EXCEPTIONAL CASE REPORT

blood advances

Bendamustine-induced immune hemolytic anemia: a case report and systematic review of the literature

Maverick Chan,[1,*] William K. Silverstein,[2,*] Anna Nikonova,[1] Katerina Pavenski,[1-3] and Lisa K. Hicks[1,2,4]

[1]Division of Hematology-Oncology, St. Michael's Hospital, Toronto, ON, Canada; [2]Department of Medicine and [3]Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, ON, Canada; and [4]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

Key Points

- Bendamustine can cause severe autoimmune hemolytic anemia (AIHA), which may require plasma exchange and aggressive immunosuppression.
- Bendamustine-induced AIHA can be delayed, and many, but not all, cases report prior exposure to fludarabine.

Introduction

Drug-induced immune hemolytic anemia (DIIHA) is a rare, but potentially devastating, complication of treating blood cancers. Although DIIHA is estimated to affect only 1 per 1 000 000 patients annually, it is associated with high mortality (15%).[1-3] Over 130 drugs have been implicated in reports of DIIHA, including fludarabine.[4] Bendamustine is a bifunctional mechlorethamine derivative that is widely used to treat non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL).[5,6] It shares a purine ring with fludarabine, the most common drug to induce red blood cell autoantibodies.[3,6]

We report a case of severe bendamustine-induced immune hemolytic anemia causing renal failure in a patient with splenic marginal zone lymphoma (SMZL). We also report the results of a systematic review summarizing all previous reports of bendamustine-induced hemolytic anemia in the English-language literature.

Case description

A 65-year-old man presented to the emergency department with severe fatigue, myalgias, dark urine, and fever, hours after day 1 of his fourth cycle of bendamustine and rituximab (BR) for symptomatic SMZL. His medical history was otherwise notable for HIV with a CD4 count of 310, as well as undetectable viral load, essential hypertension, hypothyroidism, and previous exposure to hepatitis B virus with evidence of immunity. Medications included bictegravir, emtricitabine, tenofovir, ramipril, L-thyroxine, and trimethoprim-sulfamethoxazole. He had no prior chemoimmunotherapy exposure. The patient received the first cycle of BR without complication. He experienced a grade 3 hypersensitivity reaction during his second cycle, with hypotension and fever. He tolerated a modified third cycle of BR, with full-dose bendamustine, split rituximab dosing, and concurrent dexamethasone. However, 8 hours after the day 1 bendamustine infusion of his fourth cycle finished, he presented with the aforementioned findings. He had not yet received the rituximab component of his BR.

His examination was notable for fever (39.1°C) and jaundice. Laboratory investigations revealed a hemoglobin of 81 g/L (from 102 g/L [reference (ref), 130-170 g/L]), acute kidney injury (creatinine, 194 μmol/L; baseline, 113 μmol/L [ref, 52-112 μmol/L]), and biochemical evidence of hemolysis (total bilirubin, 124 μmol/L [ref, 0-23 μmol/L]; indirect bilirubin, 93 μmol/L; lactate dehydrogenase, 1476 U/L [ref, 100-195 U/L]; haptoglobin, $<$0.01 g/L [ref, 0.3-2.0 g/L]). Urine microscopy demonstrated heme-granular casts. Blood film revealed polychromasia, but no schistocytes or spherocytes. His reticulocyte count was 18. Concomitant disseminated intravascular coagulopathy was noted (platelets, 11×10^9/L [ref, 140-400 $\times$ 10^9/L]; thrombin time, 25.1 seconds [ref, 12.5-16.0 seconds]; activated partial thromboplastin time, 28.3 seconds [ref, 24.0-37.0 seconds]; fibrinogen, 1.0 g/L [ref, 1.8-4.0 g/L]; D-dimer, $>$5000 ng/mL [ref, $<$230 ng/mL]). He had no clinical manifestations of hemorrhage or thrombosis. His blood group was A^+, and his antibody screen was positive for a panagglutinating immunoglobulin G (IgG) autoantibody. The direct antiglobulin test (DAT) was strongly positive for IgG and a panagglutinating IgG antibody was eluted off of his red cells. He was diagnosed with warm autoimmune hemolytic anemia (AIHA), presumed to be secondary to bendamustine based on the timing of his presentation. He received 80 mg of methylprednisolone per day for 12 days, 1 g/kg IV immunoglobulin

Submitted 24 February 2020; accepted 26 March 2020; published online 28 April 2020. DOI 10.1182/bloodadvances.2020001726.

*M.C. and W.K.S. are listed alphabetically due to similar contributions and share first authorship.

Data-sharing requests may be e-mailed to the corresponding author, William K. Silverstein, at william.silverstein@mail.utoronto.ca.

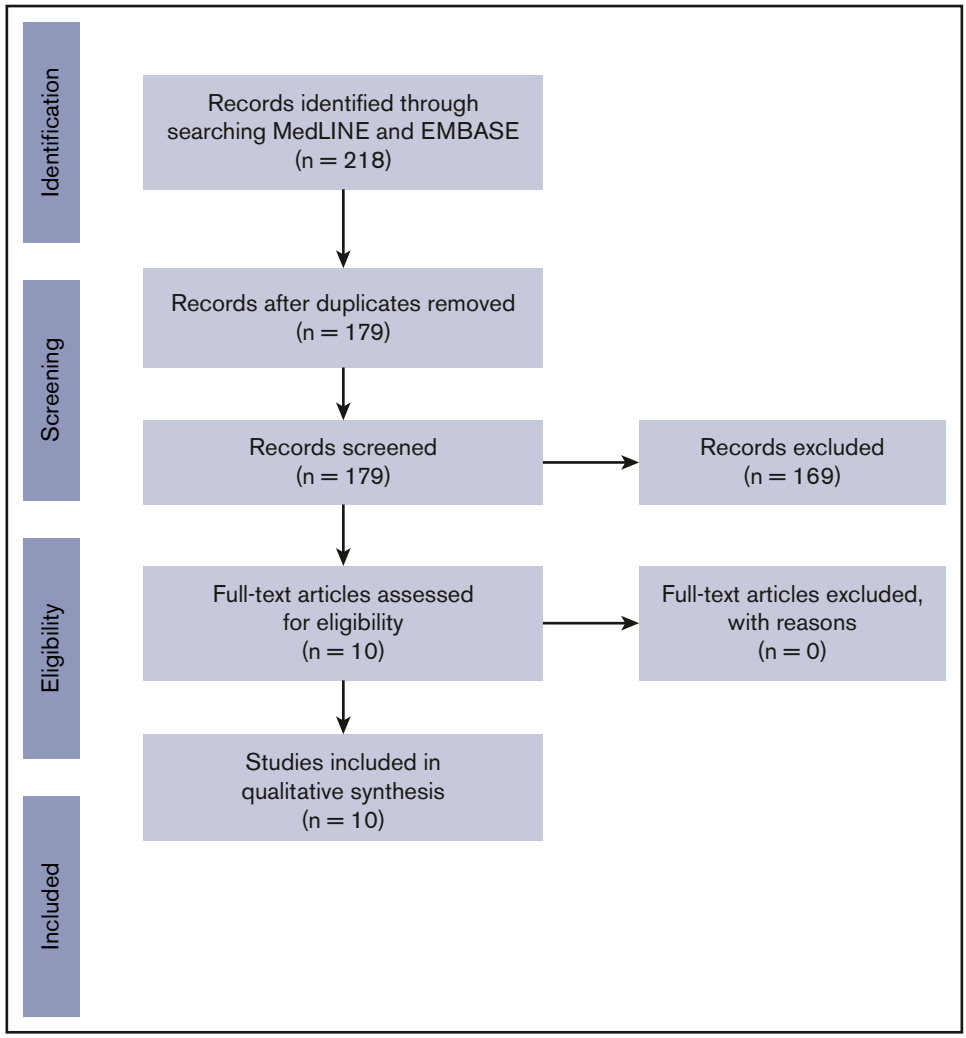

Figure 1. PRISMA 2009 flow diagram. For more information, visit www.prisma-statement.org. Adapted from Moher et al.[24]

per day for 2 days, and 1 IV dose of 375 mg/m^2 rituximab. He was also treated with plasma exchange using frozen plasma daily for 2 days. He was then transitioned to 1 mg/kg prednisone, which was tapered off over the ensuing 4 weeks. He required 3 weeks of intermittent hemodialysis for renal dysfunction secondary to acute tubular necrosis from heme-pigment deposition. His hemolysis resolved, his hematologic parameters recovered to baseline, and his renal function normalized over 4 weeks. His DAT remained positive for 2 months. His chemotherapy regimen was then transitioned to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone with good tolerance and response.

Methods

We searched 2 electronic databases, Medline and EMBASE, using a date range from 1947 to 8 August 2019. The following keywords and medical subject headings were used: (bendamustine) AND (hemolysis OR hemolytic anemia OR autoimmune hemolytic anemia OR AIHA OR Evans syndrome). The database search was conducted by 2 authors (M.C. and W.K.S.). Bibliographies of articles and review articles were hand-searched to identify primary articles that may have been missed in the initial search. Only English-language papers were included. All publications reporting 1 or more cases of hemolytic anemia in the context of bendamustine use were included. Two authors (M.C. and W.K.S.) independently extracted data from all studies into data summary tables.

Results and discussion

As outlined in Figure 1, our search yielded 218 potentially relevant reports, of which 39 were duplicates. A total of 179 unique articles were screened for eligibility; 10 met full inclusion criteria (Figure 1). Twenty-six cases of bendamustine-induced AIHA are documented (Table 1).[7-16] All cases occurred in patients with CLL, except for 1 in a patient with follicular lymphoma.[9] Similarities to our patient included DAT positivity in a majority of cases (9 of 14 reported cases). Unlike our patient, most had previous exposure to purine nucleoside analogs (20 of 26), and DIIHA occurred after a median of 2 cycles of BR (range, 1-6). There was no documented renal failure in any case. All patients were treated with systemic corticosteroids; rituximab was used in 8 patients and IV immunoglobulin was used in 1 patient. No patients received plasma exchange. One patient died of overwhelming septic shock; all others recovered.

Purine analogs, such as bendamustine, cause a drug-independent DIIHA that is serologically indistinguishable from warm AIHA.[3,17] In

Table 1. Summary of case reports and series of bendamustine-induced immune hemolytic anemia

Reference/year	n	Age, y/sex	Hematologic diagnosis (n)	No. of bendamustine cycles prior to hemolysis	Prior nonbendamustine purine analog exposure (n)	Low platelets (nadir platelet count)	DAT status	Treatment	Outcome
Cuneo et al[7]/2018	2	NR	CLL (2)	NR	Fludarabine Chlorambucil	NR	NR	NR	NR
Fischer et al[8]/2011	2	NR	CLL (2)	NR	Fludarabine Fludarabine	NR	NR	NR	NR
Glance et al[9]/2009	1	64/female	FL (1)	4	No	Yes (16)	Negative	P 1 mg/kg	Recovered
Goldschmidt et al[10]/2013	5	69/male 63/female 66/female 59/male 54/male	CLL (5)	1 2 6 1 1	Fludarabine Fludarabine Chlorambucil Fludarabine Fludarabine	NR	IgG$^+$ C3$^+$ Negative IgG$^+$ Negative	P, R P, R, C P M, I, R, C P, R	Recovered (4/5) Death (1/5)
Haddad et al[11]/2014	1	70/female	CLL (1)	3	Fludarabine	NR	IgG$^+$, C3$^+$	P 1 mg/kg	Recovered
Hodskins et al[12]/2014	1	62/male	CLL (1)	1	No	NR	Positive	P	Recovered
Knauf et al[13]/2009	2	NR	CLL (2)	NR	No (2)	NR	NR	NR	NR
Laurenti et al[14]/2016	6	58/female 62/female 68/male 64/female 63/female 68/male	CLL (6)	6 4 2 3 4 1	No No Fludarabine Fludarabine Fludarabine Chlorambucil	NR	Positive IgG$^+$ Positive Negative Negative IgG$^+$	P P P, R, C, V R P P	Recovered (6/6)
Nyatanga et al[15]/2015	5	63 (median) 56-69 (range)	CLL (5)	NR	Fludarabine (3)	NR	NR	P (3) P, R (1) P, R, C (1)	Recovered (5/5)
Spacek et al[16]/2019	1	NR	CLL (1)	NR	NR	NR	NR	NR	NR

C, cyclophosphamide; FL, follicular lymphoma; I, IV immunoglobulin; M, methylprednisolone; NR, not reported; P, prednisone; R, rituximab; V, vincristine.

these cases, patients acquire a circulating drug-induced antibody when initially exposed to the drug, which may then cause acute reactions with subsequent administrations.[3] These patients have a DAT positive for IgG and/or C3.[3] Risk factors for bendamustine-induced immune hemolytic anemia include previous purine analog exposure and a diagnosis of CLL. To diagnose DIIHA, other secondary causes of AIHA, such as infection and malignancy, need to be excluded.[17] Our patient had SMZL and HIV. Although AIHA is seen in ~10% of SMZL patients, our patient had no evidence of hemolysis at baseline, or immediately prior to his fourth cycle of bendamustine.[18,19] HIV is an extremely rare cause of AIHA, with <20 documented reports in the literature; moreover, all cases occurred in patients with CD4 counts <200.[20] Given that our patient's CD4 count was >200 and his viral load was undetectable, we find it extremely unlikely that HIV caused AIHA.

There is little evidence informing the treatment of DIIHA. A 2017 British Society for Haematology guideline recommended cessation of the offending drug and supportive care.[17] The utility of steroids is unclear as their benefit is difficult to distinguish from the effects of stopping the drug.[17] Despite this, 85% of patients with DIIHA receive corticosteroids.[21] Rituximab, azathioprine, cyclophosphamide, cyclosporine, danazol, mycophenolate, and IV immunoglobulin may also be effective for severe or refractory AIHA.[22,23] Hematologic recovery usually occurs within 1 to 2 weeks of treatment and drug cessation.[3,17] The decision to undertake plasma exchange was in light of his severe presentation and rapidly deteriorating renal function. Plasma was used instead of albumin to mitigate further exacerbations of his concurrent coagulopathy.

In summary, we report a case of severe bendamustine-induced AIHA and renal failure in a patient with SMZL. We believe that this is the correct diagnosis given the temporal association of his hemolytic abnormalities with exposure to bendamustine, absence of other agents that cause DIIHA, and lack of other risk factors for secondary AIHA. We also present a systematic review of the English-language literature on hemolytic anemia associated with bendamustine use. Unlike the presented case, most previous reports occurred in patients with CLL after a median of 2 cycles of bendamustine. Prior exposure to fludarabine was frequently reported. In conclusion, DIIHA is a rare, but potentially life-threatening, complication of bendamustine chemotherapy. Clinicians with past or current knowledge of similar cases are encouraged to report their cases to facilitate better understanding of this rare complication of treatment. Future studies should evaluate risk factors that predict bendamustine-induced AIHA, and validate effective treatment options.

Authorship

Contribution: W.K.S., M.C., and L.K.H. devised the study; W.K.S. and M.C. collected all data and conducted data analysis; W.K.S., M.C., A.N., K.P., and L.K.H. reviewed data and read and approved the final manuscript; W.K.S. drafted the manuscript; and M.C., A.N., K.P., and L.K.H. revised the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profile: W.K.S., 0000-0002-4133-7369.

Correspondence: William K. Silverstein, Department of Medicine, University of Toronto, 2075 Bayview Ave, Toronto, ON M4N 3M5, Canada; e-mail: william.silverstein@mail.utoronto.ca.

References

1. Ahrens N, Genth R, Kiesewetter H, Salama A. Misdiagnosis in patients with diclofenac-induced hemolysis: new cases and a concise review. *Am J Hematol*. 2006;81(2):128-131.
2. Garratty G. Immune hemolytic anemia associated with drug therapy. *Blood Rev*. 2010;24(4-5):143-150.
3. Liesveld JL, Rowe JM, Lichtman MA. Variability of the erythropoietic response in autoimmune hemolytic anemia: analysis of 109 cases. *Blood*. 1987; 69(3):820-826.
4. Salama A. Drug-induced immune hemolytic anemia. *Expert Opin Drug Saf*. 2009;8(1):73-79.
5. Alberta Health Services. Lymphoma. Clinical practice guideline LYHE-002 version 12. albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf. Accessed 21 September 2019.
6. Provincial Health Services Authority. Bendamustine. British Columbia Cancer Drug Manual. Revised 1 October 2018. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/Bendamustine_monograph.pdf. Accessed 21 September 2019.
7. Cuneo A, Follows G, Rigolin GM, et al; GIMEMA, European Research Initiative on CLL (ERIC) and UK CLL forum. Efficacy of bendamustine and rituximab as first salvage treatment in chronic lymphocytic leukemia and indirect comparison with ibrutinib: a GIMEMA, ERIC and UK CLL FORUM study. *Haematologica*. 2018;103(7):1209-1217.
8. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. *J Clin Oncol*. 2011;29(26):3559-3566.
9. Glance LE, Cumpston A, Kanate A, Remick SC. Bendamustine-associated hemolytic anemia. *Ann Pharmacother*. 2009;43(11):1903-1906.
10. Goldschmidt N, Gural A, Ben-Yehuda D, Gatt ME. Short communication: bendamustine-related hemolytic anemia in chronic lymphocytic leukemia. *Cancer Chemother Pharmacol*. 2013;72(3):709-713.
11. Haddad H, Mohammad F, Dai Q. Bendamustine-induced immune hemolytic anemia in a chronic lymphocytic leukemia patient: a case report and review of the literature. *Hematol Oncol Stem Cell Ther*. 2014;7(4):162-164.
12. Hodskins J, Houranieh J, Fleischman RA. Ibrutinib-associated autoimmune hemolytic anemia in CLL [abstract]. *Blood*. 2014;124(21). Abstract 5671.
13. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27(26):4378-4384.
14. Laurenti L, Autore F, Innocenti I, et al. Autoimmune hemolytic anemia during bendamustine plus rituximab treatment in CLL patients: multicenter experience. *Leuk Lymphoma*. 2016;57(10):2429-2431.
15. Nyatanga N, Anne M, Barrientos JC. Autoimmune hemolytic anemia following treatment with bendamustine: a case series [abstract]. *J Investig Med*. 2015;63(3):584-585.
16. Špaček M, Obrtlíková P, Hrobková S, et al. Prospective observational study in comorbid patients with chronic lymphocytic leukemia receiving first-line bendamustine with rituximab. *Leuk Res*. 2019;79:17-21.
17. Hill QA, Stamps R, Massey E, Grainger JD, Provan D, Hill A; British Society for Haematology Guidelines. Guidelines on the management of drug-induced immune and secondary autoimmune, haemolytic anaemia. *Br J Haematol*. 2017;177(2):208-220.
18. Thieblemont C, Felman P, Callet-Bauchu E, et al. Splenic marginal-zone lymphoma: a distinct clinical and pathological entity. *Lancet Oncol*. 2003;4(2): 95-103.
19. Oladiran O, Dhital R, Donato A. Recurrent autoimmune hemolytic anemia in splenic marginal zone lymphoma. *J Community Hosp Intern Med Perspect*. 2018;8(4):244-245.
20. Wu DPH, Caperna J, Reid E. Autoimmune hemolytic anemia in HIV: a case series and review of the literature [abstract]. *Blood*. 2006;108(11). Abstract 3858.
21. Garbe E, Andersohn F, Bronder E, et al. Drug induced immune haemolytic anaemia in the Berlin Case-Control Surveillance Study. *Br J Haematol*. 2011; 154(5):644-653.
22. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. *Blood*. 2017;129(22):2971-2979.
23. Zuercher AW, Spirig R, Baz Morelli A, Käsermann F. IVIG in autoimmune disease - Potential next generation biologics. *Autoimmun Rev*. 2016;15(8): 781-785.
24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.