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Challenges and practical considerations in the management of blastic plasmacytoid dendritic cell neoplasm: A single-center experience

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ABSTRACT

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare and often life-threatening complex hematologic malignancy that can commonly infiltrate the skin, lymph nodes, central nervous system, and bone marrow. In the setting of the infrequency of confirmed diagnoses of BPDCN, and given limited prospective studies, it has been associated with lackluster outcomes with a median overall survival between 9 and 23 months. We herein discuss our experience treating five consecutive patients with BPDCN at our center since the approval of TAG. We also present some of the challenges that face oncology providers treating this disease due to exceptional rarity and aggressive nature of this disease in addition to overall limited experience and effective therapies

1. Introduction

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare and often life-threatening complex hematologic malignancy that can commonly infiltrate the skin, lymph nodes, central nervous system, and bone marrow. It is characterized by aberrant transformation of the precursor plasmacytoid dendritic cells, which are generally identified by expression of certain pathologic markers including CD4, CD56, CD123 and TCL-1 [1,2]. BPDCN makes up <0.5 % of all newly diagnosed hematologic malignancies annually in the US[3] with an unknown true incidence due to, in part, known diagnostic challenges over the last several years [3]. Historically, it has been associated as predominantly affecting men with median age at diagnosis in the mid 60′s-70s[2] [4],.

In the setting of the infrequency of confirmed diagnoses of BPDCN, and given limited prospective studies, it has been associated with lackluster outcomes with a median overall survival between 9 and 23 months [5]. Treatment routinely consisted of conventional chemotherapy, followed by allogeneic hematopoietic stem cell transplantation (Allo-HSCT) in medically fit patients with suitable donors. Intensive regimens for acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) such as combination of anthracycline plus cytarabine (7+3), or combination of fludarabine, cytarabine, granulocyte colony stimulating factor, and idarubicin (FLAG-IDA) or hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high dose methotrexate and cytarabine (HyperCVAD) have all been used in patients who can tolerate intensive therapies [6,7]. Based on retrospective data, patients treated with ALL based regimens may have slightly better overall survival (OS) compared to AML regimens (8.7 months versus 7.1 months respectively) [8]. Nevertheless, despite having initial responses rates in the range of 41–94 %, approximately 80 % of the patients will experience relapse and have very poor outcomes subequently [9]. In those patients who are medically fit, allo-HSCT can have an estimated OS of 68 % and 58 % at 1-year and 3-year respectively [10]. Besides allo-HSCT, the most notable progress in the treatment of this disease has been the development of the CD-123 targeted immunotoxin, tagraxofusp (TAG) [7]. Initial phase I/II study showed an overall response rate of 90 % with complete response in 54 % of the patients [11]. Furthermore, about half of the patients were able to undergo allo-HSCT, and OS at 2 years was about 52 %. The drug was associated with multiple toxicities including transaminitis, peripheral edema and capillary leak syndrome. In addition to close monitoring of complete blood tests, liver function tests, serum chemistries, physicians must be aware of capillary leak syndrome and hypoalbuminemia that can occur in up to 50 % of the patients [8,11]. TAG received FDA approval for the treatment of BDPCN in 2018.

We herein discuss our experience treating five consecutive patients with BPDCN at our center since the approval of TAG (Table 1). We also present some of the challenges that face oncology providers treating this

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disease due to exceptional rarity and aggressive nature of this disease in addition to overall limited experience and effective therapies. This study was approved by the IRB committee at our center.

2. Patient case #1

A 65-year-old male presented with a soft tissue mass in the left neck and later underwent an excisional biopsy at an outside hospital. Immunohistochemistry stains performed showed that the malignant cells were positive for CD 43, CD68, CD 123, and TCL-1 consistent with new diagnosis of BPDCN. Bone marrow biopsy was done and also showed involvement by the disease. He was treated with HyperCVAD with intrathecal chemotherapy and was able to achieve remission. He then underwent Allo-HSCT from his sibling and his course was complicated by graft versus host disease requiring prolonged treatment with steroids, mycophenolate mofetil, and later sirolimus. He was in remission for about 5 years but ultimately had disease recurrence. Patient decided to transfer care to outside institution to receive treatment with TAG in addition to clinical trial evaluation.

3. Patient case #2

A 76-year-old man presented with fatigue and several large left skin leg lesions and was found to have WBC of 50,000. He underwent a bone marrow biopsy which showed extensive involvement by blastoid cells that were positive CD303, CD123, and TCL1. He also underwent a skin biopsy which showed a dermal infiltrate of monotonous immature appearing atypical cells that were positive for CD4, CD45, CD123, CD303, and TCL-1, consistent with BPDCN. Subsequent CSF analysis demonstrated involvement by malignant cells. PET CT showed mildly FDG-avid lymphadenopathy above and below the diaphragm, and hypermetabolic splenomegaly. He was diagnosed with BPDCN involving the skin, bone marrow, lymph nodes and central nervous system.

The patient was started on TAG and intrathecal chemotherapy and tolerated 10 cycles before developing capillary leak syndrome that was managed successfully. Due to age and the presence of other comorbidities, he was not felt to be an eligible candidate for Allo-HSCT. Unfortunately, patient had disease relapse and was switched to azacitdine with venetoclax but passed after 2 cycles due to disease and associated complications.

4. Patient case #3

A 70-year-old gentleman with no significant past medical history presented to the dermatologist's office with complaints of chronic fatigue and several large, raised, erythematous and purplish skin lesions on bilateral upper extremities. He underwent a biopsy of the skin lesions which showed cells that were strongly positive for CD 123, as well as CD45, CD43, CD4, CD56, and TdT, consistent with BPDCN. His PET CT scan was negative for other signs of disease and CSF analysis was negative for malignant cells. He was started on treatment with TAG with improvement in skin lesions after 1 cycle. He completed 3 cycles of treatment and repeat bone marrow showed a partial response. The patient was then switched to HyperCVAD and venetoclax salvage therapy and was able to achieve complete remission. Due to age and comorbidities he was not a candidate for Allo-HSCT and instead he underwent autologous stem cell transplantation followed by maintenance therapy with venetoclax. He was in remission until about 10–12 months but eventually developed relapsed disease in the skin and bone marrow. He passed away shortly after from complications.

5. Patient case #4

An 88-year-old male with atrial fibrillation on chronic anticoagulation was transferred from an outside hospital for a newly diagnosed acute leukemia after presenting with fatigue, and chest discomfort and found to have WBC of 116,830, with 93,460 blasts in addition to anemia and thrombocytopenia.

Bone marrow biopsy showed abnormal cells expressing CD4, CD123, CD56, and TCL1 consistent with BPDCN. The patient was planned to start TAG with intensive clinical monitoring in the inpatient setting. However, his hospital course was complicated by acute kidney injury secondary to tumor lysis syndrome and E.coli bacteremia with fast clinical decline and so he decided to not pursue any cancer therapies and subsequently passed away shortly after while in hospice care.

6. Patient case #5

A 64-year-old man with history of hypertension presented to his dermatologist with a growing flat purple lesion on his forehead without any associated systemic symptoms. He underwent a biopsy of the lesions which showed cells that were positive for CD 123, CD4, and TCL-1, consistent with BPDCN. He was noted to have multiple other skin lesions with biopsies showing both basal cell carcinoma and BPDCN. No other sites of disease were otherwise noted including on bone marrow biopsy, PET imaging and CSF analysis. The patient was started on therapy with TAG and prophylactic IT chemotherapy which he tolerated well for 6 cycles prior to progression in the skin and bone marrow. He was then switched to HyperCVAD and venetoclax with dose modifications due to age and tolerated 2 cycles well with partial response. He is currently getting ready to undergo Allo-HSCT from fully matched unrelated donor.

7. Discussion

We present 5 consecutive cases of patients with BPDCN treated in the "real-world setting" – i.e., non-clinical trial approaches with standard therapies, notably, in the setting of five years post-TAG approval from the completion of the original clinical trial led by Pemmaraju et al. [11]. Collectively, these patient cases illustrate : 1)the feasibility of delivering TAG outside of the clinical trial sites first involved in the original studies; 2) the ability to deliver TAG in the setting of elderly patients with

Table 1
Patients with BPDCN treated at our center over the last 5 years.

Case	Age at time of diagnosis	Sex	Organs involved by disease	Treatment Summary	Best response	Status at last follow up
Patient 1	65	Male	Soft tissue mass in the neck, bone marrow	HyperCVAD Allo-HSCT	Remission for approximately 5 years	Deceased from disease and associated complications
Patient 2	76	Male	Skin, bone marrow, CNS and lymph nodes	Tagroxofusp Azacitidine with venetoclax	Remission for approximately 1 year	Deceased from disease and associated complications
Patient 3	70	Male	Skin, bone marrow	Tagroxofusp HyperCVAD with venetoclax Autologous HSCT	Remission for approximately 1 year.	Deceased from disease and associated complications
Patient 4	88	Male	Bone marrow	Declined cancer therapies due to age and clinical status	Progressive disease	Deceased from disease and associated complications
Patient 5	64	Male	Skin, bone marrow	Tagraxofusp HyperCVAD with venetoclax (dose reduced)	Partial remission	Alive in partial remission, planned for allo-HSCT

"real-world" co-morbidities, in some cases, not directly included or studied on the original studies and 3)demonstration of treating BPDCN with non-CD123-directed therapies and 4)demonstration of the clinically aggressive nature of BPDCN if left untreated or even with multi-agent chemotherapy and allo-HSCT in some settings. It is of foremost importance to familiarize oneself with clinical presentation of BPDCN and expedite appropriate work up. As advancements in diagnostic modalities including immunohistochemistry and flow cytometry grow, we can better differentiate BPDCN from AML with cutaneous involvement and reactive plasma dendritic cells. In a rare disease with evolving treatment options, it is not only important to have a timely diagnosis, but also to initiate proper front line treatment as soon as possible. In the past, treatment options were only limited to chemotherapy which carried several side effects, especially in the elderly population, but with the introduction of the novel treatment, TAG, complete responses, or clinical complete response rates are superior with longer follow up data showing no new safety concerns and manageable safety profile. As the use of TAG increases outside of clinical trials, recognizing the adverse effects is crucial in the management of the patient; this includes capillary leak syndrome which requires awareness of all stakeholders involved, advanced planning by the care team which can be done with notice and preparation to plan for intensive clinical monitoring and immediate treatment with aggressive diuresis and respiratory support while awaiting recovery [12,13].

The role of consolidation with allo-HSCT is also important to highlight, ideally after achieving response to initial chemotherapy or novel therapies. CIBTMR analysis conducted by Murthy and colleagues showed that in patients who underwent allo-HSCT, the 5-year OS was 51.2 % [9]. In patients who underwent allo-HSCT after first complete remission the progression free survival (PFS) was 85 % at 3 years compared with 55 % in those who did not undergo transplantation [14]. Moreover, the median PFS was superior in patients who underwent allo-HSCT at initial remission compared to later in the disease course [9, 15–17]. Similarly, the 3-year-OS rate was 52 % in patients who underwent allo-HSCT in first remission, compared with 29 % in those patients transplanted later in the clinical course. Therefore, patients must be referred for an allo-HSCT evaluation earlier in the treatment course as it remains one of the most effective therapies available for this disease.

While there have been excellent headways in the understanding and management of BPDCN, more data is required to improve overall survival of our patients, especially in those with suspected CNS disease and cardio-pulmonary co-morbidities, which are increasing quite commonly recognized in patients with BPDCN [16]. Through our case scenarios, we hope to elucidate the current natural history of an aggressive and uncommon malignancy.

CRediT authorship contribution statement

Haripriya Andanamala: Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Naveen Pemmaraju:** Conceptualization, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Taha Al-Juhaishi:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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