

Recent developments in the treatment of blastic plasmacytoid dendritic cell neoplasm

Minas P. Economides¹, Marina Konopleva and Naveen Pemmaraju

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Abstract: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive hematologic malignancy derived from precursors of dendritic cells and involves most frequently the skin, bone marrow and lymph nodes. Diagnosis depends upon identification of specific tumor markers including CD4, CD56 and CD123. Historically, the median survival has been less than 2 years in most reported series. While for many years, conventional chemotherapy followed by stem cell transplantation was the standard of care, recently tagraxofusp, a cytotoxin directed against CD123, received United States Food and Drug Administration approval specifically for patients with BPDCN. In this review, we will discuss the markers used for diagnosis of BPDCN and focus on the new targeted treatments available. Specifically in BPDCN, tagraxofusp was highly effective with a safety profile found to be acceptable overall, with the noted occurrence of capillary leak syndrome. Future directions in therapy approaches for patients with BPDCN will include the development of other CD123-targeted agents, agents targeting beyond CD123 and investigation of rational combination approaches of CD123-directed therapy with other therapies.

Keywords: BPDCN, CAR T-cells, stem cell transplantation, tagraxofusp, venetoclax

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Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a historically rare, but clinically aggressive hematologic malignancy that most commonly manifests with cutaneous lesions with or without bone marrow involvement and often, lymph node involvement.¹ BPDCN is usually associated with transformation to acute leukemia and poor outcomes.² One of the earliest modern descriptions of BPDCN was in 1995, with the name ‘acute agranular CD4-positive natural killer cell leukemia’ but the name for this disease has changed numerous times, adding to difficulty in identifying BPDCN over time.³ As per the World Health Organization (WHO) 2008 guidelines, it was originally classified as a member of the acute myeloid leukemia (AML)/related family neoplasms;⁴ however, greater understanding of the disease biology following the discovery that BPDCN may originate from type 2 dendritic cells (plasmacytoid), classification under WHO 2016 guidelines allowed

BPDCN to be named in its own category among myeloid malignancies.¹

The exact incidence of BPDCN is unknown but may represent 0.5% of all hematologic malignancies.⁵ It has been described in both sexes and all age groups but is most common in male adults over 70 years old.^{6–8} BPDCN can occur as a primary malignancy or in the context of other hematologic neoplasms. Approximately 10–20% of patients have a previous or concomitant history of hematological malignancies including myelodysplastic syndrome, chronic myelomonocytic leukemia and known high transformation rates to AML.^{5–7} Clinically, BPDCN most commonly affects the skin, followed by the bone marrow and lymph nodes, with other extramedullary sites also frequently involved. While there is no dominant cytogenetic lesion characterizing the disease, the most commonly observed mutations include *TET2*, *ASXL1*, *RAS* and *TP53*; the classic triad of tumor markers that helps identify the disease includes

Correspondence to:
Naveen Pemmaraju
Department of Leukemia,
The University of Texas MD
Anderson Cancer Center,
1515 Holcombe Boulevard,
Houston, TX 77030, USA
npemmaraju@mdanderson.org

Minas P. Economides
Department of Internal
Medicine, The University of
Texas School of Health
Sciences at Houston,
Houston, TX, USA

Marina Konopleva
Naveen Pemmaraju
Department of Leukemia,
The University of Texas MD
Anderson Cancer Center,
Houston, TX, USA

CD4, CD56 and CD123. The overexpression of CD123 or interleukin-3 receptor subunit alpha (IL3RA) occurs in essentially all cases of BPDCN.⁹⁻¹¹ In addition, specific plasmacytoid dendritic cell-associated antigens (CD303, TCF4, TCL1 and CD2AP) and transcription factors (TCF4) can help establish the diagnosis and exclude diseases that present similarly to BPDCN.¹²⁻¹⁶ Specifically, exclusion of other lineage-specific antigens, such as AML markers (MPO, CD13, CD64), B-cell acute lymphocytic leukemia (ALL) markers (B-CD19, B-CD20, B-CD79a) and T-cell ALL markers (TcytCD3), is important for the diagnosis of BPDCN. Due to the overlapping features of these diseases and the heterogeneity in clinical presentation, diagnosis still remains very challenging. In conclusion, a confident diagnosis can be made when four antigens among CD4, CD56, CD123, TCL1, CD303 and TCF4 are present, and other lineage-specific antigens are absent.^{7,13,16,17}

Although an initial response to chemotherapy is common, BPDCN continues to have very poor prognosis with most patients relapsing into drug-resistant malignancy with poor overall survival (OS).^{5,18-20} Therefore, new targeted agents have been developed recently with early encouraging results.²¹ In this paper, we will review the pathobiology of BPDCN, the current treatment and will focus on the current targeted therapies under investigation.

Genetics of BPDCN

Several genomic studies over recent years have begun to investigate the molecular basis of BPDCN.^{2,17,22-27} Most of these studies document that patients with BPDCN often have a complex karyotype, including frequent chromosomal losses (*5q*, *12p13*, *13q21*, *6q23-ter*, *9*), inactivation of tumor suppressors (*RB1*, *TP53*, *CDKN1B*, *CDKN2A*), activation of oncogenes (*KRAS*, *NRAS*, *HES6*, *RUNX2*, *FLT3*), mutations in epigenetic regulators (*TET2*, *TET1*, *DNMT3A*, *IDH1*, *IDH2*) and aberrant activation of the nuclear factor (NF)- κ B pathway (*BCL2* and *IRF4*). Bi-allelic loss of *9p21.3* has been, in some studies, associated with poor prognosis.²⁸

Current treatment

BPDCN has historically been a difficult disease to treat. We describe some of the current options in

clinical development and focus on the recently approved agent tagraxofusp.

Conventional cancer treatment

Surgical excision and radiation. In patients who present solely with skin manifestations, surgical excision and focal radiation has been studied previously.²⁹⁻³¹ Although these approaches are initially effective with often near-complete resolution of cutaneous lesions, systemic recurrence is common and this localized approach for treating patients, now recognized as a systemic malignancy, appears to be suboptimal, limited and mainly for palliative purposes.^{30,32}

Chemotherapy. In the absence of approved therapies and no consensus approach to treating patients, regimens used for other acute leukemias have long been used in the treatment of patients with BPDCN. In one of the largest retrospective case series, 43 patients with BPDCN received an acute leukemia-type regimen, including 26 cases (60%) of AML-type treatment and 15 cases (35%) with ALL-type treatment.⁵ The median OS was 8.7 months with estimated survival rates of 28% and 7% at 12 and 24 months respectively. Complete remission (CR) was achieved in 17 (41%) patients (7 after AML and 10 after an ALL-type regimen). Of the patients who achieved CR, 6 (35%) patients eventually relapsed at a median time of 9.1 months after diagnosis.⁵ The clinical benefit of using an ALL-type regimen in terms of response duration has also been shown in a cohort of 22 patients with BPDCN from Greece.³³ In addition, a CR rate of 90% has been reported from our group in 10 patients with BPDCN treated with HCVAD (hyper-fractionated cyclophosphamide, vincristine, adriamycin, dexamethasone/methotrexate and cytarabine) with a median duration of response of 19 months and a median OS of 29 months.³⁴ In a systematic review evaluating ALL-based regimens in BPDCN, the overall response rate was as high as 90%, but the durability of response was short. Median survival rates ranged between 12 and 16 months.³⁵

There is an active phase II clinical trial evaluating combination chemotherapy that consists of methotrexate, L-asparaginase, idarubicin and dexamethasone in patients with newly diagnosed BPDCN being conducted in France (ClinicalTrials.gov

Table 1. Current clinical trials for the treatment of BPDCN.

Agent	Mechanism of action	Eligible patients	Phase	NCT	Primary outcome
IDA/DEX/L-ASP/MTX	Multiple	Newly diagnosed BPDCN	II	NCT03599960	CR after three cycles
Tagraxofusp	CD123i	AML, BPDCN	II	NCT02113982	Safety, efficacy
IMGN632	ADC	R/R AML, ALL, BPDCN	I	NCT03386513	MTD
XmAb14045	MAb	CD-123 expressing heme malignancies	I	NCT02730312	Safety
Venetoclax	BCL-2i	BPDCN	I	NCT03485547	Dose-limiting toxicity
UCART123	CAR T	BPDCN	I	NCT03203369	Safety

ADC, antibody–drug conjugate; BCL-2i, B-cell lymphoma 2 inhibitor; BPDCN, blastic plasmacytoid dendritic cell neoplasm; CAR T, chimeric antigen receptor T-cells; CR, complete remission; DEX, dexamethasone; IDA, idarubicin; L-ASP, L-asparaginase; MAb, monoclonal antibody; MTD, maximum tolerated dose; MTX, methotrexate; R/R, relapsed–refractory.

identifier: NCT03599960). The primary outcome of this trial will assess the percentage of patients who achieve CR after three cycles of therapy. A sample of the active clinical trials evaluating different treatment options for BPDCN are depicted in Table 1.

In everyday practice, the treatment algorithm in most cases includes one of the following therapeutic strategies.

HCVAD. HCVAD is the most commonly used treatment regimen in patients with BPDCN. From our own experience, when used in the frontline setting, more than 80% overall response rate was observed.³⁶ Specifically, in the 23 patients that received HCVAD, median OS was 24.3 months and the first complete remission (CR1) rate was 83%. In the overall cohort ($n = 58$), the CR1 rate was 62% and median OS was 22.8 months.³⁶

HCVAD plus venetoclax. The B-cell lymphoma-2 (BCL-2) protein inhibitor, venetoclax, has been heavily studied in various types of leukemia and of particular interest is the finding that BPDCN is dependent on BCL-2 and sensitive to venetoclax.^{37,38} Based on these results, a phase I clinical trial is currently underway in our institution to study the use of venetoclax in patients with BPDCN (ClinicalTrials.gov identifier: NCT03485547). From our experience, in relapsed/refractory cases with BPDCN, the off-label combination of HCVAD plus venetoclax has

shown promising results thus far; all of the first three patients treated with this combination in our institution, achieved CR with no major side effects noted.³⁹

Hypomethylating agents. For patients that are older and not fit for intensive chemotherapy regimens, similar to other myeloid malignancies, a hypomethylator agent-based strategy is preferred. There have been several case reports of azacitidine and decitabine in patients with BPDCN that show good tolerability but moderate efficacy especially when used as monotherapy.^{40–42} However, combinations of hypomethylating agents with venetoclax in patients with relapsed–refractory myeloid leukemias, including BPDCN, were a viable salvage treatment option with an objective response in 21% ($n = 9$) of patients after a median of two treatment cycles.⁴³

Central nervous system prophylaxis. Given the high prevalence of central nervous system (CNS) involvement with BPDCN, both at presentation but most frequently after disease recurrence, intrathecal chemotherapy may be of great importance in patients treated with conventional chemotherapy.^{5,6,44,45} CNS relapse is frequent in patients with BPDCN and in three of six patients with relapse, no intrathecal prophylaxis was administered in a report by Pagano and colleagues.⁵ CNS prophylaxis with intrathecal infusion of cytarabine should be routinely incorporated in the induction treatment when conventional chemotherapy regimens are being

used. One major emerging question in the field will be investigating the need for, and timing of, CNS prophylaxis during the course of patients with BPDCN treated with novel and targeted therapies.

Stem cell transplantation. Stem cell transplantation (SCT) with myeloablative or reduced intensity conditioning regimens, has been associated with improved survival in younger and select older patients, especially if the procedure is performed after the first CR.^{19,20} The clinical course and response to treatment varies significantly between children and adults.^{6,30} BPDCN in some pediatric patients appears to benefit from treatment as high-risk ALL and frequently achieves a second CR after allogeneic SCT for relapsed disease.⁴⁶ In older patients who present with more aggressive disease, an OS benefit with allogeneic SCT is noted only after the first CR, and the median OS in these studies ranges from 19 to 28 months.^{5,20,47} The major clinical problem is that the median age of diagnosis in adults is between 68 and 72 years, an age that usually precludes them from getting an intensive myeloablative conditioning regimen and thus undergoing SCT.

The role of autologous SCT in BPDCN is controversial. Few case series are available, with the larger one of them showing that of 11 patients undergoing autologous SCT after the first CR, the 4-year OS was 82% and 4-year PFS was 73%, regardless of the type of induction regimen used.¹⁹ Given the paucity of literature, the identification of the subset of patients that will benefit the most from autologous SCT is tough to elicit. It appears, however, that patients with active and refractory disease are not likely to achieve sustained remission.^{19,29}

Targeted agents

Targeted therapy has emerged in the field of oncology over the recent years. Several agents have been developed recently and have been tried in BPDCN. Tagraxofusp was the first drug to be specifically approved for the treatment of BPDCN.⁴⁸

Anti-CD123. Tagraxofusp (formerly known as DT-IL3 and later known as SL-401) is a CD123-directed cytotoxin that consists of recombinant human interleukin-3 fused to truncated diphtheria alpha-toxin, a potent inhibitor of protein

synthesis.^{49–51} The rationale behind the development of this drug was that BPDCN, as noted previously, is characterized virtually in all cases by overexpression of CD123 (or IL3RA).^{9–11} Tagraxofusp has shown antitumor activity in both *in vivo* and *in vitro* models at low concentrations specifically for BPDCN.⁵² In a pilot study conducted by Frankel and colleagues, seven of nine evaluable patients (78%) demonstrated major responses, with adverse events including hypotension, edema, fevers and chills, being easily manageable and fully reversible.⁵⁰ Based on these results, a phase I/II study of the same agent, finally known now as tagraxofusp, was initiated.²¹ In this open-label multicenter prospective cohort of 29 patients with untreated BPDCN, tagraxofusp led to a combined CR and clinical CR in 21 (72%) patients.²¹ Survival rates at 18 and 24 months were 59% and 52% respectively. Notably, 13 of the 29 previously untreated patients (45%) were successfully bridged to SCT after the first CR (10 underwent allogeneic SCT and 3 underwent autologous SCT). In the same study, among 15 patients with BPDCN that were previously treated, tagraxofusp led to 67% response rate with a median OS of 8.5 months. Serious adverse events included capillary leak syndrome (CLS) which led to two deaths in the study. Common side effects included elevated levels of alanine aminotransferase (64%), aspartate aminotransferase (60%) and hypoalbuminemia (55%). On the basis of this study, tagraxofusp was recently approved by the United States Food and Drug Administration for BPDCN in adults and in children 2 years of age or older.⁴⁸ Tagraxofusp is being administered intravenously at 12 µg/kg once daily once daily on days 1–5 of a 21-day cycle. Treatment is continued until disease progression or unacceptable toxicity occurs.⁵³

CLS is a serious complication that has been observed with administration of tagraxofusp.^{21,50} It was observed in 8 (18%) of 44 patients who received high-dose tagraxofusp (12 µg/kg).²¹ CLS is mostly seen during cycle 1 and is manageable with close monitoring and pre-emptive measures (intravenous albumin and antihistamine administration). Similar targeted agents have been found to cause severe CLS. CLS is a black box warning for denileukin diftitox, an engineered protein that combines interleukin-2 and diphtheria toxin.⁵⁴ Additionally, moxetumomab pasudotox-tdfk is a CD22-directed cytotoxin combined with fragment of *Pseudomonas* exotoxin A that is approved

for relapsed–refractory hairy cell leukemia and is also highly associated with CLS.^{55,56}

IMGN632 is a humanized antibody–drug conjugate that consists of a humanized anti-CD123 receptor alpha immunoglobulin (Ig)G1 monoclonal antibody conjugated *via* a cleavable linker, to a cytotoxic, DNA-alkylating payload, with potential antineoplastic activity. It has been shown to be highly active and prolong survival in AML xenograft models.⁵⁷ IMGN632 is currently being studied in patients with relapsed–refractory AML, BPDCN, ALL and other CD123-positive malignancies in a phase I trial (ClinicalTrials.gov identifier: NCT03386513).

Finally, XmAb14045 is an anti-CD123/anti-CD3 bispecific monoclonal antibody, in which most of the naturally occurring Fc domain is maintained with potential immunostimulatory and antineoplastic activities. There is an active phase I clinical trial evaluating the safety and tolerability of XmAb14045 in patients with CD123-expressing hematologic malignancies (ClinicalTrials.gov identifier: NCT02730312).

BCL-2 protein inhibition. It was recently discovered that BPDCN cells are dependent on the antiapoptotic protein BCL-2.³⁷ In addition, clinical case reports have shown that the BCL-2 inhibitor, venetoclax, leads to great responses in selected patients.^{37,58} As shown above, venetoclax in addition to HCVD had a 100% CR rate in the first three patients treated with that regimen with an excellent safety profile.³⁹ The trial investigating the role of venetoclax in BPDCN is ongoing (ClinicalTrials.gov identifier: NCT03485547). Finally, venetoclax in combination with low-intensity chemotherapy, including hypomethylating agents and low-dose cytarabine, has been put forward as another approach to be investigated in the treatment options, even in patients with BPDCN.⁴³

Chimeric antigen receptor T-cell therapy. UCART 123 cells represent genetically modified allogeneic T-cells that contain an anti-CD123 chimeric antigen receptor and a RQR8 depletion ligand that confers susceptibility to rituximab. UCART123 has been reported to have *in vitro* cytotoxic activity and to cause BPDCN-specific killing with T-cell degranulation and robust production of interferon-gamma.⁵⁹ There is a phase I

study that was launched evaluating the clinical safety of UCART123 in patients with BPDCN (ClinicalTrials.gov identifier: NCT03203369) and in AML (ClinicalTrials.gov identifier: NCT03190278).

Future directions

BPDCN is a rare disease arising from precursors of dendritic cells with very poor prognosis historically. Accurate diagnosis is often challenging and requires a multidisciplinary approach with oncologists and histopathologists. Diagnosis is often based on specific clinical characteristics, along with the identification by immunohistochemistry of tumor marker characteristic for BPDCN. Due to the rarity of the disease, and its rather indolent presentation, a high index of suspicion is required. Until recently, conventional chemotherapy using ALL-type regimens followed by SCT after first remission was the usual management of patients with BPDCN. With the approval of tagraxofusp, the first-in-class CD123-directed cytotoxin, new options have come forward for treatment options. When studied prospectively in patients who were both treatment-naïve and patients with previous treatment, tagraxofusp was shown to have high efficacy with high CR rates in all settings.²¹ Major side effects included CLS with frequent observation of elevation of liver function enzymes.

Other agents that have been used in other types of leukemias over the past decade, including the BCL-2 inhibitor, venetoclax, have shown promising results when studied alone in BPDCN. Future combinations of BCL-2 and CD123-targeted therapy may be a pathway to be put forward for investigation in patients with BPDCN.

In everyday practice, for a patient that presents to our clinic with suspicion of BPDCN, we would first elicit a detailed history regarding prior chemotherapy/radiation exposure. We proceed with bone marrow aspiration and biopsy, including immunohistochemistry and flow cytometry studies. If a diagnosis of BPDCN is confirmed, we evaluate treatment options based on clinical presentation, patient performance status, presence of comorbidities and consideration of baseline chemistries (importantly, albumin, creatinine and liver function tests) and begin to decide between frontline treatment with tagraxofusp, and if we cannot qualify then we consider clinical trials,

conventional chemotherapy, venetoclax-based therapies or other options. Patients are referred to our SCT team to evaluate whether they are candidates for transplant. Further treatment depends on the patient's performance status and SCT candidacy. For patients that are SCT candidates and have suitable donors, we proceed with allogeneic SCT after CR1 is achieved. If CR1 is not achieved, we proceed with clinical trial options. For patients who are not SCT candidates, after frontline treatment with tagraxofusp we aim to enroll patients on select clinical trials on a case-by-case basis.

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ORCID iD

Minas P. Economides  <https://orcid.org/0000-0003-4625-421X>

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