Leukemia Research Reports 20 (2023) 100380

Contents lists available at ScienceDirect

Leukemia Research Reports

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

Venetoclax monotherapy as front-line therapy for blastic plasmacytoid dendritic cell neoplasm

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ARTICLE INFO

Keywords:
Blastic plasmacytoid dendritic cell neoplasm
Venetoclax
Targeted therapy
Allogeneic hematopoietic stem cell transplantation

ABSTRACT

Venetoclax is an approved treatment for relapsed/refractory Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN). We report a unique case of venetoclax monotherapy used for front-line induction and as a bridge to allogeneic hematopoietic stem cell transplantation (HCT). Venetoclax therapy resulted in rapid complete resolution of skin lesions, however, treatment interruption due to neutropenia led to brisk cancer recurrence. Fortunately, the patient responded to re-challenge and was able to undergo HCT. Venetoclax is active in the first-line treatment setting for BPDCN, however its effect on blood counts and durability of response should be further studied.

1. Introduction

Blastic Plasmacytoid Dendritic Cells Neoplasm (BPDCN) is a rare and aggressive hematologic malignancy arising from precursors of plasmacytoid dendritic cells that commonly manifests as cutaneous lesions with or without marrow involvement [1]. The 2022 fifth edition of World Health Organization Classification of Haematolymphoid Tumors has classified BPDCN as a myeloid neoplasm with derivation from common myeloid progenitors that give rise to cells of monocytic/histiocytic/dendritic lineages [2].

BPDCN has an overall incidence rate of 0.04 cases per 100,000; however, it is most common in male patients over 60 [3]. BPDCN expresses sensitivity to B-cell lymphoma-2 (BCL-2) inhibition [4]. The diagnosis of BPDCN is established through immunophenotyping with expression of plasmacytoid dendritic cell markers including CD123, TCL1, BDCA2/CD303, and TCF4, and SPIB [5].

Front-line treatment generally includes chemotherapy or tagraxofusp [2], a CD123-directed cytokine consisting of recombinant human IL-3 fused to a truncated diphtheria toxin. Eligible patients receive consolidation with allogeneic or autologous hematopoietic stem cell transplantation (HCT). Given the sensitivity of BPDCN cells to BCL-2 inhibition, BH3 mimetics were evaluated as therapeutic treatment options. Venetoclax was found to displace pro-apoptotic proteins such as BCL-2 Interacting Mediator of Cell Death (BIM) from sequestration by BCL-2 and triggered apoptosis in BPDCN cells [4].

Venetoclax is a BCL-2 inhibitor that is FDA indicated for treatment of adult patients with chronic lymphocytic leukemia/small lymphocytic leukemia as well as in combination with a hypomethylating agent or low dose cytarabine for patients with acute myeloid leukemia who are more than 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy [6]. Since the initial report by Montero et al., several reports have documented the successful use of venetoclax in patients with refractory or relapsed BPDCN and in combination with other agents [7]. Here we describe a unique case of venetoclax used for the front-line treatment of BPDCN as a bridge to allogeneic HCT.

2. Case

A 50-year-old man, with a history of obstructive sleep apnea and essential hypertension, noticed painless and non-pruritic skin lesions comprised of two dominant skin lesions: a 1 × 1 cm lesion on the left flank and a 3 × 4 cm lesion on the back noted to be well demarcated with a dusky center, mamillated surface, with surrounding erythema. After unsuccessful trials of over-the-counter treatments, punch biopsy of the back lesion was carried out. Histologic section demonstrated atypical

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https://doi.org/10.1016/j.lrr.2023.100380
Received 5 January 2023; Received in revised form 30 May 2023; Accepted 1 July 2023
Available online 3 July 2023

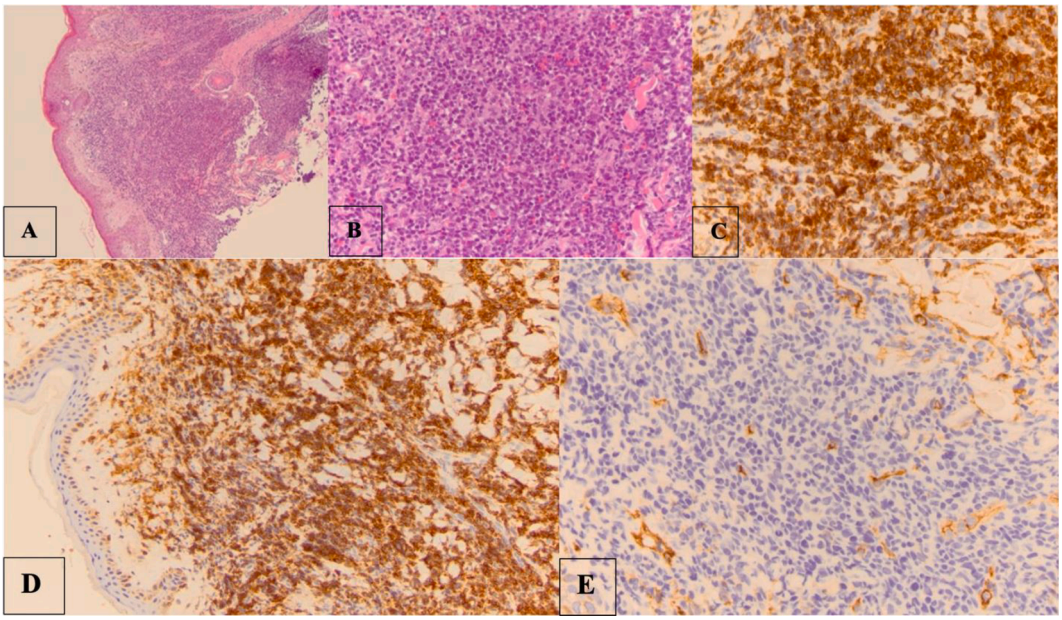

Fig. 1. (A-E). Histopathology. A: Hematoxylin & eosin (H&E) stained sections consist of skin shave biopsy demonstrating an atypical lymphoid infiltrate seen in a diffuse distribution within dermal and periadnexal spaces (10x magnification). **B:** Higher magnification shows diffuse lymphoid infiltrate is composed of atypical lymphoid cells that are intermediate to large in size which are blastic in appearance (40x magnification). **C:** CD56 immunohistochemistry is diffusely positive within neoplastic hematopoietic cells (40x magnification). **D:** CD123 immunohistochemistry shows diffuse membranous staining (20x magnification). **E:** CD34 immunohistochemistry is negative within neoplastic hematopoietic cells. CD34 highlights background vessels (40x magnification).

appearing interstitial infiltrate in the dermis with peri-adnexal accentuation and intermediate to large cells with blastic appearance. Immunohistochemical studies showed that the tumor cells were positive for terminal deoxynucleotidyl transferase (subset), CD43 (strong), CD123, CD56, and CD4, and negative for CD20, CD68, CD34, CD117, CD3, CD1a, CD8, myeloperoxidase, and muramidase. The findings were consistent with BPDCN (Fig. 1). The patient was staged as Ann Arbor Stage IV given cutaneous involvement. He had no constitutional symptoms. Laboratory evaluation was unremarkable except for a mildly elevated LDH 291 U/L (upper limit of normal 280 U/L). Bone marrow aspirate and biopsy did not support morphologic evidence of BPDCN involvement. Computed tomography showed no evidence of extracutaneous disease.

After lengthy discussion, a treatment decision in favor of venetoclax as initial therapy was made based on discussion of new data demonstrating efficacy of venetoclax [4] in conjunction with the patient's preference to avoid cytotoxic chemotherapy if possible. Venetoclax was ramped up to 400 mg daily dose by week 4 with grade 3 neutropenia leading to dose reductions. Complete resolution of skin lesions was quickly achieved without evidence of tumor lysis syndrome. Venetoclax was continued for 3 months, however again interrupted due to recurrent grade 3 neutropenia. During this interval of venetoclax interruption, rapid recurrence of the characteristic skin lesions on the back and chest developed, prompting restart of venetoclax at 100 mg daily. This rechallenge led again to clinical complete remission of skin lesions. At 5 months after initial start of venetoclax monotherapy, the patient underwent matched sibling allogeneic peripheral blood HCT with reduced-intensity fludarabine (40 mg/m^2 x 4 doses) and busulfan (130 mg/m^2 x 2 doses) conditioning with tacrolimus (target trough 8–12 ng/mL) and mini-methotrexate (5 mg on Day +1, +3, +6, and +11) graft-versus-host-disease (GVHD) prophylaxis. Venetoclax was discontinued at transplant admission. The early post-HCT course was unremarkable, without evidence of acute GVHD or opportunistic infection. However, at Day+107, the characteristic skin lesions once again

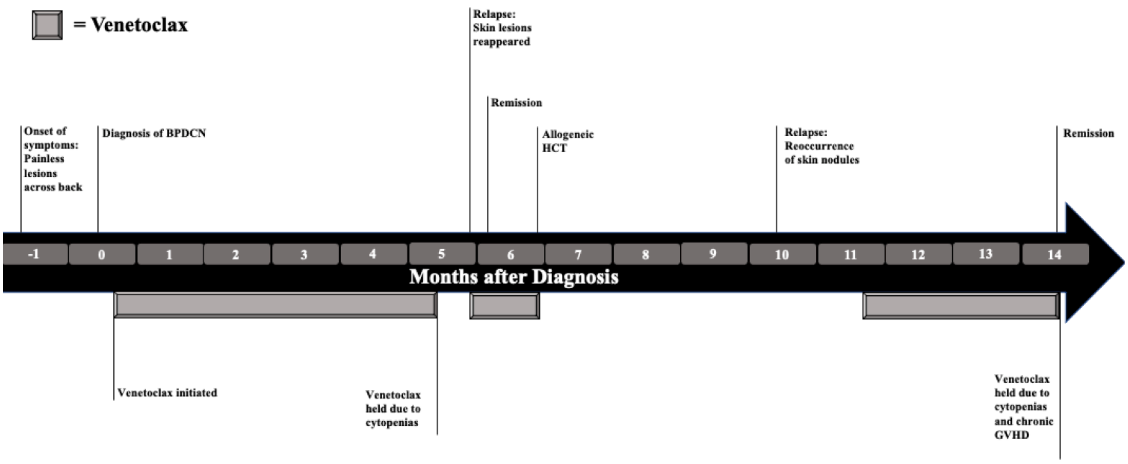

Fig. 2. Timeline of events from onset of symptoms to remission. BPDCN = blastic plasmacytoid dendritic cell neoplasm; HCT = hematopoietic cell transplant. GVHD = graft-versus-host disease.

recurred on the back. Repeat staging studies showed isolated skin involvement. Tacrolimus immune suppression was rapidly tapered off and venetoclax restarted at 100 mg daily. The skin recurrence disappeared, and the patient was again in complete remission by 3 months post-relapse. However, complications of neutropenia and chronic GVHD requiring systemic corticosteroid treatments led to discontinuation of venetoclax once more (Fig. 2). At more than 4 years post-HCT, the patient continues to be in clinical remission and has therefore not been re-challenged with venetoclax. He remains on minimal immune suppression for treatment of chronic GVHD of eyes, mouth and skin.

3. Discussion

BPDCN is an aggressive hematologic malignancy, typically distinguished by skin lesions with or without bone marrow involvement and potential leukemic dissemination. The current treatment paradigm includes chemotherapy or tagraxofusp-based induction followed by HCT in eligible patients. Venetoclax, a BCL-2 inhibitor, is an established treatment option in relapsed/refractory BPDCN.

This highlights a case of front-line induction treatment of BPDCN with venetoclax monotherapy resulting in complete remission and allogeneic HCT. Venetoclax treatment led to rapid clinical resolution of skin lesions; however, hematologic toxicity requiring dose adjustments and interruptions likely resulted in recurrence of skin lesions. Rechallenge with venetoclax was effective in resolving recurrent BPDCN lesions and allowed the patient to proceed to allogeneic HCT. The rapid recurrences while off-therapy raise questions about the depth of responses with venetoclax. Aggressive tapering of immunosuppression and post-HCT venetoclax monotherapy fortunately resulted in durable disease control, albeit complicated by chronic GVHD.

Venetoclax is a treatment option for patients with relapsed and refractory BPDCN [4,7–10], although published data are limited. Furthermore, there is very little data on the role of venetoclax in the front-line treatment of BPDCN. One case report described the use of venetoclax as front-line monotherapy for an 88-year-old patient with cutaneous BPDCN, with almost complete resolution of skin lesions by week 8 of therapy with 400 mg daily. The main complication of the therapy was transient neutropenia, which resolved with temporary suspension of venetoclax. This patient did not proceed to allogeneic HCT [10].

Venetoclax monotherapy, while effective as a bridge to allogeneic HCT as seen in our case, may be suitable in patients with limited performance status or significant comorbid risk factors. The durability of response as well as perceived lack of adequate central nervous system penetration are concerns with using venetolax monotherapy. To our knowledge, this is the first case report of venetoclax monotherapy as front-line therapy leading to allogeneic HCT. Prospective studies (NCT03485547) and multi-agent front-line studies are in progress.

4. Conclusion

Venetoclax is a promising therapeutic agent for BPDCN, although its hematologic toxicities require further study in this setting. Induction with chemotherapy or tagraxofusp followed by allogeneic HCT remains the standard of care for this rare and aggressive hematologic malignancy.

Declaration of Competing Interest

None.

Funding information

TPW is a K12 Scholar supported by the National Cancer Institute of the National Institutes of Health under Award Number K12CA226330. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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