Blastic Plasmacytoid Dendritic Cell Neoplasm: Progress in Cell Origin, Molecular Biology, Diagnostic Criteria and Therapeutic Approaches*

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Summary: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy characterized by recurrent skin nodules, an aggressive clinical course with rapid involvement of hematological organs, and a poor prognosis with poor overall survival. BPDCN is derived from plasmacytoid dendritic cells (pDCs) and its pathogenesis is unclear. The tumor cells show aberrant expression of CD4, CD56, interleukin-3 receptor alpha chain (CD123), blood dendritic cell antigen 2 (BDCA 2/CD303), blood dendritic cell antigen 4 (BDCA4) and transcription factor (E protein) E2-2 (TCF4). The best treatment drugs are based on experience by adopting those used for either leukemia or lymphoma. Relapse with drug resistance generally occurs quickly. Stem cell transplantation after the first complete remission is recommended and tagraxofusp is the first targeted therapy. In this review, we summarize the differentiation of BPDCN from its cell origin, its connection with normal pDCs, clinical characteristics, genetic mutations and advances in treatment of BPDCN. This review provides insights into the mechanisms of and new therapeutic approaches for BPDCN.

Key words: blastic plasmacytoid dendritic cell neoplasm; plasmacytoid dendritic cell; genetic mutations; immunophenotype; therapeutics

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) was initially described by Adachi *et al*^[1], who reported a 67-year-old Japanese man with a novel dermic lymphoma. The lymphoma was characterized by an aggressive clinical course with progression to the bone marrow and the central nervous system quickly and a CD2⁻, CD4⁺, and CD56⁺ immunophenotype. More cases were reported of this disease with a tendency for skin involvement and expression of CD56. However, its origins remain unclear, and subsequently, the disease was called agranular CD4⁺ natural killer cell leukemia; agranular CD4⁺, CD56⁺ hematodermic neoplasm; blastic natural killer cell lymphoma/leukemia, and other names^[2-4]. With understanding of BPDCN, the entity was classified as a precursor neoplasm of acute myeloid leukemia (AML) in the 2008 revision of the World Health Organization classification of hematopoietic tumors and as a distinct form of AML in the 2016 revision^[5,6].

The characteristics and mechanisms of BPDCN are not well understood. BPDCNs originate from

plasmacytoid dendritic cells (pDCs)^[7-10]. Although BPDCN cells and pDCs both express the molecular markers interleukin-3 receptor alpha chain (CD123), blood dendritic cell antigen 2 (BDCA 2/CD303), CD2AP, CD4, and T cell lymphoma antigen 1 (TCL1) and transcription factors such as transcription factor (E protein) E2-2 (TCF4), interferon regulatory factor 7 (IRF7), interferon regulatory factor 8 (IRF8), BCL11A, and SPIB^[11-18], the two cell types have different cell morphologies, functions, molecular markers, and gene expression. Chaperot *et al*^[7] reported that CD4⁺, CD56⁺ hematological neoplasms generated interferon 1 (IFN1) in response to the influenza virus; those neoplasms could transform into dendritic cells (DCs) upon the stimulation of interleukin-3 (IL-3), expressed major histocompatibility complex class II (MHCII), and potently stimulated the polarization of naive T cells and Th2 cells, confirming a leukemic counterpart of pDC. Sapienza *et al* further discovered that gene expression levels of BPDCNs are similar to those of myeloid-derived resting pDCs, and this similarity could explain the absence of IFN1-producing genes between BPDCNs and resting pDCs; meanwhile, the nuclear factor kappa B (NF-κB) pathway that is abnormally activated in BPDCNs might be a new therapy target^[19].

This review summarizes the current studies on the different biological, molecular, ontogenetic,

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morphological, and functional features of BPDCNs and pDCs. Recent advances have greatly enhanced our understanding of BPDCNs and have led to new insights into mechanisms involved in dysregulated gene expression in pDCs and BPDCNs. The new knowledge has pointed to new therapeutic approaches for patients with BPDCN.

1 CHARACTERISTICS, DEVELOPMENT AND FUNCTIONS OF NORMAL PDCS

1.1 Distribution and Morphology of Normal pDCs

pDCs were formerly called “plasmacytoid T cells” or plasmacytoid T-zone cells^[20, 21]. Later, they were named plasmacytoid monocytes because they have some myelomonocytic markers, such as CD15 and CD68, and lack other specific T-lineage markers^[22]. The term pDCs was adopted after their origin and biological function were better understood^[23–25]. Functionally, pDCs are a subpopulation of DCs; the other subpopulation of DCs is conventional DCs (cDCs), which play an important role in the immune system by processing and presenting antigens and then exerting their role in phagocytosis and stimulating the proliferation of specifically cytotoxic T cells and Th2 cells^[26]. pDCs display an intermediate-size, round-ovoid shape, an eccentric nucleus, scattered fine chromatin, small but distinctive nucleoli, dark basophilic cytoplasm with a pale Golgi zone, and abundant rough endoplasmic reticulum^[27]. Nodal pDCs are present in clusters or dispersed near high endothelial venules^[28]. In other lymphoid tissues, pDCs are dispersed and never aggregated.

pDCs, produced in the bone marrow, account for a proportion of less than 0.05% of mononuclear cells in blood^[29]. Most pDCs are located in lymph nodes and tonsils, and small quantities can be found in the spleen, thymic medulla, and mucosa-associated tissue^[28, 30], whereas pDCs are almost never found in other lymphoid tissues and peripheral nonlymphoid tissues^[21]. Activation of an immune response induces the accumulation of pDCs in lymphoid tissues^[23], while the recruitment of pDCs to nonlymphoid tissues suggests an inflammatory or neoplastic state^[31–33]. The abnormal activation of pDCs could lead to Kikuchi-Fujimoto disease, Hodgkin disease, Castleman disease, and autoimmune diseases^[23, 31–33].

1.2 pDCs Development

Early hematopoietic myeloid progenitors differentiate into common dendritic cell progenitors (CDPs) through macrophage-DC progenitors or produce CDPs directly^[34–37]. CDPs then differentiate into cDCs or pDCs, a process controlled by lineage-specific regulatory signals^[38–40]. Rodrigues *et al.*^[41] reported that pDCs develop predominantly from Lin[−]c-Kit^{int-lo}Flt3⁺M-CSFR–IL-7R α ⁺ cells, which

possess major pDC differentiation potential and pDC lineage specification at the Ly6D⁺SiglecH⁺ progenitor stage; such pDCs mostly show pure pDC properties, unlike a small group of pDCs called “pDC-like” cells, which are derived from CDPs and share functional properties with cDCs. pDCs and pDCs-like cells share phenotypic similarities but have distinct transcription and function^[41, 42]. In the bone marrow, both pDCs and cDCs could be developed from CDPs, and FMS-related tyrosine kinase 3 (FLT3) ligands function as the critical cytokines for the development and differentiation of both pDCs and cDCs^[43, 44](fig. 1). However, the mechanisms of regulatory signals that control lineage diversification have not yet been clearly illustrated.

Efforts have been undertaken to identify the regulatory and developmental factors that affect pDCs and cDCs^[40, 45–49]. TCF4 plays a key regulator function in commitment to and maintenance of pDC lineage by controlling the transcriptional network. Its absence induces a conversion from pDC to cDC lineage^[45–48]. Further, the loss of ID-2 (an E-box transcription factor inhibitor target that is necessary for cDC development), transforms cDCs into pDCs^[47]. PU.1, an ETS-domain transcription factor, is able to control the expression of the cytokine receptors FLT3, M-CSFR, and GM-CSFR, which are indispensable for the development of all DCs^[40, 48, 49]. The interferon-regulatory factor IRF2 can change pDC proportions by inhibiting IFN1 genetic transcription, which is mediated by IRF1^[49]. Other transcription factors controlling pDC development, such as IRF8 (ICSBP), zinc-finger DNA-binding protein Ikaros, growth factor independent 1 (GFI1), and SPIB, are necessary for both pDC and cDC development^[40, 48, 49]. However, STAT5 inhibits pDC development by suppressing the IRF8 pathway^[49, 50]. Additionally, TCF4 directly targets transcription factors such as SPIB, IRF8, BDCA2, ILT7, PTCRA, and IRF7 in pDCs, whileas these genes, in turn, regulate TCF4 expression; therefore, these factors constitute a TCF4-orchestrated regulatory network that maintains pDC lineage identity^[45–47, 49]. Collectively, cDC and pDC lineage development requires both E proteins and the PU.1-IRF8 axis working together^[49], but the interactions between the E2-2-ID-2 and PU.1-IRF8 axes need further investigation to discover the identities of transcription factor-targeted genes.

1.3 Function and Heterogeneity of pDCs

The pDCs bridge the innate and adaptive immune systems mainly by recognizing nucleic acid sequences and working as antigen-presenting cells, a process that is mediated by the toll-like receptor (TLR) 7/9-MyD88-IRF7 pathway^[51–54]. In the setting of inflammatory response, pDCs generate a set of cytokines dominated by IFN- α and inflammatory chemokines such as IL-6, IL-8, and IL-12. These cytokines bring about the activation of T cells, natural killer cells, and

Fig. 1 In the bone marrow, hematopoietic stem cells generate myeloid progenitors (MPs) and lymphoid progenitors. MPs differentiate into common dendritic cell progenitors (CDPs) through macrophage-DC progenitors (MDPs) or produce CDPs directly; CDPs then differentiate into conventional dendritic cells (cDCs) or plasmacytoid dendritic cells (pDCs). Most pDC populations in bone marrow and other tissues (including lymph nodes, tonsils, spleen, thymic medulla, and mucosa-associated tissue) originate from an IL-7 α^+ progenitor cell population that parallels the previously identified pre-cDC population, while a minor transcriptionally and functionally distinct pDC population, called pDC-like cells, is independently derived from CDPs. pDCs and pDC-like cells are two distinct cell populations that share phenotypic similarities but are distinct in transcription and function. CDPs: common dendritic cell progenitors; HSCs: hematopoietic stem cells; LPs: lymphoid progenitors; MDPs: macrophage-DC progenitors; MPs: myeloid progenitors; pDCs: plasmacytoid dendritic cells; BPDCN: blastic plasmacytoid dendritic cell neoplasm

macrophages in various adaptive immune responses, including inflammation and autoimmune diseases (fig. 2).

The pDC population is heterogeneous and is classified into two subsets called pure pDCs and pDC-like cells^[41, 42]. Pure pDCs originate from IL-7R $^+$ lymphoid progenitors and are capable of producing IFN- α and, to a lesser extent, stimulating T cells. The pDC-like cells are derived from CDPs, highly express MHCII after stimulation by CpG-A, and are capable of processing antigens and prompting T cell proliferation. They have characteristics that resemble those of cDCs.

2 GENETIC AND FUNCTIONAL LINKS BETWEEN PDCS AND BPDCNS

The genetic background of BPDCN cells shows the heterogeneity of genetic abnormalities. In 2008, Marafioti *et al* found that 47 pDC-derived neoplasms co-express the majority of pDC-associated markers, including transcription factors (BCL11A, E47, FOXP1, IRF8, and PU.1), signaling molecules (BLNK, BTK, CD2AP, DAP12, IRAK1, Lyn, Syk, and TCB1D4), and receptor molecules [CD79b, toll like receptor 7 (TLR7), and TLR9]^[14]. Sapienza *et al*

proved that BPDCNs are derived from resting pDCs of myeloid origin. The aberrant activation of NF- κ B and upregulation of the cyclin D1 gene (*CCND1*) and two NF- κ B targets (*BCL2* and *IRF4*) were identified in BPDCNs^[19]. Years later, BPDCN cells originating from non-activated pDCs were proposed again because, *PTPRS*, the gene inhibiting the activation of normal pDCs, was found to be overexpressed in BPDCN, to prevent immune-mediated inflammation, which may be linked with the immune deficiency of BPDCN^[55]. Recently, Villani *et al*^[56] further demonstrated that BPDCNs co-expressed genes with pDCs and cDCs by single-cell RNA sequencing in four patients with BPDCN. An analysis of the genes similarity between BPDCN cells, pure pDCs, and cDCs showed that although BPDCNs expressed several pDC-associated genes (e.g., *NRP1*, *IL3RA*, *DERL3*, *LAMP5*, *PTCRA*, and *PTPRCAP*), a set of important functional genes for pDCs were missing or slightly expressed in BPDCN cells (including *GZMB*, *IRF7*, *CD303*, and *SLC15A4*). Only a fraction of cDC genes (*SIGLEC6*, *LTK*, *FCER1A*, *CD59*, *CADMI*, and *TMEM14A*) were present in BPDCN cells. All the BPDCN samples also expressed some genes associated with B cells (e.g., *FCRLA*, *IGLL1*, *TCL1A*, and *IGLL5*) or hematological

Fig. 2 The activation and regulation modes in the plasmacytoid dendritic cells (pDCs)

In pDCs, viruses and bacteria activate TLR7 and TLR9 through endolysosomes, and UNC93B1 interacts with these TLRs in the endoplasmic reticulum and is essential for this trafficking. Activation of TLR7 or TLR9 recruits MyD88, IRAK4, and TRAF6, which activates IRF5 and NF- κ B for inflammatory cytokine induction and IRF7 for type I interferon induction. For IRF7 activation, IRAK1- and IKK α -dependent phosphorylation is required, and TRAF3 locates at upstream of these kinases. OPN1 is involved in IRF7 activation, and IRF8 facilitates NF- κ B activation. I κ B serves as a negative regulator. TRAF6 also activates TAK1, then TAK1 phosphorylates IKK β leading to I κ B degradation and releasing of NF- κ B.

progenitors (e.g., *SOX4* and *CLEC11A*). Despite co-expressing some genes that play key roles in B cell molecular signaling, BPDCN cells were found to more closely resemble pDCs. However, these results suggest that the origin and genetic background of BPDCNs are complex and similar to those myeloid-origin resting pDCs.

Notably, *TCF4*, an indispensable gene in the regulation of pDC development, may be a driver gene in the transformation of pDCs to BPDCNs. Based on RNAi screening analysis, Ceribelli *et al*^[57] demonstrated that downregulation of *TCF4* led to the loss of BPDCN-specific genetic expression programming and induction of apoptosis. The researchers also found that a subgroup of *TCF4*-activated oncogenes, including *BCL2*, *TCL1A/B*, and *MYC*, were expressed at higher levels in BPDCNs than in pDCs; in contrast, a subset of *TCF4*-activated functional genes, including *BCL11A*, *SPIB*, *IL3RA*, and *CLEC4C*, were expressed at higher levels in pDCs than in BPDCNs. Additionally,

TCF4-activated genes were highly enriched for pDC-specific genes (CD123⁺). Conversely, *TCF4*-repressed genes were strongly enriched for cDC genes (CD16⁺ and BDCA⁺). This result highlights that *TCF4* functions as one of the master regulators in BPDCNs and could be cited as a reliable diagnostic marker of BPDCN. Thus, *TCF4* acts as a “lineage-survival oncogene” of BPDCN. BPDCN cells inherit *TCF4* target transcriptional procedures from their normal counterpart cells pDCs, but the pDC-specific function of *TCF4* was impaired in BPDCN to support oncogenic gene expression procedures. This is in line with the traditional conception that transcriptional programs inherited from the normal original cell are re-orchestrated to exert the malignant procedures of tumor cells, and those *TCF4* upregulated genes may lead to the BPDCN malignant phenotype and clinical behaviour. How *TCF4* regulatory network changes from pDCs to BPDCNs is unclear, and further studies involving driving factors of BPDCN are needed.

3 CHROMOSOMAL ABNORMALITIES AND GENETIC MUTATIONS OF BPDCN

The majority of patients with BPDCN have chromosomal abnormalities detected by conventional karyotyping, and up to 75% have a complex karyotype^[58] (fig. 3). Collectively, previous studies identified frequent chromosomal losses including 5q21 or 5q32 (72%), 12p13 (64%), 13q13–21 (64%), 6q23-ter (50%), 15q (43%), 9 (28%)^[59]; other low frequency events 4q34.1-4q34.2, 9p13.2-9p11.2, 9q12-9q34.3, and 13q12.11-13q31.1; and overexpression of the oncogenes *HES6*, *RUNX2*, and *FLT3* without the associated genomic amplification^[60]. Genetic mutations involving *TET2*, *ASXL1*, *NRAS*, and *ATM* were common, and less common mutations included *NPM1*, *IKZF*, *KRAS*, *IDH2*, *MET*, *APC*, *BRAF*, *KIT*, *MLH1*, *RB1*, *RET*, *TP53*, *ZEB2*, *HOXB9*, *UBZ2*, *SRSF2*, and *VHL*^[61–63]. Recently, rearrangement of *MYC* on 8q24 (in 38% of patients with BPDCN) or a balanced translocation t(6;8) (p21;q24) has been reported^[64, 65], and a high rate of monoallelic and biallelic 12p13/*ETV6* deletions was identified in BPDCN tumors and in the bone marrow of patients with BPDCN without detectable disease, indicating that such alterations may be involved in pathogenesis^[66, 67].

Fig. 3 Schematic representation of pDCs and summary of molecular and immunophenotypic biomarkers in BPDCN. Chromosomal abnormalities are shown in pink background. Genetic mutations are shown in grey background. Epigenetic regulators, oncogenes, and tumor suppressors are displayed in green background.

Collectively, inactivation of tumor suppressors (*RB1*, *TP53*, *CDKN2A*, and *CDKN1B*)^[68], activation of oncogenes (*NRAS*, *KRAS*, *HES6*, *RUNX2*, and *FLT3*)^[60, 63], and mutations in epigenetic regulators (*TET2*, *TET1*, *DNMT3A*, *IDH1*, and *IDH2*)^[69, 70] that are also frequently mutated in AML were identified in BPDCN. These findings may explain BPDCN's histological characteristics such as tight accumulation of malignant cells, high aggressiveness, and resistance to chemotherapy (fig. 3).

4 CLINICAL FEATURES, MICROSCOPIC MORPHOLOGY, IMMUNOPHENOTYPE OF BPDCN

4.1 Clinical Features

BPDCNs account for less than 1% of all hematopoietic neoplasms^[71]. According to recent Surveillance Epidemiology and End Results (SEER) data, the morbidity of this disease in the United States is 0.04 cases per 100 000 individuals^[72]. BPDCN is more common in men than in women. Although the median age of patients at diagnosis is 53 years, this disease can happen at any age and appears to show a bimodal morbidity pattern that peaks in those younger than 20 years and older than 60 years, according to the SEER data^[72].

Cutaneous lesions occur in 64% of patients with BPDCN and are often the first symptom for patients seeking medical care^[73]. Julia *et al*^[74] reported that isolated skin damage was frequent (73% of patients), and cutaneous lesions could vary in size (from a few millimeters to 10 cm) and color (erythematous, reddish, or bluish) and present with bruise-like patches (12%), disseminated lesions (14%), and mucosal lesions (6%), as shown in fig. 4. Lymphadenopathy, splenomegaly, and cytopenia caused by bone marrow infiltration at diagnosis or during disease progression can be observed easily; at the same time, thrombocytopenia, anemia, and neutropenia in the peripheral blood can be found frequently because bone marrow is involved^[75]. Spreading to the central nervous system is common, and approximately one-third of patients with BPDCN has central nervous system involvement when their disease relapses^[75, 76]. Other affected sites include the liver, lung, tonsils, soft tissues, and eyes^[8, 73, 75, 77].

A subset of patients with BPDCN displays leukemic manifestations without noticeable cutaneous presentation^[75, 77, 79]. In a study reporting the largest number of patients with BPDCN and leukemic manifestations, about 23% of patients had no skin presentation at diagnosis, and only two had cutaneous manifestations during disease progression^[75]. A large proportion of patients with BPDCN had a history of myeloid neoplasms, such as acute/chronic myeloid leukemia, chronic myelomonocytic leukemia, or myelodysplastic syndrome^[8, 80].

4.2 Microscopic Morphology of BPDCN

PDCNs are expressed in two unique forms. The first variant, mature pDCs, is associated with myeloid neoplasms, and the other form, termed BPDCN cells, is associated with highly aggressive hematological tumors^[18]. The morphology of BPDCNs is heterogeneous and complex. Skin biopsies often display a suffused infiltration of monomorphic medium-sized blast cells characterized by irregular, eccentrically located nuclei; finely dispersed chromatin; and one or more small but distinctive nucleoli^[8, 80–82]. The

cytoplasm is dispersed and never granular. Mitoses are varying in number, and angioinvasion and coagulative necrosis are almost never found. Generally, malignant cells infiltrate the dermis and subcutaneous tissues but do not involve the epidermis^[81]. Lymph node involvement can be observed, and the tumor cells have an infiltration pattern similar to leukemic cells, which begin in the medulla and then develop in the interfollicular areas until completely infiltrating the lymph nodes and damaging the lymph node structure. Bone marrow involvement is common and may vary from small fractional infiltration to suffused bone marrow dissemination on bone marrow biopsy^[83]. On blood and marrow smears, tumor cells may show blastoid features similar to lymphoblastic morphology, with cytoplasmic microvacuoles, pseudopodia-shaped expansions, and lack of granules or crystals^[8]. Dysplastic alteration can manifest in the remaining hematopoietic tissues, especially in megakaryocytes^[8, 84], as displayed in fig. 4.

4.3 Immunophenotype of BPDCN

The diagnosis of BPDCN requires immunophe-

notyping and fundamentally relies on the expression of the typical CD4, CD56, CD123, CD303, and TCL1 molecular markers and lack of other lineage-specific markers^[7–10, 16, 85] (fig. 4 and table 1). The immunophenotype of a representative patient diagnosed with BPDCN in our hospital is shown in fig. 4 and immunophenotypic features are summarized in fig. 5. TCF4 can increase the specificity of the diagnosis more than all typical molecular markers identified recently^[57]. However, atypical immunophenotype is frequently reported, and several other lineage-specific antigens can be present, including CD2, CD5, CD7, cCD3, CD43, CD45RA, CD68, CD33, CD31, CD34, CD36, CD38, CD79a, CD117, HLA-DR, TdT, BCL2, BCL6, MUM1, and S100. Most of these are variably expressed in BPDCNs, which makes diagnosis difficult, especially when typical markers are absent^[15, 17, 81–83, 85–89]. To improve the diagnostic methods for BPDCN, many immunophenotype-related studies have proposed multiple suggestions as knowledge of this aggressive disease progresses.

BPDCNs show clinical and immunophenotypic

Fig. 4 Representative images showing cutaneous lesions and immunohistochemical expression in patients with BPDCN

A–C: The cutaneous lesions can vary in size (from a few millimeters to 10 cm) and color (erythematous, reddish, or bluish) and present with bruise-like patches, disseminated lesions, and mucosal lesions; D and E: HE staining of cutaneous lesions; F–I: Images with expression of CD4 (F), CD56 (G), CD123 (H), and BDCA-2 (CD303) (I). D, G, H (40×); E, F (100×); I (200×)

Table 1 The summary of BPDCN immunophenotypes

Immuno-phenotype	Expression rate (%)	Characteristics
CD45	100	Often located in the blast gate (dim CD45 with a low side scatter)
HLA-DR	100	Uniform bright in all cases
CD123	100	Decreased expression in 84% of cases
CD303	25	Decreased in neoplastic cells: negative expression in 75% and positive expression in 25% but decreased expression in BPDCNs when compared to reactive pDCs
CD56	97	Uniform positivity with the remaining few cases being partially positive
CD38	70	Decreased expression
CD7	69	Uniform expression in 50% cases
CD2	17	
CD33	45	Partial expression in 14% cases and uniform positivity in the remaining 86% cases.

BPDCN: blastic plasmacytoid dendritic cell neoplasm; ALL: acute lymphoblastic leukemia. pDCs: plasmacytoid dendritic cells

Fig. 5 Schematic representation and summary of immunophenotypic profiling in BPDCN by flow cytometry
A: Representative flow cytometry plots show critical biomarker expression in patients with BPDCN. B: biomarkers distribution in patients with BPDCNs

heterogeneity, and some studies have been conducted to account for this heterogeneity in diagnosing the disease. Garnache-Ottou *et al*^[85] developed a scoring system for diagnosis of BPDCN using a large series of markers based on flow cytometry of 20 BPDCN cases and 113 lymphoid and myeloid acute leukemia cases. They identified the expression of CD4 (CD56⁺) and lack of CD11c, cCD3, cCD79a, and MPO scored 1 point; CD123high and BDCA4+ scored 1 point each; and the expression of BDCA2 scored 2 points. The diagnosis of BPDCN is trustworthy when the total score is more than two points, which is applicable for typical or atypical

BPDCN immunophenotype. Julia *et al*^[82] described that the co-expression of the five most common markers, CD4, CD56, CD123, CD303, and TCL1, only occurred in 46% of patients with BPDCN. Based on an analysis of the immunohistochemical marker expression in skin biopsies for 91 well-documented cases, a confident diagnosis could be built when four of these five markers are present. The molecular markers CD2AP and SPIB were also identified as contributors to the diagnosis for BPDCN^[14, 15, 17]. The typical immunophenotypes of BPDCN are summarized in fig. 5.

The fact that BPDCNs show clinical and

immunophenotypic heterogeneity is undoubted; however, the connection between these tumors' clinical behavior and phenotype has not been identified, and the different phenotypic maturation stages are unknown. Some studies have since tried to shed light on these problems. Julia *et al*^[82] found that TdT⁺/S100⁺ BPDCN cells are more mature than TdT⁺/S100⁻ cells. Martin-Martin *et al*^[73] showed that patients with immature pDC phenotype (CD34⁺ and CD117^{-dim} with coexisting non-pDC lineage blast cells) exhibit a rare CD56⁻ phenotype, which are mixed with CD34⁺ non-tumor cells, and typically manifest in disease that is confined to the bone marrow. Conversely, patients with a more mature blast cell phenotype (e.g., CD34⁺CD117^{dim} is intermediately mature and CD34⁺CD117⁻ is mature) more commonly have skin and extramedullary involvement and extension into secondary lymphoid tissues. These results exhibited a highly different mature profile of BPDC tumor cells, which led to a heterogeneous clinical behavior of alteration from acute leukemia to peripheral mature lymphomas. Because phenotypes and clinical manifestations overlap between BPDCN and other tumors, distinguishing BPDCN from other misleading diseases is important. Because there is no uniform understanding of BPDCN, we need further exploration of the immunophenotype of BPDCNs.

5 CLINICAL COURSE AND TREATMENT OF BPDCN

BPDCN is a heterogeneous disorder, and little is known about its clinical abnormalities, disease associations, treatments, and outcomes. No standard of care regimens has been well developed, but recently the largest review of BPDCN evaluated the effectiveness of various different treatment regimens in 357 patients, including 74 pediatric and 283 adult patients^[90]. The results indicated that any type of chemotherapy or radiotherapy had better outcomes than no treatment, and the most effective chemotherapy regimens appeared to be those used to treat acute lymphoblastic leukemia. There was significantly higher remission rate for pediatric patients than for adult patients who received similar therapeutic regimens for acute lymphoblastic leukemia (93% vs. 77%, $P=0.04$), AML (77% vs. 47%, $P=0.05$), and lymphoma (80% vs. 53%, $P=0.05$). Children also were less likely than adult patients (27% vs. 57%, $P<0.01$) to relapse after complete remission. We also listed the response rates and survival outcomes with different regimens of the main BPDCN patients reported in literature^[8, 73, 75, 86, 91–95] (table 2).

The challenge in treating BPDCN is that, despite a high frequency of initial complete remission with chemotherapy, relapse is common and overall survival is typically less than 2 years^[74]. Allogenic stem cell

transplantation has been shown to increase mean survival duration^[8, 74, 90, 96, 97]. A systematic review of 128 patients receiving allo-hematopoietic cell transplantation for BPDCN was also reported^[96]. The pooled 2-year overall survival rate was 50% for all patients. Among patients allografted in their first complete remission, pooled 4-year overall survival and progression-free survival/disease-free survival rates were 67% and 53%, respectively. For patients allografted after the first complete remission, overall survival and progression-free survival/disease-free survival rates were 7% for both outcomes. Relapse rates were higher in patients treated with reduced intensity regimens than in those treated with myeloablative allo-hematopoietic cell transplantation regimens (40% vs. 18%). Compared with conventional chemotherapy, hematopoietic stem cell transplantation is most likely to benefit survival. Allogeneic hematopoietic stem cell transplantation could be the most beneficial to survival after patient accepted the first complete remission; For those patients only eligible for autologous stem cell transplantation, autologous transplantation is recommended after the first remission.

Promising data were recently reported using targeting or immunomodulatory agents, including SL-401, bortezomib, and venetoclax, to treat BPDCN (table 3). The immunotoxin tagraxofusp (SL-401) targets the IL-3 receptor alpha (CD123), which is typically overexpressed by pDC blasts. Of the 47 patients with BPDCN who received tagraxofusp treatment, 32 patients had first-line treatment and 15 received previous treatment. Among the 29 previously untreated patients who received tagraxofusp, the primary outcome occurred in 21 (72%), and the overall response rate was 90%; survival rates at 18 and 24 months were 59% and 52%, respectively. Among the 15 previously treated patients, the response rate was 67%, and the median overall survival was 8.5 months. Until now, tagraxofusp was the first new target agent approved for BPDCN treatment^[98, 99]. Lenalidomide, in a mouse xenograft with BPDCN cells, reduced tumor growth by increasing apoptosis and cell cycle arrest and decreasing tumor cell engraftment and tumor vascularization^[100]. Bortezomib, a proteasome inhibitor, could significantly reduce BPDCN cell growth *in vivo* and *in vitro*; the drug also decreased phosphorylation of the NF- κ B subunit, RelA^[19, 101]. Recently, Marmouset *et al* described the use and value of a lenalidomide/bortezomib/dexamethasone regimen for the treatment of three patients with BPDCN. After five cycles of chemotherapy, two patients obtained complete responses and one clinical remission^[102]. Additionally, the BCL-2 inhibitor venetoclax increased apoptosis in BPDCN cells and survival in mouse xenograft models^[103]. Montero *et al* reported two patients with relapsed/refractory BPDCN whose disease responded

Table 2 Summary of studies on BPDCN patients treated with methods related with ALL/lymphoma-type, AML-type, palliative therapy and radiotherapy

Treatment methods	<i>n</i>	CR <i>n</i> (%)	Relapse <i>n</i> (%)	Median relapse (Mon, range)	Median OS (Mon, range)	References
ALL/Lym-type	16	14 (87.5)	10 (71.4)	n.r.	ALL-type: n.a.; Lym-type: 10 (4–16)	Martin-Martin <i>et al</i> ^[73]
AML-type	9	9 (100)	7 (77.8)	n.r.	11 (8–14)	
ALL/Lym-type	15	10 (66.7)	6 (60)	n.r.	12.3 (1–32.9)	Pagano <i>et al</i> ^[75]
AML-type	26	7 (26.9)	0 (0)	n.r.	7.1 (0.2–19.5)	
ALL/Lym-type	13	11 (84.6)	n.r.	n.r.	12 (4–21)	Hashikawa <i>et al</i> ^[94]
AML-type	4	0 (0)	n.a.	n.a.	5.5 (1–18)	
Radiotherapy	4	3 (75)	n.r.	n.r.	6.5 (3–14)	
ALL/Lym-type	13	9 (69.2)	4 (44.4)	20.5 (11–36)	13 (8–72)	Lucioni <i>et al</i> ^[93]
Radiotherapy	3	2 (67)	1 (50)	8 (n.a.)	14 (13–30)	
Palliative therapy/None	3	0 (0)	n.a.	n.a.	3 (1–6)	
ALL/Lym-type	13	12 (92.3)	5 (41.7)	n.r.	n.r.	Tsagarakis <i>et al</i> ^[92]
AML-type	6	3 (50)	1 (33.3)	n.r.	n.r.	
Palliative therapy/None	3	0 (0)	n.a.	n.r.	n.r.	
ALL/Lym-type	20	16 (80)	n.r.	n.r.	n.a.	Jegalian <i>et al</i> ^[91]
AML-type	3	n.r.	n.r.	n.r.	6 (2–37)	
ALL/Lym-type	26	14 (53.8)	n.r.	6 (2–42)	12 (3–42)	Dalle <i>et al</i> ^[86]
AML-type	12	5 (41.7)	n.r.	12 (4–22)	19 (3–77)	
Radiotherapy	5	4 (80)	n.r.	5.5 (2–9)	19 (8–36)	
Palliative therapy/None	4	0 (0)	n.a.	n.a.	2 (1–12)	
ALL/Lym-type	15	12 (80)	9 (75)	6 (4–12)	12 (4–98)	Feuillard <i>et al</i> ^[8]
AML-type	6	6 (100)	6 (100)	10.5 (3–18)	14.5 (5–37)	
Palliative therapy/None	2	0 (0)	n.a.	n.a.	3 (3)	
ALL/Lym-type	131	98 (74.8)	n.a.	n.a.	n.a.	Total
AML-type	66	30 (47.6)				
Radiotherapy	12	9 (75)				
Palliative therapy/None	12	0 (0)				

BPDCN: blastic plasmacytoid dendritic cell neoplasm; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR: complete remission; OS: overall survival; Mon: month; n.r.: not reported; n.a.: not available; Lym-type: lymphoma-type; C(H)OP: cyclophosphamide, (daunorubicin), vincristine, and prednisone regimen; DVLP: doxorubicin, vincristine, asparaginase, and prednisone; hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; DA: doxorubicin, cytarabine; IA: idarubicin, cytarabine

Table 3 New or potential therapy for BPDCN

Regimen	Targeting	<i>n</i>	Treatment outcomes	Status
Tagraxofusp	IL-3	47	For 21 untreated patients, 19 (90%) obtained ORR, and survival rates at 18 and 24 months were 59% and 52% respectively; for previously treated patients, 10 (67%) obtained ORR, and median OS was 8.5 months.	A open-label, multicohort phase I – II study
IMGN632	IL-3	NA	NA	Phase 1 underway
XmAb14045	IL-3 and CD3	NA	NA	Phase 1 underway
CAR-T cell	IL-3	NA	NA	Phase 1 underway
Lenalidomide	Multiple (angiogenesis, NF-κB)	NA	Increased apoptosis, decreased cell engraftment and decreased tumor vascularization	Preclinical trial
Bortezomib	Proteasome and NF-κB signaling	NA	Decreased circulating BPDCN cells and RelA NF-kappaB signaling, increased mouse survival	Preclinical trial
Venetoclax	BCL-2	3	PR in 2 cases (at 4 weeks), CR in one case (at 5 months, response 5 months)	Preclinical trial

BPDCN: blastic plasmacytoid dendritic cell neoplasm; ORR: overall response rate; CR: complete remission; PR: partial remission; CAR-T cell: chimeric antigen receptor T cell; NA: not available

to venetoclax: both patients experienced a partial response at 4 weeks, suggesting BPDCN sensitivity to BCL2 inhibition^[103]. Another publication reported a patient with BPDCN who suffered a recurrence after combined cyclophosphamide, doxorubicin

hydrochloride, vincristine sulfate, and prednisone therapy followed by autologous hematopoietic stem cell transplantation. His skin biopsy at the time of recurrence showed BCL-2 positive disease, and he achieved complete remission after 5 months of

treatment with venetoclax and maintained complete remission at 10 months, which supports the potential effectiveness of venetoclax^[104]. Quick complete response was achieved with venetoclax and azacitidine in a case of relapsed disseminated BPDCN^[105].

Other therapies are being evaluated that also target CD123, a novel antibody-drug conjugate, IMGN632, which incorporates an anti-CD123 antibody with a DNA-alkylating agent and has shown significant preclinical activity both in myeloid and lymphoblastic leukemia^[106, 107]. This is currently being evaluated in a phase 1 study for BPDCN (NCT03386513). A bispecific antibody, XmAb14045, targeting CD123 and CD3 has been developed that crosslinks CD123-positive cancer cells to cytotoxic T lymphocytes, and is also being evaluated in a phase 1 trial that includes BPDCN patients. Chimeric antigen receptor T (CAR-T) cell therapy has shown promise for a number of hematologic malignancies, and CAR-T cells against CD123 have shown preclinical activity in AML models^[108]. CD28/4-1BB CD123 CAR-T cells displayed strong efficacy and low or no cytotoxicity against various subsets of normal cells with low CD123 expression in BPDCN^[109]. There are phase 1 trials underway to evaluate anti-CD123 CAR-T cell therapy in patients with BPDCN and AML (NCT03203369 and NCT02159495).

Recently, the development of bromodomain and extra-terminal domain inhibitors (BETis) has challenged the traditional notion that transcription factors cannot be targeted. BETis were shown to silence the expression of these BPDCN oncogenes causing their transcriptional control by “super-enhancers” (SEs), defined as large genomic clusters of bromodomain and extra-terminal domain (BET)-dependent regulatory regions. TCF4 acts as the major downstream target of BETis in BPDCN cells and is localized to the majority of SEs in BPDCN. BETis down-regulate several TCF4 targeted pDC-related genes, and TCF4 itself is strongly down-regulated by BETis, which may be correlated with the TCF4 locus containing a BPDCN-specific SE that is bound by BRD4. In addition, TCF4 knockdown reduces the expression of these SE-regulated genes. It is also demonstrated that ectopic TCF4 expression could rescue BPDCN cells from the toxicity of BETis. Thus, TCF4 controls a pleiotropic network of target genes in BPDCN, making it less likely that a genetic alteration targeting a single TCF4 target could overcome BETi toxicity. The application of BETis shed light on BPDCN treatment based on the strong mechanistic rational clinical evaluation^[57]. Treatment with a liver X receptor agonist decreases leukemic cell infiltration and BPDCN-induced cytopenia while increases survival in a BPDCN cell mouse xenograft model^[110]. Therefore, more research is needed to better understand the effect mechanisms of these treatments and develop predictive

markers and combination strategies.

Data on predictive factors of BPDCNs are currently unavailable. Survival analyses showed that CD303 expression, levels of TdT expression greater than 50%, and Ki-67 index higher than 67% were significantly associated with longer survival in BPDCN patients^[82], while 9p21.3 deletion was associated with shorter overall survival^[93]. Therefore, high Ki-67 and TdT expression may prolong survival. Previous publications have reported that pediatric patients without skin infiltration were expected to have better outcomes than their counterparts with skin infiltration, whereas this manifestation was not correlated with a difference in outcomes in adults^[111]. But the clinical presentation of BPDCN at the time of diagnosis in children does not differ from that in adults, especially in regard to the organs involved. Notably, younger age is an independent favorable prognostic indicator across all prognostic measures for BPDCN, including response to first-line chemotherapy, relapse rate and overall survival. In patients older than 63.5 years, the possibility of a negative result is higher^[90]. However, patients with central nervous system involvement do not show a statistically different relapse rate compared with those without^[90], in contrast to the viewpoint that central nervous system involvement may have an impact on event-free survival time^[8]. Based on the evidence as above, algorithm to guide the therapeutic strategy in patients with BPDCN is summarized in fig. 6.

6 CONCLUSION

BPDCNs originate from pDCs. However, the pDC population is divided into two subsets called pure pDCs and pDC-like cells. pDC-like cells show strong capacity for stimulating T cell proliferation, whereas pure pDCs' main function is secretion of IFN1. Additionally, pDC-like cells come from CDPs, and pure pDCs from IL-7Rα⁺Ly6D⁺SiglecH⁺ cells, suggesting that developmental encoding could exist, and in-depth research is needed. The genetic and immunophenotypic properties of BPDCNs overlap with those of pDCs and cDCs. PDC-derived tumors are rare and manifest in two main different clinical entities. The mature pDC neoplasms are associated with myeloid neoplasm while the highly aggressive BPDCNs show a distinctive cutaneous manifestation followed by rapid systemic dissemination, a heterogeneous phenotypic profile, complex but non-specific chromosome and genetic alterations, and poor prognosis. Chemotherapy regimens used for ALL have been shown to be the most effective treatment, while allo-hematopoietic stem cell transplantation can prolong survival across all age groups. High levels of expression of CD303, Ki-67, and TdT may prolong survival, whereas 9p21.3 deletion

Fig. 6 Proposed algorithm to guide the therapeutic strategy in patients with BPDCN

Adults eligible for chemotherapy may be considered for SL-401 or intensity conditioning regimens of ALL-type aggressive regimen induced therapy (i.e., VDLP, Hyper-CVAD), ALL-type and AML-type consolidation. Adults eligible for chemotherapy may be treated with low-dose chemotherapy or palliative chemotherapy. Allogeneic or autogenetic stem cell transplantation can increase mean survival duration. Experimental trial (venetoclax, bortezomib, or lenalidomide, etc.) serves as the option of relapse/resistance after HSCT or aggressive chemotherapy. AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; Ara-C: cytarabine; HSCT: hematopoietic stem cell transplantation; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone/methotrexate and cytarabine

has been associated with shorter overall survival.

Promising preclinical and clinical results have been published about BPDCN, including that target surface receptors (i.e., CD123) or inhibitors of aberrantly activated survival pathways (i.e., NF- κ B). BETis bring new sight for BPDCN treatment, other new treatments such as CAR-T cell therapy and liver X receptor agonists have been proposed, but, because of the rare incidence of the disease, progress in preclinical research for various targeted or immunomodulatory agents is slow, and the differences between monotherapy or combination therapy still need further exploration. Studies of biomarkers and immune monitoring are ongoing and may benefit future patients with BPDCN.

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Conflict of Interest Statement

The authors declared they had no conflicts of interest to this work.

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