Chapter 18
Blastic Plasmacytoid Dendritic Cell Neoplasm

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Introduction

First described in 1994 [1], blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematopoietic neoplasm. It has been variably known as blastic NK-cell lymphoma, agranular CD4+ natural killer cell leukemia, and agranular CD4+/CD56+ hematodermic neoplasm.

The normal cellular counterpart to BPDCN is the precursor plasmacytoid dendritic cell (pDCs). These cells play central roles in infectious and inflammatory conditions, primarily through secretion of type I interferons which stimulate T-cells and B-cells, resulting in effective augmentation of anti-viral immune responses, or in the case of autoimmune conditions, generation of abnormally autoreactive T-cells and B-cells, via overstimulated antigen presenting cells [2]. Reactive pDCs are increased in the lymph nodes of patients with inflammatory disorders such as Kikuchi-Fujimoto lymphadenitis and hyaline vascular Castleman disease [3, 4].

Given its relationship to normal plasmacytoid dendritic cells, BPDCN is classified as a precursor neoplasm related to acute myeloid leukemia (AML) in the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues [5].

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Epidemiology

In large retrospective reviews, BPDCN accounts for less than 1% of all acute leukemias and lymphomas, although, until recently, markers that help to distinguish BPDCN from AML were not widely available. There is a slight male predominance (3:1), with no ethnic or racial predisposition [6]. Mean age at presentation is 60–70 years, but a large age distribution is observed, including rare congenital cases. A pre-existing myeloid neoplasm, such as myelodysplastic syndrome or chronic myelomonocytic leukemia, has been noted in 5–10% of patients [6].

Etiology

The pathogenesis of BPDCN is poorly understood, and as such, no known environmental exposures or genetic predispositions have been described.

Clinical Features

The majority of patients have cutaneous involvement at the time of diagnosis, characterized by nodules or purpuric plaque-like skin lesions (Fig. 18.1). BPDCN may also present as a leukemic infiltrate in the blood or marrow, show involvement of the lymph nodes or spleen, or demonstrate simultaneous tissue and blood/marrow involvement. In cases where the neoplasm appears confined to the skin, dissemination to peripheral blood and bone marrow occurs shortly thereafter. Thrombocytopenia, anemia, and absolute neutropenia are commonly found on peripheral blood evaluation. Clinical features are summarized in Table 18.1.

Morphology and Immunophenotyping

Morphologic Features

The morphologic features of neoplastic cells of BPDCN can be quite variable, but in the most classic cases, cells are medium-sized with rounded to slightly irregular nuclei, fine chromatin, absent or inconspicuous small nucleoli, and scant to moderate amounts of cytoplasm; small cytoplasmic vacuoles may be present (Figs. 18.2 and 18.3). In cutaneous tissues, BPDCN may show perivascular, periadnexal, or sheet-like pattern of growth in the dermis and subcutis, with sparing of the overlying epidermis (Fig. 18.2). Bone marrow evaluation may reveal patchy involvement or complete effacement.

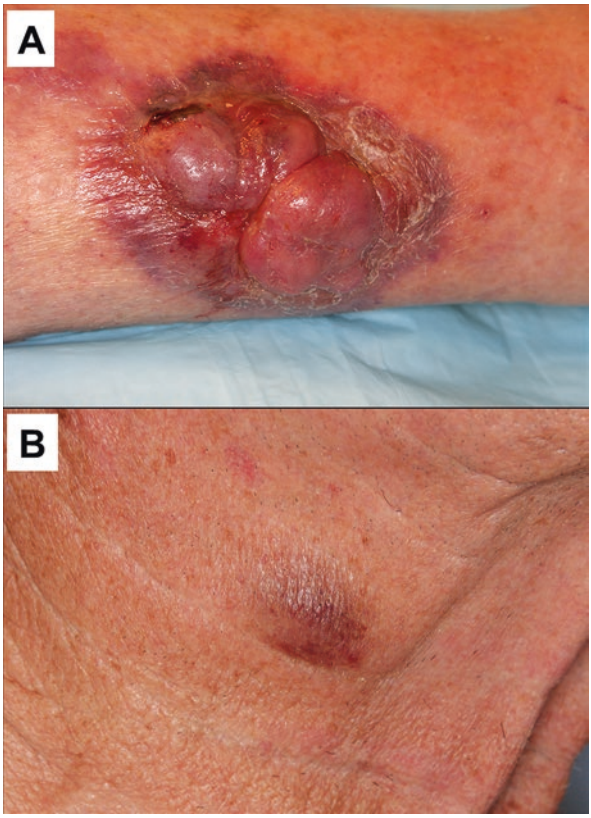

Fig. 18.1 Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm (BPDCN). (**a**) Violaceous nodules can be seen with skin infiltration by BPDCN. (**b**) Plaques are also commonly seen (Images courtesy of Dr. Youn Kim, Stanford University)

Table 18.1 Clinical features of BPDCN

Age
Median 65 year (range, 0–95)
Gender
M:F 3:1
Sites involved at diagnosis
Skin 70–90%
Peripheral blood 50–70%
Bone marrow 60–90%
Lymph node 50–70%
Spleen 40–60%
Other clinical findings
Cytopenias 70–90%

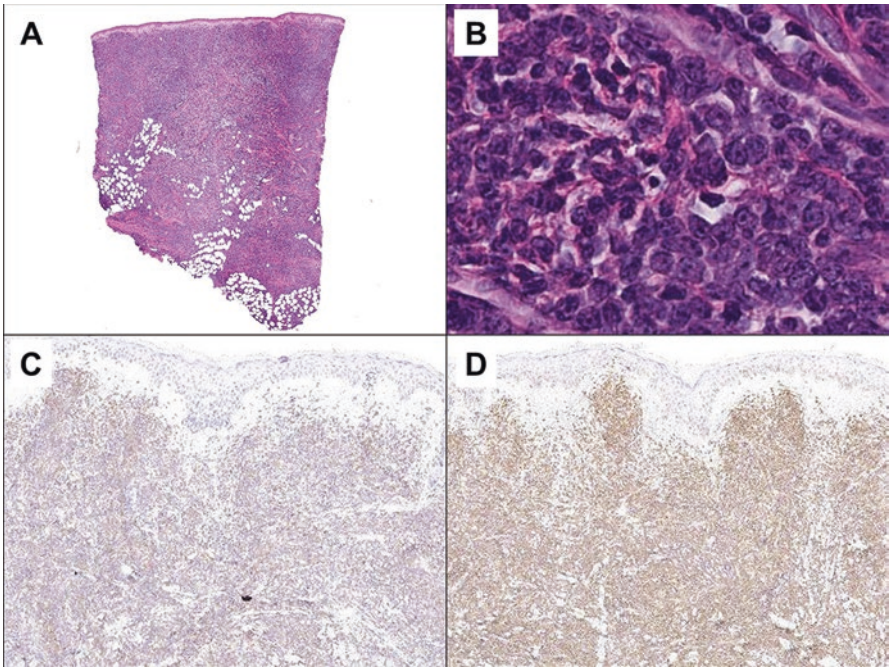

Fig. 18.2 Morphologic and immunohistochemical features of skin infiltration by blastic plasmacytoid dendritic cell neoplasm (BPDCN). (**a**) Sheet-like infiltration of mononuclear cells with sparing of the epidermis (H&E, 1×) (**b**) With higher power magnification showing neoplastic cells to have blastic chromatin with small to indistinct nucleoli (H&E, 400×). Positive immunohistochemical stains for (**c**) CD123 (40×), and (**d**) TCL1 (40×) are shown

Immunophenotype

Immunophenotypic analysis is critical in order to make the diagnosis of BPDCN and distinguish it from other entities. These proliferations consistently show expression of CD4 and CD56; however, this combination is nonspecific, as it can also be seen in the setting of NK/T-cell malignancies and AML, particularly those with monocytic differentiation. CD45 intensity can be dim or moderate by flow cytometry, also raising the possibility of AML or lymphoblastic leukemia/lymphoma. Bright CD123 expression is a hallmark of BPDCN and a useful feature in distinguishing it from AML. While expression of the myeloid-associated antigens CD13 and CD33 can be present, other markers of the myelomonocytic lineage (CD14, CD163, myeloperoxidase, lysozyme) are uniformly absent. Expression of CD303/BDCA-2, CLA/CD162, TCL1, and TdT is variable, which some investigators speculate may reflect the stage of maturation of the pDC that gives rise to the neoplastic clone [7]. T-cell-associated antigens CD2 and CD7 were found to be expressed in 37% and 11% of cases studied in the largest series [8]. There are isolated reports of

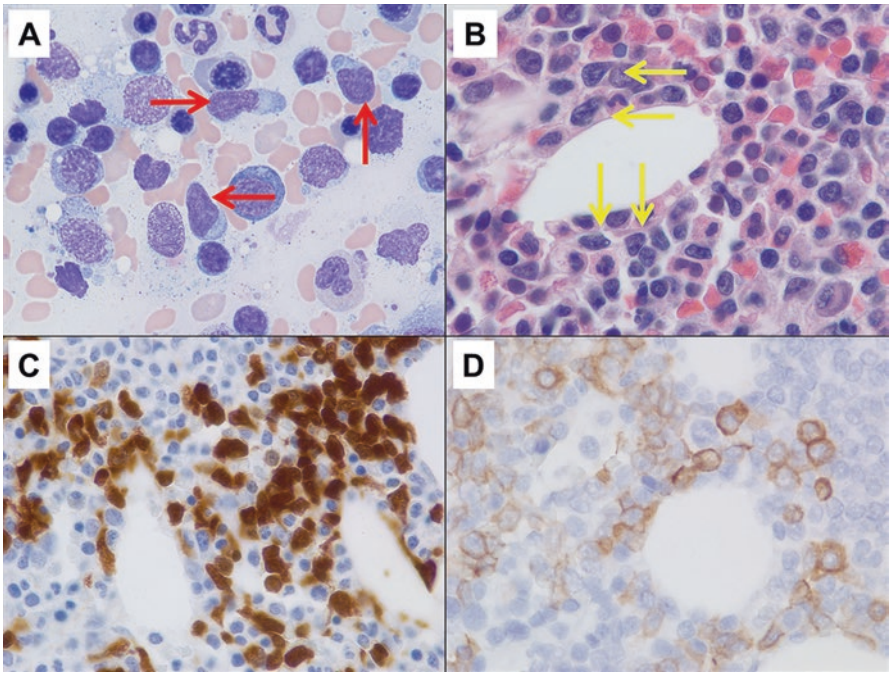

Fig. 18.3 Features of bone marrow infiltration by blastic plasmacytoid dendritic cell neoplasm (BPDCN). (**a**) Morphologic evaluation of a bone marrow aspirate shows scattered mononuclear cells with fine/blastic chromatin and small to indistinct nucleoli, and eccentric nuclei (*red arrows*; Wright-Giemsa, 1000×). (**b**) An H&E stained bone marrow core biopsy shows BPDCN cells (*yellow arrows*; H&E, 400×). Positive immunohistochemical stains for (**c**) TCL1 (400×) and (**d**) CD123 are shown (400×)

cytoplasmic CD3 expression in BPDCN; however, it has been attributed to the use of a polyclonal antibody and consensus guidelines suggest that the presence of CD3 should exclude a diagnosis of BPDCN [9]. Expression of B-lineage-associated antigens (CD19, CD20, PAX5) has not been described. CD22, a B-lineage marker, has been documented in a few cases when using the s-HCL-1 antibody clone; however, evaluation of 5 additional anti-CD22 clones showed no significant staining, indicating a clone-specific phenomenon [10].

Because of the clinical, morphologic, and immunophenotypic overlap with AML, a panel of antibodies is commonly performed to arrive at the correct diagnosis. Several groups have attempted to define the optimal antibody panel for distinguishing AML from BPDCN. Sangle and coworkers determined that a panel comprising CD4, CD56, CD123, lysozyme, myeloperoxidase, TCL1, and MxA proved useful in discriminating AML from BPDCN [11]. BPDCN was strongly associated with positive staining for CD4, CD56, CD123, TCL1, and MxA expression. Further, the expression of MPO and lysozyme confirmed the diagnosis of AML. CLA/CD162 and CD303 expression showed no significant association

with the reference diagnosis, although only 7 of 17 cases of BPDCN were studied with these two markers. Julia et al. studied the immunoprofile of 91 BPDCN cases and propose that a diagnosis of BPDCN can be established when at least 4 of 5 markers (CD4, CD56, CD123, CD303, and TCL1) are expressed, in agreement with a prior study by Cronin and colleagues [8, 12]. None of the cases showed simultaneous absence of CD4 and CD56. CD303, a specific marker of plasmacytoid dendritic cells, was found to be expressed in 63% of the 85 cases tested. Recently, myeloid cell nuclear differentiation antigen (MNDA) expression was found to be expressed in the majority of AML and uniformly negative BPDCN, providing another marker to help sort out the differential diagnosis. [13]. Immunohistochemical markers useful in differentiating BPDCN from mimics are summarized in Table 18.2.

Cytogenetics and Molecular Features

Karyotypic abnormalities are a common finding, with up to 80% of BPDCN showing complex (≥3) clonal abnormalities [14]. A few recurring chromosomal loci are deleted in BPDCN, namely 5q, 12p, 13q, 6q, 15q, and 9 (Table 18.3) [14–16]. In a handful of cases, a t(6;8)(p21;q24) translocation involving *MYC* has been identified [14, 17–19].

Sapienza and investigators subjected 27 BPDCN samples from untreated patients to gene expression profiling (GEP), which revealed that BPDCN appears significantly more related to normal myeloid precursors than lymphoid precursors, and closely resembles resting pDCs [20]. Further analysis showed that BPDCN tended to look more similar to AML on the molecular level, but shared patterns of gene deregulation that overlapped with both AML and ALL. GEP studies have demonstrated altered expression of tumor suppressors (*RB1, LATS2, CDC14B, DBC1, SYK, KPNA3*) and oncogenes (*HES6, RUNX2, FLT3*) [21].

Recently, whole-exome sequencing of BPDCN by Menezes identified 38 genes of interest [22]. Interrogation of 28 cases yielded mutations in a number of genes with known pathogenic effects in myeloid malignancies, including genes involved in DNA methylation (*TET2, DNMT3A, IDH1, IDH2)*, chromatin remodeling (*ASXL1*), cell proliferation (*NRAS, KRAS*), transcription factors (*ETV6, IKZF1/2/3*, *RUNX1*), splicing machinery (*SF3B1, SRSF2, U2AF1, ZRSR2),* protein kinases (*FLT3, JAK2, KIT)*, tumor suppressors (*TP53*), and ubiquitination (*CBLB, CBLC, UBE2G2).* Subsequently, 33 additional cases of BPDCN were subjected to massively paralleled sequencing, identifying many of the same molecular aberrations [23]. However, none of these mutations is specific for BPDCN and the prognostic significance of these mutations remains to be determined. A summary of pathogenic mutations detected by sequencing methods is presented in Table 18.4. Below we review in detail some of the more commonly described abnormalities and possible pathogenetic mechanisms.

Table 18.2 Immunohistochemical profile of BPDCN

Marker	CD2	CD4	CD7	CD13	CD33	CD34	CD43	CD56	CD68	CD117	CD123	CD163	CD303	Lysozyme	MPO	TCL1	TdT	MX-1	S100
# of cases tested	92	193	96	12	30	15	38	193	102	28	185	9	113	14	40	172	161	85	82
% Positive	38	99	21	0	73	0	97	94	79	11	97	0	50	0	0	95	29	67	32

Composite from Julia [8], Marafioti [54], Sangle [11], Johnson [13], Alayed [29], Herling [53], and Boiocchi [55]

Table 18.3 Chromosomal regions frequently deleted in BPDCN

Chromosome locus involved	Frequency (%)
5q	70
12p	60
13q	60
6q	50
15q	40
9	30

Adapted from Leroux et al. [14]

Table 18.4 Summary of somatic point mutations and insertion/deletion mutations identified by sequencing

Gene	Frequency of mutation (%)
DNA methylation	
TET2	30–50
IDH1/2	10
DNMT3A	10
Chromatin remodeling	
ASXL1	30
RAS family	
NRAS	10–30
KRAS	10
Transcription factors	
ETV6	10
RUNX1	Rare (<5)
IKZF1/2/3	20
Splicing machinery	
SF3B1	10
SRSF2	10
U2AF1	0–10
ZRSR2	10
Protein kinases	
FLT3	0–10
ATM	20
KIT	0–10
Tumor suppressors	
TP53	5–10
RB1	5–10

Adapted from Stenzinger et al. [23] and Menezes et al. [22]

Cell Cycle Genes (RB1, CDK Inhibitors, IKZF1, TP53)

Loss of gene loci important in the normal function of the cell cycle is common in BPDCN. *RB1* is a cell cycle gene located at 13q13.1-q14.3 and deletion or down-regulation of *RB1* has been identified in approximately half of cases studied (13/26, 50%) [14, 21, 24]. Normally, Rb1 prevents cells from transitioning from the gap 1 (G1) phase (G1) of the cell cycle into the synthesis (S) phase. Thus, in the case of

BPDCN, with loss of Rb1, the deletion or downregulation of its activities is believed to alleviate the block from G1 to S phases.

CDK inhibitors are also frequently (23/30, 77%) disrupted in BPDCN, resulting in unimpeded entry into the cell cycle [15, 24]. *CDKN1B* ($p27^{Kip1}$), *CDKN2A* ($p16^{INK4A}$), and *CDKN2B* ($p15^{INK4B}$) are CDK inhibitors that each play a role in controlling the G1/S-phase transition in the cell cycle. Deletion of the 9p21.3 locus (including *CDKN2A/CDKN2B*) and 12p13.2-p13.1 locus (including *CDKN1B*) was discovered in 67% and 57% of BPDCN studied by array-based comparative genomic hybridization (aCGH) [24]. Although this was a small series of nonuniformly treated patients, multivariate analysis suggested that the presence of homozygous 9p21.3 deletion was an independent prognostic factor. Jardin et al. identified loss of *CDKN2A/CDKN2B* and *CDKN1B* loci in a similar proportion of cases, suggesting that these alterations are important in the pathogenesis of BPDCN.

In about 20% of BPDCN cases, a locus on 7p12.2 that contains *IKZF1* is deleted [24]. Furthermore, Menezes and coworkers found frame shift and missense mutations in the *IKZF* gene family in an additional 20% of cases [22]. *IKZF1* encodes Ikaros, a DNA- and protein-binding transcription factor with zinc finger binding motifs. Ikaros plays a crucial role in the cell cycle regulation and cell differentiation, including an important role in lymphocyte development [25]. The significance of *IKZF1* mutations and deletions in BPDCN is still unknown.

Mutations of *TP53,* or loss of the chromosome region, 17p13, encompassing *TP53* are seen in many cases of BPDCN [15, 26]. The protein product of *TP53*, p53, is a tumor suppressor, and is activated during cellular stress and exerts antiproliferative effects at the G1/S and G2/M checkpoints in the cell cycle primarily through activating the CDK inhibitor p21. P53 also functions as a pro-apoptotic protein by activating *BAX*. Germline *TP53* mutations are seen in Li-Fraumeni syndrome (LFS). In LFS, patients have a 25-fold increased risk of developing cancer by age 50. Breast and adrenal carcinomas, gliomas, sarcoma, and leukemia are the most common neoplasms encountered in this setting.

Genes Involved in Hematopoiesis (ETV6, TET2, FLT3, ASXL1)

In slightly more than half of the BPDCN cases studied, Leroux et al. found deletions in the locus surrounding *ETV6*, suggesting that loss of transcriptional repression by *ETV6* may play an important role in BPDCN pathogenesis [14]. In addition, a rare case of BPDCN harboring an *ETV6* rearrangement with an unknown partner gene has also been reported [27].

ETV6 encodes a protein that mediates cell proliferation and differentiation, and is required for establishing embryonic hematopoiesis in the bone marrow [28]. How deletions and mutations affect the pathogenesis of BPDCN is still unknown, though the *ETV6* locus is frequently translocated in cases of AML and B-lymphoblastic leukemia (B-LBL). *ETV6* functional effects in translocations are dependent on its partner and ultimately result in oncogenesis.

TET2 (Ten-Eleven Translocation-2) is part of a family of dioxygenases that promote DNA demethylation and mutations have been found in approximately 50% of the BPDCN cases interrogated [22, 26, 29]. These mutations are heterozygous, with most occurring in exons 3 and 11 as frame shift or nonsense mutations. Changes in *TET2* expression and function can lead to alterations in posttranscriptional modification of histones and ultimately changes in gene expression.

Yet another gene mutated in BPDCN, *FLT3*, encodes the protein FMS-like tyrosine kinase 3, which is a receptor tyrosine kinase that transmits signals important for cellular proliferation and survival. *FLT3* is critical for normal development of the hematopoietic systems, including pDCs [30–33]. A significant proportion of cases of AML harbor *FLT3* mutations, either in the form of internal tandem duplications (ITD) involving the juxtamembrane domain or tyrosine kinase domain (TKD) mutations and affect prognosis [34]. While BPDCN shows some morphologic, immunophenotypic, and genetic overlap with AML, only rare published cases have demonstrated *FLT3* mutations, including both ITD and TKD mutations [22, 26]. *FLT3* inhibitors are being evaluated in the treatment of AML and may be of utility in *FLT3*-mutated BPDCN [35].

ASXL1 is mutated in roughly one-third of the BPDCN cases interrogated [22]. *ASXL1* mutations are not unique to BPDCN, as they are found in a number of myeloid malignancies, including chronic myelomonocytic leukemia, myelodysplastic syndrome, and AML. *ASXL1* can act independently and in concert with BRCA1-associated protein (BAP1) to promote deubiquitination of histone proteins, some of which are involved in cell proliferation. Although this pathway is thought to be important for regulating myelopoiesis, specific mechanisms of tumorigenesis in the setting of *ASXL1* mutations are largely unknown [36–40].

DNA Repair Genes (HINT1, EWSR1, NPM1)

Studies of the 5q commonly deleted region in BPDCN have yielded a few known cancer-related genes, including *HINT1* [41]. *HINT1* (histidine triad nucleotide-binding protein 1) encodes a purine phosphoramidase that inhibits transcriptional activity of activation protein-1 (AP-1), α-catenin, MITF, and USF2 (upstream transcription factor 2, c-fos interacting). *HINT1* deficiency impairs acetylation of the ATM protein, which inhibits DNA repair mechanisms [42]; its functional role in BPDCN is unknown.

EWSR1 is a member of the *TET2* family of genes; it binds DNA/RNA and has a general role in gene expression and cell signaling. Additionally, *EWSR1* plays a role in controlling DNA-damage-induced alternative splicing of some oncogenic proteins, such as *BRCA1* [43]. *EWSR1* gene fusions are common in sarcomas, including the Ewing sarcoma family of tumors. A single case of BPDCN has shown *EWSR1* rearrangement with an unidentified translocation partner, suggesting that this locus may play a role in the pathogenesis of some cases of BPDCN [44].

NPM1 encodes the protein nucleophosmin, which mediates a number of different cellular processes, including DNA repair, regulation of the *TP53* tumor suppressor pathway, and cell cycle events. *NPM1* mutations have been identified in 20% of

the cases of BPDCN analyzed, and include frame shift, nonsense, and missense mutations [22]. *NPM1* is familiar in the context of AML, where it is mutated in approximately 50% of cases, and can affect prognosis [45]; however, the role of *NPM1* mutations in BPDCN is unclear.

Therapy and Prognosis

As a rare entity, a uniform approach to therapy for BPDCN has not been devised. Non-Hodgkin lymphoma (hyper-CVAD, CHOP, or CHOP-like), AML, and ALL-type regimens have been employed [46–49]. While the majority of patients are able to achieve complete remission (CR), nearly all relapse, regardless of therapy, with a median overall survival (OS) of approximately 12 months [5].

Pagano et al. retrospectively identified 43 patients with BPDCN [50]. Of those treated with induction therapy, 60% were treated with an AML regimen and 35% were treated with an ALL regimen. CR was obtained in 17 patients, and though ALL-directed therapies showed significantly better initial remission rates than those that received AML-directed treatment ($p = 0.02$), patients treated with ALL therapy were more likely to experience eventual relapse. Hypomethylating agents (e.g., 5-azacitidine), which are commonly used in the treatment of myeloid malignancies, have been used in the treatment of a few BPDCN patients; however, despite good initial responses, the patients showed dismal outcomes [51]. Hyper-CVAD has also been shown to have some efficacy with median OS of 18 months and median CR of 21 months in at least one study [49].

The role of allogeneic and autologous stem cell transplant is still not well understood but in some instances, prolonged survival can be seen in patients [49, 50]. In the study by Pagano et al., the median OS of 6 allogeneic hematopoietic stem cell transplant recipients was 23 months, compared to 7 months in the 35 patients who did not undergo transplant. In a separate study by Pemmaraju et al., allogeneic and autologous stem cell transplant (SCT) patients had an overall similar median OS (18 months), compared to non-SCT patients treated with hyper-CVAD, CHOP, and other therapies (23 months).

Given the expression of CD123 and CD56 in BPDCN, clinical trials with anti-CD123 therapy (SL-401) and anti-CD56 (lorvotuzamab) are underway. In a prospective study of SL-401 therapy, Frankel et al. found that 7/9 patients had objective response, with 3 patients alive and in remission (3, 7, and 20 months follow-up) [52]. Clinical trials using lorvotuzamab for BPDCN are ongoing [49].

Conclusion

BPDCN is a rare, aggressive malignancy derived from immature plasmacytoid dendritic cells that shows a characteristic CD4+/CD56+/CD123+ immunophenotype. Even with aggressive therapy, including stem cell transplant, the prognosis is

dismal. Although there is significant morphologic, immunophenotypic, mutational overlap with AML, recent gene expression profiling studies have shown distinct differences between these two entities, possibly providing new avenues for developing targeted therapies. While there are notable differences, the spectrum of gene alterations discovered by sequencing methods suggests at least a partial overlap with AML and implies that therapeutic strategies targeting aberrant methylation, chromatin remodeling, and splicing machinery in AML should also be investigated in BPDCN. Early results with anti-CD123 therapy have shown promising results; however, additional investigation will be required to determine whether this provides improved recurrence-free or overall survival. Increased awareness of this entity and further investigation of pathogenic mechanisms using modern techniques will serve to better define and devise optimal treatment strategies for BPDCN.

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