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Facts About **Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)**

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, highly aggressive hematologic malignancy with no currently approved therapies, no universally accepted standard of care and a historically poor prognosis. Diagnosis of BPDCN can be difficult due to its heterogeneity and overlapping features with other hematologic malignancies. Recently, improved understanding of the biology of BPDCN has led to better diagnosis and targeted therapies in clinical trials having the potential to improve outcomes. This publication will detail the diagnosis, current treatment regimens, and emerging therapies for BPDCN.

Highlights

- BPDCN constitutes less than 1% of all hematologic malignancies, resulting in an estimated 1,000 to 1,400 cases occurring annually in the US and Europe combined.
- While BPDCN can occur at any age, the median age at diagnosis is in the mid-60s, with approximately 75% of cases occurring in men.
- While initial response to combination chemotherapy is high, patients regularly relapse and have a median overall survival of approximately 1 year.
- 90% of patients with BPDCN present with asymptomatic skin lesions – and early recognition can be challenging due to overlapping features with other benign and malignant disorders.
- Accurate diagnosis requires a biopsy showing the morphology of plasmacytoid dendritic blast cells and immunophenotypic criteria established by either immunohistochemistry or flow cytometry.
- There is no accepted standard of care for BPDCN. Patients treated with high-dose acute leukemia-based chemotherapy followed by allogeneic stem cell transplant during the first remission appear to have better outcomes.
- Several clinical trials are underway with therapeutic agents targeting CD123, a cell surface receptor highly expressed in BPDCN (and also in numerous other hematologic malignancies) and minimally expressed on normal cells.

Background and Prevalence

BPDCN is a highly aggressive, rare malignancy derived from the precursors of plasmacytoid dendritic cells (pDCs), immune cells that specialize in the production of type I interferons in response to bacterial and viral stimuli.[1-3] Accurate diagnosis of this malignancy has been complicated by a number of factors, including shifting nomenclature over the years – BPDCN has been referred to as agranular CD4+ natural killer cell leukemia, blastic natural killer-cell leukemia/lymphoma and CD4+/CD56+ hematodermic neoplasm.[1,4-6] As understanding of the biology and origin of this malignancy has improved, the World Health Organization (WHO) established the term *blastic plasmacytoid dendritic cell neoplasm* in 2008.[6] BPDCN is currently classified by WHO as a distinct entity within the acute myeloid neoplasms and acute leukemias.[7]

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Background and Prevalence, cont.

It is difficult to precisely estimate the incidence of BPDCN due to its rarity, evolving terminology and likely underdiagnosis, but it is thought to represent less than 1% of hematologic malignancies, resulting in an estimated 1,000 to 1,400 cases occurring annually in the US and Europe combined.[1] BPDCN is typically a disease of the middle-aged and elderly, with a median age at diagnosis in the mid-60s.[1,2,8,9] Approximately 3 times as many males as females are affected.[1,2,8] While pediatric cases have been described in children as young as 8 months of age, they are exceedingly rare.[10,11]

Historically, patients diagnosed with BPDCN have a poor prognosis with a median overall survival (OS) from diagnosis of approximately 1 year despite the use of combination chemotherapy.[1,3,4,12-14]

Presentation

Early recognition of BPDCN can be challenging, because its clinical features can be heterogeneous and can overlap other hematologic malignancies.[3,4,15,16] There is often a significant delay between the onset of symptoms and diagnosis.[17]

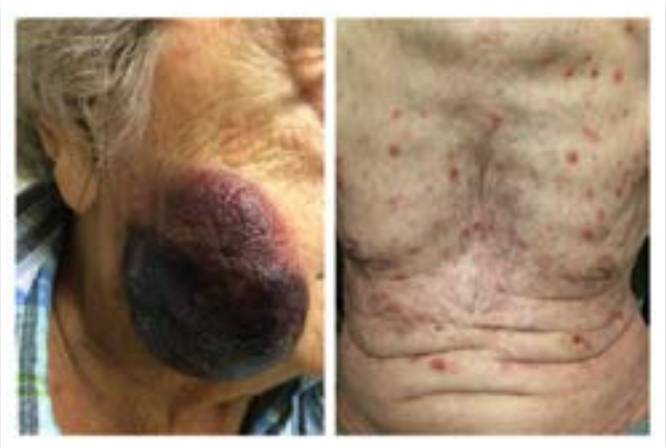
Cutaneous

Approximately 90% of patients diagnosed with BDPCN present with asymptomatic skin lesions. These lesions may appear to be indolent initially, but progression invariably occurs with involvement of multiple sites including bone marrow, peripheral blood, lymph nodes, liver, spleen and, in some cases, the central nervous system (CNS).[2,4,9,13,16]

Cutaneous lesions vary in size, shape, color and distribution and can be confused with other benign and malignant skin lesions (**Figure 1**).[1,17,18] They can appear as bruise-like or erythematous papules, plaques or tumors measuring up to 10 cm, commonly on the face, trunk and extremities, although they can occur anywhere.[1,17,18] BPDCN is often detected incidentally by dermatologists, and differentiating BPDCN from other lesions is critically important. When BPDCN is suspected, consultation with a dermatopathologist is advised and assessment for the immunohistochemical criteria for BPDCN is recommended (see below).[1,13]

A significant percentage (40% to 50%) of patients initially present with involvement of the bone marrow and lymph nodes.[8,18] Extracutaneous involvement that may be observed at presentation includes lymph nodes, spleen, liver, tonsils, and central nervous system.[16,18]

Figure 1. Cutaneous lesions in BPDCN



Courtesy of Shapiro R, et al. J Cell Sci Ther. S8:008. Doi:10.4172/2157-7013.S8-008.[8]

Leukemic

In fewer cases, BPDCN patients present with systemic dissemination characteristic of acute leukemia, with or without skin involvement.[1,4,13,17,20] In most of these cases cytopenia is also present, with highly variable rates of bone marrow infiltration.[20] Coexistence of BPDCN with myelodysplastic syndrome (MDS) has been observed in 10% to 20% of cases, and MDS with skin lesions should be screened for the presence of BPDCN.[1,8,18]

Diagnosis

Many patients with BPDCN present with what may appear to be indolent disease, but due to the invariable progression and extremely poor prognosis, rapid and accurate diagnosis is critical for planning appropriate therapy. Identification of several pDC-related antigens in recent years has aided this effort.[17] Diagnosis of BPDCN requires a biopsy showing the morphology of plasmacytoid dendritic blast cells and immunophenotypic criteria established by either immunohistochemistry or flow cytometry, depending on what tissue is available for analysis.[1] Most cases of BPDCN are diagnosed with a skin biopsy.[17]

The immunohistochemical criteria for BPDCN include positivity for CD4, CD56, CD123, and TCL-1, in the absence of other myeloid leukemia markers, particularly myeloperoxidase and lysozyme. CD56 can be negative in rare cases, which does not rule out BPDCN if the other markers are positive. Other pDC-associated markers, such as CD2AP or CD303/BDCA2 may also be used to confirm the diagnosis.[1-3,8,15,17,20]

Markers that can be used to distinguish BPDCN from acute myeloid leukemia (AML), leukemia cutis (LC), and myeloid sarcoma (MS) are shown in **Table 1.**[1] Atypical immunophenotypes have been reported, however, in which common markers such as CD4 and CD56 are absent.[4,17] Myeloid markers, including CD33, CD68 and CD43, may also be expressed in BPDCN.[1,3,4,13]

Table 1. Immunohistochemical markers for BPDCN[1]

		BPDCN	AML/LC/MS
SHARED MARKERS	CD4	80%-100%	10%-20%
	CD56	90%-100%	5%-50%
	CD123	85%-100%	15%-45%
	TCL1	80%-100%	5%-20%
UNIQUE MARKERS		CD2AP	MPO
		CD303/BDCA-2	Lysozyme
			CD34
			CD14
			CD11c
			CD163

Range of positive cases are shown for shared markers. AML = acute myeloid leukemia; LC = leukemia cutis; MS = myeloid sarcoma; CD = "cluster of differentiation"; TCL1 = T-cell leukemia 1; CD2AP = CD2-associated protein; BDCA-2 = blood dendritic cell antigen 2; MPO = myeloperoxidase.

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If BPDCN presents as the leukemic form or if there is bone marrow involvement, flow cytometry is appropriate. A recent study has demonstrated that BPDCN can be successfully distinguished from AML, T-cell lymphoblastic leukemia/lymphoma, and NK-cell lymphoma/leukemia using a 10-color AML flow cytometry panel.[3] BPDCN was characterized by positivity for CD4 (bright), CD33 (dim), CD56 (heterogeneous), CD123 (bright), CD36, CD38, HLA DR, and CD71.[3]

Treatment

Conventional Therapy

There is currently no approved therapy or established standard of care for BPDCN due to its rarity and the lack of prospective clinical trials.[1,4,2,9] Even in patients who present with apparently localized lesions to the skin, early and aggressive systemic chemotherapy has been recommended in patients able to tolerate it.[2]

Induction therapy with non-Hodgkin lymphoma (NHL)-, acute lymphoid leukemia (ALL)-, or acute myeloid leukemia (AML)-type chemotherapy regimens has resulted in high initial response rates (complete response [CR] = 40% to 90%).[1,3] While never compared prospectively, patients given ALL-like regimens appear to do better.[2,3,20] Relapse occurs frequently with any of these regimens (50% to 90%), with a median OS of approximately 1 year. [1,3,4,13,14]

The lack of a durable response to chemotherapy justifies the consideration of stem cell transplant (SCT) when patients are sufficiently fit. While there are no studies comparing SCT to conventional treatment, long-term remissions have been seen with allo-SCT during the first remission.[1,2] Relapse following transplantation occurs in approximately 30% of patients.[1] Transplantation beyond the first remission or in patients who have not achieved a complete remission appears to have a negative effect on OS and progression-free survival.[1,2] While auto-SCT has been used for consolidation and can improve survival, high-dose ALL-based chemotherapy with allo-SCT during the first remission has appeared to offer the best results.[1,2]

A recent study has shown CNS involvement in the majority of BPDCN cases at presentation (60%) despite patients having no neurologic symptoms.[21] The CNS is also a potential site of relapse.[1,4] Systemic or intrathecal chemotherapy for CNS prophylaxis during treatment has been recommended for BPDCN patients in some guidelines, although prospective data supporting this approach is lacking.[1,2,21]

BPDCN is generally a disease of people in their 60s and older, and fitness for aggressive systemic chemotherapy and conditioning for transplant are recognized challenges in this population. Improved understanding of the biology of BPDCN has led to the welcome development of several targeted therapies in clinical trials with the potential to improve outcomes.

Emerging Therapies Targeting CD123

CD123 (interleukin-3 receptor alpha subunit, or IL-3Rα) is highly expressed in BPDCN (in addition to a wide range of other hematologic malignancies) and minimally expressed on normal cells, suggesting it is an appropriate target for therapy.[1,2] There are currently 5 potential therapies for BPDCN in clinical trials that target CD123.

SL-401

SL-401 is a novel biologic targeted therapy directed to CD123 (IL-3R). SL-401 is a recombinant fusion protein consisting of human IL3 (the natural ligand of CD123) fused to a truncated diphtheria toxin (DT) engineered such that IL-3 replaces the native DT receptor binding domain. The IL3 domain of SL-401 directs the cytotoxic DT payload to cells expressing CD123 (its natural receptor). Upon internalization, SL-401 inhibits protein synthesis and induces apoptosis of the target cell.[2,22-24]

Results from the recently completed pivotal phase 2 trial in BPDCN (n=42 patients) are encouraging.[25] In first-line patients who received SL-401 at the optimal dose (12 mcg/kg/day), the overall response rate was 90%, with a 72% rate of complete response (CR) + clinical complete response + complete response with incomplete hematologic recovery. Forty-five percent of these patients were successfully bridged to SCT. The most common treatment-related adverse events included alanine aminotransferase increase, aspartate aminotransferase increase, hypoalbuminemia, thrombocytopenia, and capillary leak syndrome.[25] SL-401 has been granted Breakthrough Therapy and Orphan Drug Designation by the FDA for the treatment of BPDCN.[26]

UCART123

Chimeric antigen receptor (CAR) T-cell therapy leverages the natural ability of the human immune system to attack and destroy cancer cells. CARs are genetically engineered cell surface receptors that equip T cells with the abilities to recognize and bind antigens found on tumor cells and activate the T cell to kill the target cell. *(More information about CAR T-cell therapy can be found here: Facts About CAR T-Cell Therapy.)*

UCART123 is an experimental therapy that differs from 2 FDA-approved CAR T-cell therapies, Kymriah™ and Yescarta™, in which the engineered CAR gene is transferred into the patient's own T cells. UCART123 is a "universal" or "off the shelf" therapy in which the CAR, directed to CD123, is expressed in T cells derived from healthy donors which have been genetically engineered to remove endogenous T-cell markers, allowing for allogeneic therapy. The CAR expressed in UCART123 recognizes and binds CD123.

Phase 1 dose-finding studies are underway for UCART123 in BPDCN and AML (ClinicalTrials.gov Identifier: NCT03203369)

A clinical hold issued by the FDA in September 2017 following the death of a BPDCN patient has recently been lifted with revisions to the protocol, including lowering the dose of UCART123 cells.[27]

CD123CAR with Truncated Epidermal Growth Factor receptor

An additional phase 1 study with CD123-directed CAR T cells is underway in patients with AML and BPDCN. In addition to the CD123-binding domain, this CAR construct includes a truncated epidermal growth factor receptor (EGFRt). The EGFR sequence lacks the EGF binding domain and intracellular signaling domain but retains the epitope for the anti-EGFR monoclonal antibody cetuximab. In addition to providing a traceable marker for the CAR T cells, this provides a potential mechanism to destroy CAR T cells– a CAR T-cell "off switch" – in the event of life-threatening toxicities, which could provide a desirable safety measure for this emerging therapy.[28]

Unlike UCART123, this construct is designed to be transfected and expressed in a patient's (or patient's donor's) T cells. A phase 1 dose-finding and safety study is ongoing with these CAR T cells in relapsed/refractory AML and persistent or recurrent BPDCN. (ClinicalTrials.gov Identifier: NCT02159495)

XmAb14045

XmAb14045 is a "bispecific" antibody that binds two targets, CD123 and CD3. It functions to "bring together" tumor cells expressing CD123 and cytotoxic T cells, which bind CD3. The T cells are then activated to kill the CD123-expressing target cells.

A phase 1 study to determine the safety and tolerability of XmAb14045 is currently underway in patients with CD123-expressing hematologic malignancies, including AML, B-cell ALL, BPDCN, and chronic myeloid leukemia (CML). (ClinicalTrials.gov Identifier NCT02730312)

IMGN632

IMGN632 is an antibody-drug conjugate that consists of a humanized anti-CD123 antibody fused to an indolino-benzodiazepine agent (IGN). When delivered to a target cell via the anti-CD123 antibody, the IGN payload alkylates DNA without crosslinking, which kills the CD123-expressing target cell.[29]

A phase 1 trial in patients with CD123-expressing hematologic malignancies including ALL, BPDCN, myeloproliferative neoplasms and AML is ongoing. (ClinicalTrials.gov Identifier NCT03386513)

Emerging Therapy Targeting PD-1

Nivolumab (Opdivo®) is an antibody that blocks programmed death receptor-1 (PD-1). PD-1 serves as an immune system "checkpoint," preventing the immune system from destroying normal cells displaying its ligands PD-L1 and PD-L2. Studies have shown that tumor cells often express PD-L1, allowing them to evade the immune response. Nivolumab can prevent PD-L1 from binding to PD-1, "unleashing" the immune system to destroy the cancer cells. Nivolumab is approved to treat multiple malignancies, including metastatic melanoma, renal cell carcinoma, and non-small cell lung cancer.

A phase 2 study is currently underway to determine how patients with relapsed and refractory peripheral T-cell lymphomas, including BPDCN, respond to nivolumab. (ClinicalTrials.gov Identifier NCT03075553)

Emerging Therapy Targeting BCL-2

Venetoclax (Venclexta™) is an orally bioavailable small molecule that inhibits the anti-apoptotic protein BCL-2. Venetoclax is FDA-approved for treatment of patients with chronic lymphocytic leukemia (CLL), and is currently being tested alone and as part of combination therapy in many hematologic malignancies. A recent study found that BPDCN cells are highly dependent on BCL-2 for survival and are sensitive to treatment with venetoclax. In that study, 2 patients were treated off-label with venetoclax and experienced significant clinical benefits.[30] A formal clinical trial of venetoclax in BPDCN is underway. (ClinicalTrials.gov Identifier: NCT03485547)

Conclusion

Due to the aggressive clinical course of BPDCN and its historically poor outcome with conventional chemotherapy, referral to a clinical trial either at diagnosis or after relapse should be considered for all patients, if available. Outside of a clinical trial, high-dose chemotherapy to achieve remission followed by allogeneic SCT for patients able to tolerate it is recommended.

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