Brentuximab-induced hand-foot syndrome in a patient with cutaneous T-cell lymphoma

Guy Shaposhnik, MS,a Sekwon Jang, MD,b and Jennifer A. DeSimone, MDa,b
Washington, D.C and Fairfax, Virginia

Key words: brentuximab vedotin; cutaneous T-cell lymphoma; drug eruption; drug reaction; hand-foot syndrome; oncologic therapy.

INTRODUCTION
Brentuximab vedotin (BV) is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody conjugated to microtubule-disrupting agent monomethyl auristatin E (MMAE) and is indicated in the treatment of cutaneous T-cell lymphomas (CTCL).1 The most widely reported side effect associated with BV therapy is peripheral neuropathy, affecting 67% of the patients.2 This report highlights a case of grade 3 hand-foot syndrome (HFS) developing in a patient with CTCL treated with BV.

CASE REPORT
A 36-year-old Hispanic man with a new diagnosis of stage 1B (T2, N0, M0, B1b) CTCL presented to a multidisciplinary clinic with multifocal, 5-15 cm, indurated, lichenified plaques covering approximately 30% of his body surface area, including the torso, extremities (sparking the hands and feet), scalp, neck, and with extensive involvement of the genitalia and perineum. The patient failed a 3-month trial of twice-daily high-potency topical steroids. He was uninsured, which precluded the use of phototherapy, topical nitrogen mustard, imiquimod, or oral bexarotene. Additionally, the genital distribution precluded the use of nonsteroidal topicals. We secured hospital-based coverage on a charity basis and initially treated the patient with pralatrexate 15 mg/m2 over 3 of 4 weeks. He had stable disease after 6 cycles. Approximately 3 months later, his lesions progressed, and he began BV 1.8 mg/kg every 3 weeks. After 3 infusions, he presented to the clinic with severe desquamation of the palms and soles, causing severe pain and limitation in activities of daily living (Figs 1 and 2).

Given his minimal response to BV and his severe adverse events (AEs), the brentuximab treatment was discontinued, and the patient received oral prednisone. Follow-up examination demonstrated complete resolution of both palmar and acral HFS, with full re-epithelialization and resolution of pain (Fig 3).

DISCUSSION
BV is a Food and Drug Administration-approved antibody-drug conjugate treatment for relapsed/refractory CD30+ CTCL. BV binds to cell-surface CD30 molecules and is internalized by endocytosis. A protease in lysosomes subsequently cleaves the conjugate molecule, releasing MMAE into the cytosol. MMAE is cytotoxic and induces cell-cycle arrest via inhibition of microtubule formation.1,3 The CD30 molecule is a transmembrane receptor that is highly expressed on the surface of various cancer cells, with low expression on nonmalignant cells.1 Given this mechanism of action and the favorable results in the international randomized phase III trial, ALCANZA, BV is an ideal treatment for CD30+ malignancies.5 Interestingly, BV has shown efficacy in patients with CTCL with varying levels of CD30.

From the Georgetown University School of Medicine, Washington, D.C.; and INOVA Schar Cancer Institute Melanoma and Skin Oncology Center, Fairfax.

Funding sources: None.

IRB approval status: Not applicable.

Correspondence to: Jennifer A. DeSimone, MD, Inova Health System, 8081 Innovation Park Drive 3rd floor, Administration Office, Fairfax, VA 22031. E-mail: Jennifer.a.desimone@gmail.com.

JAAD Case Reports 2022;21:123-5.

2352-5126 © 2022 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

https://doi.org/10.1016/j.jdcr.2021.12.032
Fig 1. Clinical presentation. Palmar desquamation on the left (A) and right (B) hand after brentuximab vedotin therapy.

Fig 2. Clinical presentation. Acral desquamation (A) and dorsal digital involvement (B) after brentuximab vedotin therapy.

Fig 3. Resolution of hand-foot syndrome after discontinuation of brentuximab vedotin and administration of oral prednisone therapy.
positivity, including patients like ours with <10%. In the ALCANZA trial the most common AE was peripheral neuropathy, occurring in 67% of patients in the BV group. Other AEs included nausea (36%), diarrhea (29%), and fatigue (29%).

HFS, or palmar-plantar erythrodysesthesia, occurs in approximately 2% of patients receiving chemotherapy.

The pathophysiology has not been fully elucidated; however, it is thought to be secondary to direct toxic injury to superficial and deep eccrine ducts, which are densely distributed in acral skin. The efficacy of BV relies on its internalization into target cells, trafficking to lysosomes, and cleavage of cytotoxic MMAE from its conjugate monoclonal antibody by cysteine proteases; therefore, a proposed mechanism for brentuximab-induced HFS is overaccumulation of cytotoxic MMAE in palmar and acral skin due to increased cleavage by lysosomal cysteine proteases. A literature review produced one reported case of HFS in a patient with Hodgkin lymphoma after a second infusion of BV, and a single reported case of grade 2 HFS in a patient with Sézary syndrome during BV therapy.

It is essential for dermatologists and oncologists to consider HFS as a potential AE in patients on immunotherapy so that decisions may be made to alter the course of oncologic treatment. We submit this report of a patient with Stage 1B CTCL developing grade 3 HFS during BV therapy.

Conflicts of interest
None disclosed.

REFERENCES
1. Alpdogan O, Kartan S, Johnson W, Sokol K, Porcu P. Systemic treatment of cutaneous T-cell lymphoma (CTCL). Chin Clin Oncol. 2019;8(1):10. https://doi.org/10.21037/cco.2019.01.02
2. Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician’s choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. Lancet. 2017;390(10094):555-566. https://doi.org/10.1016/S0140-6736(17)31266-7
3. Shea L, Mehta-Shah N. Brentuximab vedotin in the treatment of peripheral T cell lymphoma and cutaneous T cell lymphoma. Curr Hematol Malig Rep. 2020;15(1):9-19. https://doi.org/10.1007/s11899-020-00561-w
4. Jagadeesh D, Horwitz S, Bartlett NL, et al. Response to Brentuximab vedotin by CD30 expression: results from five trials in PTCL, CTCL, and B-cell lymphomas. J Clin Oncol. 2019;37(15_suppl):7543-7543. https://doi.org/10.1200/JCO.2019.37.15_suppl.7543
5. Sutherland MS, Sanderson RJ, Gordon KA, et al. Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-aursistatin conjugates. J Biol Chem. 2006;281(15):10540-10547. https://doi.org/10.1074/jbc.M510026200
6. Rehman JU, Kelta M, AlBeirouti B, Rashidhaider RG, Mohamed B. Brentuximab-induced hand-foot syndrome in a Hodgkin lymphoma patient. Ann Hematol. 2016;95(3):509-510. https://doi.org/10.1007/s00277-015-2538-1
7. Lewis DJ, Haun PL, Samimi SS, et al. Brentuximab vedotin for relapsed or refractory Sézary syndrome. JAMA Dermatol. 2021;157(3):317-321. https://doi.org/10.1001/jamadermatol.2020.4901