et al., Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis, Leuk. Res. 33 (11) (2009) 1481–1484.
[2] S.J. Fuller, New insights into the pathogenesis, diagnosis, and management of mastocytosis, Hematol. Oncol. Clin. N. Am. 26 (6) (2012) 1143–1168.
[3] A. Pardanani, Systemic mastocytosis in adults: 2013 update on diagnosis, risk stratification, and management, Am. J. Hematol. 88 (7) (2013) 612–624.
[4] K.H. Lim, A. Tefferi, T.L. Lasho, C. Finke, M. Patnaik, J.H. Butterfield, et al., Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors, Blood 113 (23) (2009) 5727–5736.
[5] P. Valent, W.R. Sperr, Akin C. How, I treat patients with advanced systemic mastocytosis, Blood 116 (26) (2010) 5812–5817.
[6] A. Pardanani, How I treat patients with indolent and smoldering mastocytosis (rare conditions but difficult to manage), Blood 121 (16) (2013) 3085–3094.
[7] K.H. Lim, A. Pardanani, J.H. Butterfield, C.Y. Li, A. Tefferi, Cytoreductive therapy in 108 adults with systemic mastocytosis: outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine, Am. J. Hematol. 84 (12) (2009) 790–794.
[8] J.H. Butterfield, Response of severe systemic mastocytosis to interferon alpha, Br. J. Dermatol. 138 (3) (1998) 489–495.
[9] J.H. Butterfield, A. Tefferi, G.F. Kozuh, Successful treatment of systemic mastocytosis with high-dose interferon-alfa: long-term follow-up of a case, Leuk. Res. 29 (2) (2005) 131–134.
[10] P. Casassus, N. Caillat-Vigneron, A. Martin, J. Simon, V. Gallais, P. Beaudry, et al., Treatment of adult systemic mastocytosis with interferon-α: results of a multicentre phase II trial on 20 patients, Br. J. Haematol. 119 (4) (2002) 1090–1097.
[11] A.W. Hauswirth, I. Simonitsch-Klupp, M. Uffmann, E. Koller, W.R. Sperr, K. Lechner, et al., Response to therapy with interferon alpha-2b and prednisolone in aggressive systemic mastocytosis: report of five cases and review of the literature, Leuk. Res. 28 (3) (2004) 249–257.
[12] O. Hermine, I. Hirsh, G. Damaj, C. Granpeix, S. Barete, F. Suarez, et al., Long term efficacy and safety of cladribine in adult systemic mastocytosis: a French multicenter study of 44 patients. [ASH Annual Meeting Abstracts, Abstract 1982], Blood 116 (21) (2010) 827–828.
[13] H.C. Kluin-Nelemans, J.H. Jansen, H. Breukelman, B.G. Wolthers, P.M. Kluin, H.M. Kroon, et al., Response to interferon alfa-2b in a patient with systemic mastocytosis, NEJM 326 (9) (1992) 619–623.
[14] H.C. Kluin-Nelemans, J.M. Oldhoff, J.J. van Doormaal, J.W. van't Wout, G. Verhoef, W.B.J. Gerrits, O.A. van Dobbenburgh, et al., Cladribine therapy for systemic mastocytosis, Blood 102 (13) (2003) 4270–4276.
[15] A. Pardanani, A.V. Hoffbrand, J.H. Butterfield, A. Tefferi, Treatment of systemic mast cell disease with 2-chlorodeoxyadenosine, Leuk. Res. 28 (2) (2004) 127–131.
[16] A. Tefferi, C.Y. Li, J.H. Butterfield, H.C. Hoagland, Treatment of systemic mast-cell disease with cladribine, NEJM 344 (4) (2001) 307–309.
[17] M.J. Rummel, K.U. Chow, E. Jager, L. Leimer, D.K. Hossfeld, L. Bergmann, et al., Intermittent 2-hour-infusion of cladribine as first-line therapy or in first relapse of progressive advanced low-grade and mantle cell lymphomas, Leuk. Lymphoma 35 (1–2) (1999) 129–138.
[18] I. Alvarez-Twose, P. Gonzalez, J.M. Morgado, M. Jara-Acevedo, L. Sanchez-Munoz, A. Matito, et al., Complete response after imatinib mesylate therapy in a patient with well-differentiated systemic mastocytosis, J. Clin. Oncol. 30 (12) (2012) e126–129.
[19] J.M. Morgado, O. Perbellini, R.C. Johnson, C. Teodosio, A. Matito, I. Alvarez-Twose, et al., CD30 expression by bone marrow mast cells from different diagnostic variants of systemic mastocytosis, Histopathology 63 (6) (2013) 780–787.
[20] K. Sotlar, S. Cerny-Reiterer, K. Petat-Dutter, H. Hessel, S. Berezowska, L. Mullauer, et al., Aberrant expression of CD30 in neoplastic mast cells in high-grade mastocytosis, Mod. Pathol. 24 (4) (2011) 585–595.
[21] P. Valent, K. Sotlar, H.P. Horny, Aberrant expression of CD30 in aggressive systemic mastocytosis and mast cell leukemia: a differential diagnosis to consider in aggressive hematopoietic CD30-positive neoplasms, Leuk. Lymphoma 52 (5) (2011) 740–744.
[22] J.A. Francisco, C.G. Cerveny, D.L. Meyer, B.J. Mixan, K. Klussman, D.F. Chace, et al., cAC10-vcMMAE, an anti-CD30—monomethyl auristatin E conjugate with potent and selective antitumor activity, Blood 102 (4) (2003) 1458–1465.
[23] A. Younes, A.K. Gopal, S.E. Smith, S.M. Ansell, J.D. Rosenblatt, K.J. Savage, et al., Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma, J. Clin. Oncol. 30 (18) (2012) 2183–2189.
[24] B. Pro, R. Advani, P. Brice, N.L. Bartlett, J.D. Rosenblatt, T. Illidge, et al., Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study, J. Clin. Oncol. 30 (18) (2012) 2190–2196.
[25] P. Valent, C. Akin, L. Escribano, M. Fodinger, K. Hartmann, K. Brockow, et al., Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria, Eur. J. Clin. Invest. 37 (6) (2007) 435–453.
[26] P. Valent, C. Akin, W.R. Sperr, L. Escribano, M. Arock, H.P. Horny, et al., Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria, Leuk. Res. 27 (7) (2003) 635–641.
[27] A. Pardanani, A. Tefferi, A critical reappraisal of treatment response criteria in systemic mastocytosis and a proposal for revisions, Eur. J. Haematol. 84 (5) (2010) 371–378.
[28] J. Gotlib, A. Pardanani, C. Akin, A. Reiter, T. George, O. Hermine, et al., International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis, Blood 121 (13) (2013) 2393–2401.
[29] S.L. Buchan, A. Al-Shamkhani, Distinct motifs in the intracellular domain of human CD30 differentially activate canonical and alternative transcription factor NF-κB signaling, PLoS One 7 (9) (2012) e45244.
[30] H.-J. Gruss, N. Boiani, D.E. Williams, R.J. Armitage, C.A. Smith, R.G. Goodwin, Pleiotropic effects of the CD30 ligand on CD30-expressing cells and lymphoma cell lines, Blood 83 (8) (1994) 2045–2056.
[31] R. von Wasielewski, M. Mengel, R. Fischer, M.-L. Hansmann, K. Hübner, J. Franklin, et al., Classical Hodgkin's disease: clinial impact of the immunophenotype, Am. J. Pathol. 151 (4) (1997) 1123–1130.
[32] G. Mechtersheimer, P. Möller, Expression of Ki-1 anitgen (CD30) in mesenchymal tumors, Cancer 66 (1990) 1732–1737.
[33] V. Gattei, M. Degan, A. Gloghini, A. De Iuliis, S. Improta, F.M. Rossi, et al., CD30 ligand is frequently expressed in human hematopoietic malignancies of myeloid and lymphoid origin, Blood 89 (6) (1997) 2048–2059.
[34] B. van Anrooij, P.M. Kluin, J.N.G. Oude Elberink, J.C. Kluin-Nelemans, CD30 in systemic mastocytosis, Immunol. Allergy Clin. N. Am. 34 (2) (2014) 341–355.
[35] L. Escribano, B. Diaz-Agustin, A. Lopez, R.N. Lopez, A. Garcia-Montero, J. Almeida, et al., Immunophenotypic analysis of mast cells in mastocytosis: when and how to do it: proposals of the Spanish Network on Mastocytosis (REMA), Cytometry B Clin. Cytom. 58 (1) (2004) 1–8.
[36] C. Teodosio, A.C. Garcia-Montero, M. Jara-Acevedo, L. Sanchez-Munoz, I. Alvarez-Twose, R. Nunez, et al., Mast cells from different molecular and prognostic subtypes of systemic mastocytosis display distinct immunophenotypes, J. Allergy Clin. Immunol. 125 (3) (2010) 719–726.
[37] K. Blatt, S. Cerny-Reiterer, J. Schwaab, K. Sotlar, G. Eisenwort, G. Stefanzl, et al., Indentification of the Ki-1 antigen (CD30) as a novel therapeutic target in systemic mastocytosis, Blood 126 (26) (2015) 2832–2841.
[38] R. Chen, J. Hou, E. Newman, Y. Kim, C. Donohue, X. Liu, et al., CD30 downregulation, MMAE resistance, and MDR1 upregulation are all associated with resistance to brentuximab vedotin, Mol. Cancer Ther. 14 (6) (2015) 1376–1384.
[39] N. Nathwani, A.Y. Krishnan, Q. Huang, Y. Kim, C. Karanes, E.P. Smith, et al., Persistence of CD30 expression in Hodgkin lymphoma following brentuximab vedotin (SGN-35) treatment failure, Leuk. Lymphoma 53 (10) (2012) 2051–2053.