INNOVATIONS JOURNALS

Case Report

Overcoming Tagraxofusp-Erzs Monotherapy Resistance in Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) in a Real-World Clinical Setting

Prajwal Dhakal[1,2] **Mario Sy**[1,2] **Grerk Sutamtewagul**[1,2] **Eric Mou**[1,2] **Nanmeng Yu**[1,2] **Naveen Pemmaraju**[3]

[1]Department of Internal Medicine, Division of Hematology, Oncology, and Blood & Marrow Transplantation, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[2]Holden Comprehensive Cancer Center, University of Iowa Carver College of Medicine, Iowa City, IA, USA
[3]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Address correspondence to Prajwal Dhakal (prajwal-dhakal@uiowa.edu).

Source of Support: None. Conflict of Interest: None.

Submitted: Nov 8, 2023; First Revision Received: Feb 25, 2024; Accepted: Feb 27, 2024

Dhakal P, Sy M, Sutamtewagul G, Mou E, Yu N, Pemmaraju N. Overcoming tagraxofusp-erzs monotherapy resistance in blastic plasmacytoid dendritic cell neoplasm (BPDCN) in a real-world clinical setting. *J Immunother Precis Oncol*. 2024; 7:205–209. DOI: 10.36401/JIPO-23-43.

ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and clinically aggressive hematologic malignancy with limited treatment options. Currently, standard treatment strategies include clinical trials; chemotherapy regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD); and tagraxofusp-erzs (TAG, previously SL-401) which is the first-in-class targeted therapy against CD123. TAG received Food and Drug Administration approval for frontline BPDCN treatment in December 2018 and has increasingly become an alternative to chemotherapy, offering potentially more effective and less toxic options. However, despite promising results, there are still patients who may be resistant to TAG monotherapy and/or who respond but eventually relapse. Herein, we discuss an important patient case of BPDCN treated with TAG and review BPDCN treatment strategies.

Keywords: blastic plasmacytic dendritic cell neoplasm, tagraxofusp-erzs, antiCD123 targeted therapy, venetoclax, IMGN632

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and clinically aggressive malignancy comprising 0.44% of all hematological malignancies and 0.7% of cutaneous lymphomas.[1–3] A Surveillance Epidemiology and End Results database study reported overall incidence of BPDCN as 0.4 cases per 100,000 population in the United States.[4]

Previously, BPDCN has had several different names, but its recognition and diagnosis have improved since the World Health Organization (WHO) established specific diagnostic criteria in 2008.[5] Despite recognizing more cases after WHO classification, the prognosis continued to be poor, characterized by aggressive involvement of multiple organ systems, including hematologic, lymphatic, dermatologic, and the central nervous system (CNS), as there was no standard of care treatment.[6] Most treatment plans were assembled from combination chemotherapy regimens adopted from acute lymphoblastic leukemia, acute myeloid leukemia, and lymphoma. The goal for eligible patients has been to achieve complete remission (CR) with chemotherapy followed by an allogeneic hematopoietic cell transplant (alloHCT). However, many cases were chemo-refractory, and even if they responded initially, the disease relapsed frequently. In addition, many patients with BPDCN were ineligible for intensive chemotherapy and alloHCT, as more than half of patients are 70 years or older with multiple comorbidities, conferring a worse prognosis in this population.[7–10]

Recently, significant progress has been made in understanding BPDCN, with a crucial breakthrough being the identification of CD123 (IL3Rα) as a promising therapeutic target.[11,12] This led to the development of tagraxofusp-erzs (TAG, previously SL-401), the first-in-class targeted therapy against CD123.[13] Initial studies in patients with BPDCN yielded encouraging and durable responses, prompting the initiation of a multicenter open-label phase II clinical trial involving patients with both frontline and relapsed/refractory (R/R) BPDCN.[13,14] In the frontline

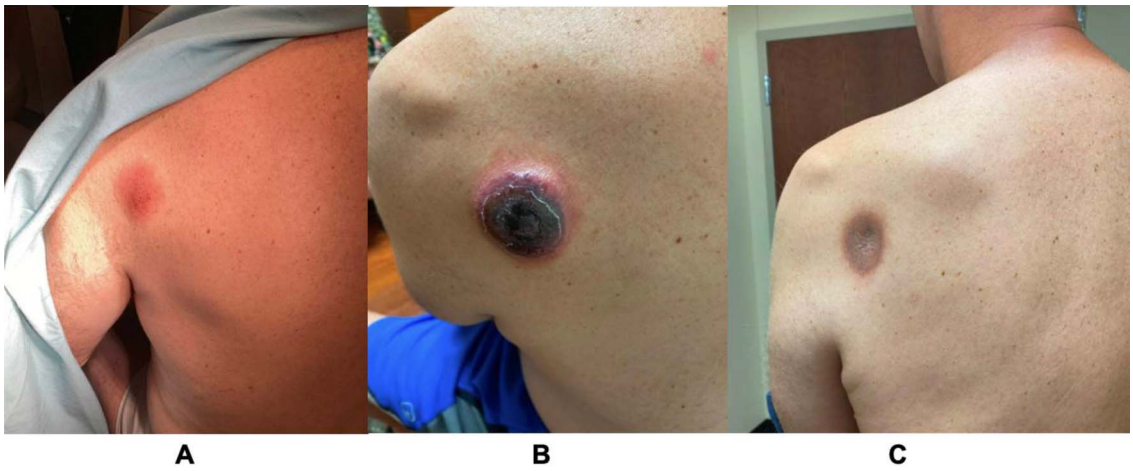

Figure 1. Skin lesion. (A) Baseline. (B) After two cycles of single-agent tagraxofusp-erzs. (C) After one cycle of tagraxofusp-erzs + azacitidine + venetoclax combination.

setting, the clinical trial demonstrated a complete response rate of 72%, with 45% of those patients subsequently able to undergo transplantation.[14] The 2-year overall survival (OS) was 52%. In R/R patients, 67% of patients achieved either CR with or without hematologic recovery or partial response, and the median OS was 8.5 months.[14] In December 2018, TAG received Food and Drug Administration approval for the treatment of BPDCN in frontline setting patients aged 2 or older. Since then, it has been increasingly utilized as an alternative to chemotherapy because of its promising results and the potential to offer more effective and less toxic treatment options for patients with BPDCN.[15,16]

Here, we discuss an interesting case of BPDCN treated with TAG and review BPDCN treatment strategies. The patient provided informed consent to publish his details in this case report.

CASE DESCRIPTION

A 65-year-old man with a history of solitary fibrous tumor was referred to our dermatology clinic in January 2023 because of a skin lesion on the left posterior shoulder, which had been present for several months (Fig. 1A). The skin lesion initially appeared as a simple patch measuring 2 cm in diameter, and it was decided to monitor without any treatment. In February 2023, a biopsy of the lesion was performed out of concern for metastatic solitary fibrous tumor.

The patient's medical history included a diagnosis of a brain tumor in 2006, which had been treated with surgical resection and whole-brain radiation therapy. However, the histological analysis of the resected mass did not yield a definitive diagnosis. For several years, the patient remained without apparent cancer-related concerns until July 2019, when bilateral acetabular fibrous lesions were identified, considered metastatic from the brain. Biopsy of these lesions confirmed solitary fibrous tumor, leading to the initiation of treatment with temozolomide and bevacizumab. Subsequently, the patient underwent resection of the right acetabular lesion with the placement of a right hip prosthesis (July 2019) followed by radioablation and cementoplasty of the left acetabular metastatic lesion (October 2019). A progressive left acetabular mass was managed with radiation therapy (April 2022). Other lesions, including right posterior pleural soft tissue implants, bilateral pulmonary nodules, and a right rib pathological fracture, were closely monitored with imaging without active treatment.

Initial diagnostic findings with the skin lesion raised concerns about malignant hematolymphoid neoplasms such as BPDCN, NK/T-cell lymphoma, mycosis fungoides, and peripheral T-cell lymphoma. Further staining revealed that atypical cells were positive for CD45, CD43, BCL2, C-MYC, CD2 (weak), CD4, CD7, CD123, and CD56, ultimately confirming the diagnosis of BPDCN in March 2023. To assess the extent of the disease, a positron emission tomography/computed tomography (PET/CT) scan was performed, revealing a hypermetabolic skin lesion on the left scapula, left axillary lymphadenopathy, large soft tissue masses on the left psoas and iliacus muscle, and small lung nodules (Fig. 2A). The left scapular lesion and axillary lymphadenopathy were indicative of BPDCN involvement, while the soft tissue mass in the left psoas and iliacus region was consistent with solitary fibrous tumor, which had decreased in size since the previous year. The lung nodules, present for more than a year and slowly growing, were likely solitary fibrous tumors rather than BPDCN. The patient's complete blood count remained within normal limits, and bone marrow biopsy did not reveal malignancy on immunohistochemistry and flow cytometry, with a normal karyotype and fluorescence in situ hybridization (FISH) analysis. Mutation testing identified *ASXL1* and *NRAS* mutations. Cerebrospinal fluid analysis showed no malignant cells.

The patient was initiated on treatment with TAG in April 2023. He tolerated the treatment well with no serious side effects including capillary leak syndrome and tumor lysis syndrome. A posttreatment PET/CT showed a slight

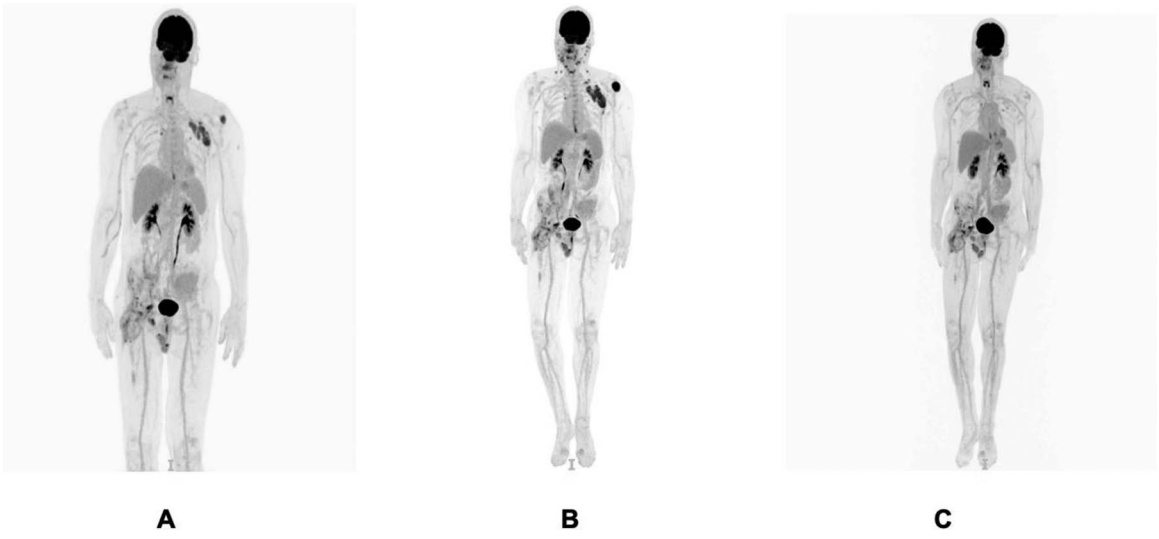

Figure 2. Positron emission tomography/computed tomography scan. (A) Baseline. (B) After two cycles of single-agent tagraxofusp-erzs. (C) After one cycle of tagraxofusp-erzs + azacitidine + venetoclax combination.

increase in fludeoxyglucose (FDG)-avidity and the size of the previous lymphadenopathy. With no new disease sites and no significant concerns about disease progression, he received the second cycle in May 2023. However, after the second cycle, the left scapular skin lesion increased in size from a maculopapular lesion to a larger nodule 4 cm in diameter (Fig. 1B). PET/CT scan also indicated progressive disease, with an increase in lymphadenopathy in the left axilla and cervical area (Fig. 2B). Peripheral blood counts remained within normal limits, but 1.7% blasts were identified. Bone marrow biopsy, which was negative at the time of diagnosis, revealed 0.7% blasts, and cytogenetics showed a positive *MYC* break-apart rearrangement. Mutation analysis showed *ASXL1, NRAS,* and *IDH1* mutations, indicating dynamic acquisition of *IDH1* mutation that was not present initially at diagnosis. In addition, cerebrospinal fluid analysis was now positive for malignant cells.

Given the progression of the disease despite two cycles of TAG, a triplet regimen was initiated in the off-protocol setting by adding azacitidine and venetoclax to TAG in June 2023. Intensive chemotherapy similar to that used in acute lymphoblastic leukemia and acute myeloid leukemia was not considered because of concerns about increased toxicity and patient's overall performance status. alloHCT was discussed but deemed inappropriate due to the presence of another active metastatic malignancy. The triplet regimen consisted of azacitidine 75 mg/m^2 on days 1–7, venetoclax 400 mg daily on days 1–21 (with a ramp-up from 100 mg to 400 mg on days 1–3 in the first cycle), and TAG 12 μg/kg on days 4–6, administered in 28-day cycles. The patient received intrathecal (IT) chemotherapy, alternating between methotrexate 12 mg and cytarabine 70 mg, to manage CNS involvement. IT chemotherapy was administered twice weekly for two doses after which cerebrospinal fluid analysis showed no malignant cells. We initially scheduled IT chemotherapy once a week for four doses after blast clearance and then one per cycle. However, following the first IT chemotherapy post-blast clearance, the patient experienced severe headache, nausea/vomiting, and dizziness. Subsequently, he decided against receiving any further IT chemotherapy. The skin lesion also improved significantly (Fig. 1C). PET/CT after the first cycle of the triplet regimen indicated a complete response in the extensive cervical and left axillary nodal disease and the left shoulder lesion (Fig. 2C). Peripheral blood counts were normal without any blasts.

The patient continued with the triplet regimen and completed cycle 2. Repeat PET/CT scans showed no evidence of progressive disease with BPDCN, and findings related to solitary fibrous tumor remained stable. Bone marrow biopsy indicated CR, although the mutation panel continued to show ASXL1, IDH1, and NRAS mutations. Biopsy of the left scapular lesion was also negative for BPDCN involvement. The patient is currently continuing treatment with the triplet regimen and has recently completed cycle 4.

DISCUSSION

Our interesting case helps us learn more about BPDCN, its typical and atypical characteristics, and treatment strategies and concerns.

The median age for diagnosis of BPDCN is 68 years, and nearly half of patients with asymptomatic skin lesions.[1,6] These skin lesions can vary widely, ranging from solitary or multiple patches, to plaques, nodules with erythema, hyperpigmentation, purpura, or ulceration. Additional involvement of bone marrow, blood, lymph nodes, spleen, liver, and CNS are also reported in a significant proportion of patients.[6] In this case, the presentation of a 65-year-old patient with a skin lesion and regional lymphadenopathy is in line with the typical clinical features of BPDCN.

Notably, at the time of diagnosis, there was no involvement of the bone marrow or CNS, but these sites became affected within a few months, underscoring the aggressive nature of BPDCN. Another noteworthy aspect is the delay in the initial diagnosis and treatment initiation because of the absence of a definitive single test for BPDCN and need for multiple less commonly used stains to establish the diagnosis. This delay in diagnosis, which can happen in many cases in real-world practice, may have contributed to the development of a more aggressive, TAG-resistant disease in our case. An intriguing fact is the coexistence of a solitary fibrous tumor, which had been diagnosed more than 17 years before the BPDCN diagnosis. This co-occurrence raises questions about potential underlying genetic factors or mechanisms that may predispose individuals to BPDCN. However, as of now, no specific genetic factors associated with BPDCN predisposition have been identified. Genetic testing was discussed with the patient, but he declined further evaluation.

Similar to our case, CNS involvement has been reported frequently in BPDCN, both historically, and in the recent modern targeted therapy era.[6,17] In one study by Pemmaraju et al.,[6] the incidence of CNS involvement was 20–30%, indicating likely poor penetrance of the newer targeted drugs through the blood-brain barrier. Many patients in the study did not have neurological symptoms indicating occult involvement and the need to evaluate CNS involvement at diagnosis. Thus, routine lumbar puncture with IT chemotherapy at diagnosis is recommended in all patients with BPDCN.[18,19]

BPDCN treatment remains a challenge despite the increasing use of targeted therapy. Currently, common treatment options include clinical trials, TAG, and chemotherapy regimens such as HCVAD. Improvements are needed in selecting optimal frontline treatment therapy and effective treatment strategies for relapsed or refractory cases. TAG has changed the treatment landscape for BPDCN over the past 5 years either as a frontline therapy or in combination with other chemotherapy or targeted therapy. Long-term follow-up of the clinical trial in TAG showed an overall response rate of 75% in treatment-naïve patients with 57% achieving CR or clinical CR.[16] Fifty-one percent of patients who achieved CR or clinical CR proceeded to alloHCT.[16] However, it is important to note that almost one-fourth of cases, similar to our patient, exhibited resistance to single-agent TAG. No specific treatment regimens exist for patients with R/R disease, which is one of the unmet needs in BPDCN. In our case, we proceeded with a triplet regimen of TAG, azacitidine, and venetoclax, which proved to be effective, resulting in CR after just one cycle.

Hypomethylating agents, decitabine or azacitidine, in combination with venetoclax have demonstrated successful outcomes in BPDCN, particularly in older patients or those unfit for intensive cytotoxic chemotherapy such as HCVAD.[20–22] Prior studies have reported that TAG resistance is mediated by DNA methylation, which can be reversed by azacitidine, and TAG plus azacitidine combination is more effective than TAG alone, as supported by xenograft models.[23] In addition, the antiapoptotic gene BCL-2 is highly expressed in BPDCN, thus making BPDCN highly sensitive to BCL-2 inhibition with venetoclax.[24] These findings provide the rationale for using the combination of TAG, azacitidine, and venetoclax, which resulted in a prompt response in our case despite initial resistance to TAG. In addition, the impressive response to the triplet regimen, despite predominantly extramedullary disease, underscores the consideration of combination chemotherapy for all patients with BPDCN to reduce R/R cases. Currently, there is an ongoing phase Ib clinical trial investigating the effects of TAG in combination with azacitidine and venetoclax in patients with acute myeloid leukemia, myelodysplastic syndrome, and BPDCN (NCT03113643). An abstract presented at the American Society of Hematology annual meeting in 2021 reported that three patients with R/R BPDCN, all of whom had previously received single-agent TAG, received TAG-azacitidine-venetoclax combination, and two of three responded with CR with incomplete count recovery and clinical CR. Both patients proceeded to alloHCT.[25] Another clinical trial investigating combination therapy involving TAG, HCVAD, and venetoclax is currently under way (NCT04216524).

All patients with BPDCN, regardless of the treatment regimen, should be considered for alloHCT, as it confers the best chance of cure and longer survival benefit than other treatment strategies.[9,10,26] Patients treated with TAG or alternative chemotherapy regimens only without alloHCT subsequently relapse with worse prognosis. A large database analysis of 164 patients with BPDCN who underwent alloHCT reported 5-year OS of 51%; alloHCT at the first CR yielded the most favorable outcomes. Age should not be the barrier to undergo alloHCT, and all patients with good functional status and no major comorbidities should be evaluated.

IMGN632, another CD123 antibody-drug conjugate, has received Food and Drug Administration breakthrough designation for R/R BPDCN. In a cohort of 23 heavily pretreated patients, nearly half of whom had prior exposure to anti-CD123 targeted therapy, the overall response rate was 30%.[27] A clinical trial studying IMGN632 in treatment-naïve and R/R patients is ongoing (NCT03386513). Chimeric antigen receptor (CAR) T-cell therapy targeting CD123 represents an exciting treatment option that is currently under investigation in early-phase clinical trials (NCT02159495, NCT04109482, NCT04318678, NCT03203369). Other novel strategies in clinical trials include CAR natural killer cells against CD123 (NCT06006403) and rapidly switchable universal CAR-T therapy, UniCAR02-T cells in combination with CD123 Target Module (TM123) (NCT04230265). Potential future treatment strategies may include bispecific antibodies targeting CD123, proteasome inhibitors, bromodomain inhibitors, checkpoint inhibitors against programmed death ligand 1, and targeted agents directed against CD56, ILT3, HA-1H, and CD303.[3,28]

CONCLUSION

Despite recent advancements, there are still numerous aspects of BPDCN that require clinical-translational investigation and further pathobiological understanding. A multidisciplinary team, comprising hematologists, dermatologists, and pathologists, is crucial for ensuring prompt diagnosis and treatment to prevent the progression of drug-resistant disease. Although TAG has emerged as the standard of care, the prevalence of R/R disease underscores the urgent need for enhanced strategies to improve overall outcomes.

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