BPDCN is a rare but aggressive hematological malignancy with a poor prognosis.


Blastic Plasmacytoid Dendritic Cell Neoplasm: Update on Molecular Biology, Diagnosis, and Therapy
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Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy with an aggressive clinical course. Most patients with BPDCN have skin lesions and simultaneous involvement of the peripheral blood, bone marrow, and lymph nodes.

Methods: A search of PubMed and Medline was conducted for English-written articles relating to BPDCN, CD4+CD56+ hematodermic neoplasm, and blastic natural killer cell lymphoma. Data regarding diagnosis, prognosis, and treatment were analyzed.

Results: BPDCN is derived from precursor plasmacytoid dendritic cells. The diagnosis of BPDCN is based on the characteristic cytology and immunophenotype of malignant cells coexpressing CD4, CD56, CD123, blood dendritic cell antigens 2 and 4, and CD2AP markers. Multiple chromosomal abnormalities and gene mutations previously reported in patients with myeloid and selected lymphoid neoplasms were identified in approximately 60% of patients with BPDCN. Prospectively controlled studies to guide treatment decisions are lacking. The overall response rate with aggressive acute lymphoblastic leukemia–type induction regimens was as high as 90%, but the durability of response was short. Median survival rates ranged between 12 and 16 months. Patients with relapsed disease may respond to L-asparaginase–containing regimens. Allogeneic hematopoietic stem cell transplantation, particularly when performed during the first remission, may produce durable remissions in selected adults.

Conclusions: BPDCN is a rare aggressive disease that typically affects elderly patients. The most commonly affected nonhematopoietic organ is the skin. Although BPDCN is initially sensitive to conventional chemotherapy regimens, this response is relatively short and long-term prognosis is poor. In the near future, novel targeted therapies may improve outcomes for patients with BPDCN.
Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and aggressive hematological neoplasm derived from the precursor of plasmacytoid dendritic cells (pDCs).\(^1\) The nomenclature of BPDCN has evolved over the last 20 years; the disease is classified under acute myeloid leukemia (AML) and related precursor neoplasms in the 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues.\(^1\) It was initially described in the mid-1990s as agranular CD4\(^+\) natural killer (NK) cell leukemia due to its unique agranular morphology and phenotype (CD4\(^+\), CD56\(^-\), CD15\(^-\), and CD3\(^-\)).\(^2,3\) It has also been termed blastic NK cell lymphoma\(^4,5\) due to its expression of NK-cell marker CD56, blastic NK cell leukemia/lymphoma, as well as CD4\(^+\) CD56\(^+\) hematodermic neoplasm/tumor based on morphology, immunophenotype, and tropism for the skin.\(^5,6\)

Epidemiology

BPDCN can occur at any age and any geographical area; however, most patients are older adults with a median age of 67 years (range, 8–105 years), and the male:female ratio is 2.2–3.0:1.0.\(^7,8\) Although the exact incidence of BPDCN is unknown, it represents 0.44% of all hematological malignancies, less than 1% of acute leukemias, 0.7% of cutaneous lymphoma cases, and 6.3% of the NK-cell lineage malignancies in Japan.\(^5,9-12\) In 2005, an estimated 100 cases were reported since its first description,\(^13\) and, since then, more than 100 new cases have been described in the literature.

Etiology

The etiology of BPDCN is unknown, with no evidence suggesting an association with Epstein-Barr virus.\(^1\) A single case of BPDCN has been reported in a carrier of human T-cell lymphotropic virus 1, favoring a random coincidence over causative relation.\(^14\) In a series of 43 patients with BPDCN, 10 patients (23%) were diagnosed with secondary leukemia.\(^8\) In 4 patients (9%), myelodysplastic syndrome (MDS) preceded BPDCN and had a median latency time of 3.5 years (range, 1–4 years); 6 patients (14%) presented with therapy-related leukemia following chemotherapy for the first neoplasm. The median time of latency between chemotherapy exposure and diagnosis of BPDCN was 5 years (range, 1–15 years).\(^8\) These observations support a hypothesis that exposure to prior chemotherapy is an important pathogenic factor, and the association with myeloid neoplasms suggests that a putative initiating mutation might reside in hematopoietic stem cells or a common myeloid/lymphoid progenitor.\(^15\)

Cell of Origin

Normal pDCs can originate from common myeloid or common lymphoid progenitors.\(^16\) Due to a lack of lineage-specific markers and CD56 expression, BPDCN was initially believed to have arisen from immature NK cells;\(^6\) however, subsequent studies identified a malignant cell counterpart in plasmacytoid monocytes.\(^5,17\) It is believed that BPDCN arises from precursor pDCs, with normal pDCs accounting for fewer than 0.4% of peripheral blood mononuclear cells.\(^3\) A small proportion of these cells reside in primary and secondary lymphoid organs.\(^10,18\) Nonmalignant pDCs can accumulate in various pathological conditions such as autoimmune diseases, classical Hodgkin lymphoma, and carcinomas.\(^19\)

pDCs are characterized by a lineage (Lin) negative human leukocyte antigen (HLA)-DR\(^+\) CD56\(^-\) CD123\(^+\) CD11c\(^-\) immunophenotype, which is distinct from the immunophenotype seen in malignant cells of BPDCN. Functionally, pDCs belong to a group of type I interferon–producing cells implicated in innate adaptive immune responses such as sensing nucleic acids of viruses and bacteria via the Toll-like receptors 7 and 9 expressed on the surface of pDCs.\(^19,21\)

An analysis of subsets of dendritic cells in normal healthy individuals identified a potential normal counterpart of BPDCN.\(^22,23\) A search for cells with the Lin\(^-\) HLA-DR\(^+\) CD56\(^-\) immunophenotype revealed a minor cell population comprising 0.03% of peripheral blood mononuclear cells among the healthy volunteers. These plasmacytoid dendritic-like cells (pDLCs) were functionally distinct from more abundant normal pDCs expressing the Lin HLA-DR\(^+\) CD56\(^-\) immunophenotype.\(^25\) The ratio of pDLC:pDC was higher in bone marrow than in peripheral blood, and pDLC also expressed BDCA2, BDCA4, myeloid antigens, and Toll-like receptors, yet produced less interferon \(\alpha\) after stimulation. These data demonstrate that pDLCs are a distinct subpopulation with an immunophenotype similar to BPDCNs.

Molecular Biology

Approximately two-thirds of patients with BPDCN have multiple karyotypic abnormalities (Table).\(^1,24-52\) Leroux et al\(^24\) reported 6 recurrent cytogenetic abnormalities, including chromosomes 5q (72%), 12p (61%), 13q (64%), 6q (50%), 15q (43%), and monosomy 9 (28%) in 21 patients; however, none were specific or diagnostic. Lucioni et al\(^25\) employed array-based comparative genomic hybridization and found the 4 most commonly deleted regions involved 9p21.3 (CDKN2A/CDKN2B), 13q13.1-q14.3 (RB1), 12p13.2-p13.1 (CDKN1B), and 13q11-q12 (LAT52), with biallelic loss or multiple heterozygous deletions of these genes in more than 90% of cases. The biallelic loss of 9p21.3 was associated with poor prognosis.

Wiesner at al\(^26\) analyzed skin samples from 14 patients using high-resolution, array-based comparative genomic hybridization and immunostaining.
and found that the most frequent chromosomal aberrations were the losses of chromosomes 9, 12, 13, and 15. A loss of the CDKN1B locus was identified in 64% of tumors, and the cell-cycle inhibitor p27 (KIP1), which is encoded by CDKN1B, was weakly expressed in the nuclei of tumor cells. A loss of the CDKN2A/ARF/CDKN2B locus occurred in 50% of patients. The cell-cycle inhibitor p16 (INK4a), which is encoded by CDKN2A, was not expressed in tumor cells, suggesting a complete loss of function. The loss of chromosome 13, including RB1, was observed in 43% of tumors.

The results of this study suggested that the loss of multiple cell-cycle checkpoints that control proteins might play a role in the malignant transformation and the aggressive biological behavior of BPDCN.

Tokuda et al reported on an infant with congenital BPDCN with clinically manifested hemophagocytic lymphohistiocytosis. An analysis of the peripheral blood leukocytes revealed a t(2;17;8)(p23;q23;p23) translocation with a CLTC-ALK fusion gene. This translocated fusion gene was identified in cells of myeloid and T-cell lineages, suggesting that the chromosomal defect occurred in a common myeloid/lymphoid progenitor.

Sapienza et al studied gene expression profiling in 27 samples of BPDCN and 8 samples of non-neoplastic resting pDCs. The up regulation of the nuclear factor (NF)-κB pathway concurrently with the upregulation of 2 NF-κB targets (BCL2 and IRF4) was detected and confirmed by immunohistochemistry. Both the proteasome inhibitor bortezomib and a selective inhibitor of IκB kinase-β induced cell cycle arrest and apoptosis in BPDCN cells.

Dijkman et al identified the overexpression of the oncogenes HES6, RUNX2, and FLT3 without the associated genomic amplification as well as the high expression of various pDC-related genes. Alayed et al also studied 16 patients with BPDCN, 5 of whom (31%) had myelodysplastic changes in their marrow. Conventional cytogenetics revealed the abnormal karyotype in 6 of the 13 (46%) patients. Targeted next-generation sequencing was performed on 5 patient samples and showed TET2 mutations but no other MDS/AML-associated mutations.

Menezes et al performed whole-exome sequencing on samples of BPDCN. Based on these data, the researchers designed a custom panel of 38 genes for a targeted resequencing of 25 samples. Their data revealed mutations in TET2 (36%), ASXL1 (32%), NPM1 (20%), NRAS (20%), IKZF1 (20%), IKZF1-3 (20%), ZEB2 (16%), HOXB9 (4%), and UBE2G2 (4%). A total of 48% of patients with gene mutations in the methylation pathways had significantly worse overall survival rates than patients without these gene mutations (11 months vs 79 months).

Taylor et al reported on the next-generation sequencing of all exons of 219 genes known to be

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aCGH = array-based comparative genomic hybridization, GEP = gene expression profiling, NA = not applicable, NGS = next-generation sequencing, TS = target sequencing, WES = whole-exome sequencing.
recurrently mutated in hematological malignancies. A discovery gene cohort was sequenced in 7 patients with BPDCN. Many mutations in genes previously described in various hematological malignancies, such as TET2 (57%), TP53 (14%), and ASXL1 (28%), were confirmed, along with multiple loss-of-function mutations in the splicing factor ZRSR2 (57% of patients). The mutations were also more frequently present in older men. Altogether, these molecular data demonstrate that BPDCN cells can carry multiple mutations that overlap with the genetic abnormalities of myeloid and lymphoid neoplasms, leading to the dysregulation of multiple pathways that may serve as targets for agents (eg, proteasome and anaplastic lymphoma kinase inhibitors).

Clinical Manifestations
Most patients present with nonpruritic cutaneous lesions, blood, bone marrow, and lymph node involvement, although patients with cutaneous disease alone have also been described. Cutaneous lesions are variable in size, shape, and color and can present as tumors, nodules, bruise-like infiltrates, or plaques (Fig 1). In a large registry study, the majority of patients manifested with skin nodules (73%) and, less frequently, with bruise-like lesions (12%). Splenomegaly, hepatomegaly, and cytopenias due to bone marrow involvement can be present at diagnosis or may occur with disease progression. Involvement of other sites, including soft tissues, the lungs, and the central nervous system, has been also reported. Less frequently, patients with BPDCN can present with in the leukemic phase without skin involvement.

Diagnosis
The diagnosis of BPDCN is pathological (Fig 2). BPDCN should be suspected in older patients with non-specific persistent skin lesions refractory to treatment; these patients should undergo skin biopsy. In addition to characteristic morphology, a demonstration of a specific immunophenotype either by immunohistochemistry or flow cytometry is required for diagnosis.

Skin biopsy typically demonstrates a diffuse, monomorphic infiltrate of medium-sized blast cells with irregular nuclei, fine chromatin, and at least 1 small nucleolus. Typically, malignant cells do not infiltrate the epidermis (Fig 3). The cytoplasm is scant and agranular. Mitoses are variable in number and angioinvasion and coagulative necrosis are absent. Bone marrow is involved in the majority of patients. Findings on bone marrow biopsy may range from small interstitial infiltrates detectable by immunohistochemistry or flow cytometry to diffuse bone marrow involvement (Fig 4). Dysplastic changes may also be present in residual hematopoietic tissue, particu-
larly in megakaryocytes. BPDCN exhibits a specific immunophenotype and coexpresses CD4, CD43, CD45RA, and CD56 as well as pDC-related antigens, including CD123 (interleukin 3α chain receptor), T-cell leukemia 1 (TCL1), cutaneous lymphocyte-associated antigen, blood dendritic cell antigen (BDCA) 2 (CD303), BDCA4/CD304, CD2AP, Spi-B transcription factor, and platelet endothelial cell adhesion molecule (CD31). Terminal deoxynucleotidyl transferase (TdT) is expressed in approximately one-third of cases. Stem cell markers, including CD34 and CD117, and Epstein–Barr virus-encoded small RNAs are negative. The immunophenotype of BPDCN overlaps with pDC, occurring in reactive lymph nodes except the expression of CD56 and TdT. CD7 and CD33 expression is common. T-cell markers (CD3, CD5) and B-cell markers (CD19, CD20, CD79a) are not expressed. Typically, lysozyme and myeloperoxidase are negative. Rarely, CD56 can be negative; in such cases, BPDCN can be diagnosed based on morphology and complete immunophenotypic profile.

Garnache-Ottou et al proposed a diagnostic algorithm for BPDCN. They determined that the coexpressions of CD4+, CD56+/−, CD123+, BDCA2+, and/or BDCA4+ and an absence of CD3−, CD11c−, MPO−, and CD79a− are diagnostic for BPDCN. If CD123 expression is negative or dim, or when CD123 is positive but cells do not express BDCA2 or BDCA4, then a diagnosis of BPDCN should not be considered. Julia et al analyzed 91 patients with BPDCN and identified that the 5 most characteristic immunophenotypic markers are CD4, CD56, CD123, CD303, and TCL1.

Fig 3. — (A) Punch biopsy of a skin lesion showing blastic plasmacytoid dendritic cell neoplasm (H & E, ×40) and (inset) medium-sized malignant cells spare the epidermis (H & E, ×1000). (B) Immunohistochemical staining demonstrates the coexpression of CD4, CD56, CD123, and (immunoperoxidase, ×200). (C) Flow cytometry identified an atypical lymphoid population (areas in red) expressing CD45 and CD56 that was negative for T-cell markers (CD3, CD8). H & E = hematoxylin and eosin, TdT = terminal deoxynucleotidyl transferase.
Simultaneous expression of all markers was observed in 46% of patients, but the expression of 4 markers was sufficient for a reliable diagnosis.  

**Differential Diagnosis**

BPDCN must be differentiated from several distinct myeloid and dendritic cell neoplasms and from cutaneous involvement with T-cell and NK-cell malignancies exhibiting the CD4⁺ or CD56⁺ immunophenotype. Extramedullary myeloid sarcoma (EMS) may be difficult to differentiate from BPDCN because immunophenotypic overlap exists among these 2 diseases and both diseases frequently manifest with skin infiltration.

Sangle et al studied the clinical utility of 3 novel markers previously described in BPDCN (myxovirus A, CD162/cutaneous lymphocyte-associated antigen, and CD303/BDCA2) on 23 paraffin samples of EMS and 17 samples with BPDCN. The results of this study suggested that BPDCN is associated with the positive coexpression of CD56, TdT, or TCL1 or negative staining for lysozyme. The EMS samples also showed positive staining for lysozyme or myeloperoxidase or negative staining for CD56, CD123, myxovirus, or TCL1. Two of the 3 novel markers (CD162 and CD303) showed a poor predictive value for differentiating BPDCN from EMS.

Patients with cutaneous T-cell lymphoma frequently present with skin lesions and blood involvement, but the disease can be differentiated from BPDCN based on morphology, disproportionate epidermotropism, and mature T-cell immunophenotype with a lack of CD56 expression. Extramedullary NK/T-cell lymphoma can manifest with skin lesions and the expression of the CD4⁺/CD56⁺ immunophenotype. This rare aggressive malignancy can be differentiated from BPDCN by demonstrating Epstein–Barr virus positivity via in situ hybridization using Epstein–Barr virus-encoded small ribonucleic acids.

Vitte et al identified 42 patients from a French database who had cutaneous involvement of malignant myeloid and dendritic cell neoplasms. Four distinct clinicopathologic groups were identified, the first of which included myelomonocytic cell tumors (n = 18) positive for CD68, myeloperoxidase, or both but negative for dendritic cell markers. The second group consisted of mature pDC tumors (n = 16) coexpressing CD123, TCL1, and CD303 but missing CD56,
CD1a, and S100 markers. The third group was composed of blastic pDC tumors (n = 4) consisting of medium-sized blasts positive for CD4, CD56, CD123, and TCL1 but negative for CD1a and S100. The fourth group included blastic indeterminate dendritic cell tumors (n = 4) that coexpressed monocytic and dendritic cell markers. A different prognosis was observed among these disease entities. A minimal diagnostic panel for stratification of all 4 entities included CD68, CD1a, S100, langerin, and CD123.

Assaf et al35 studied a heterogeneous group of cutaneous malignancies expressing the CD56 marker, including hematodermic neoplasm, AML, NK/T-cell lymphoma, and cutaneous T-cell lymphoma. Patients without a diagnosis of cutaneous T-cell lymphoma had a poor prognosis and a median survival rate of 11 months. Altogether, these data underline the complexity and difficulty of diagnosing cutaneous myeloid and dendritic cell neoplasms, which frequently require the expertise of dermatopathology and hematopathology consultants at a tertiary center.

**Therapy**

Typically, patients with BPDCN have poor outcomes. Prospective data are lacking, with retrospective case reports, case series, and disease registry reviews alone available to guide treatment decisions. Reported median overall survival rates in most of the studies reviewed ranged from 12 to 16 months.7,15,50

**Induction Therapy**

BPDCN can be initially limited to skin without obvious systemic involvement. Skin-directed therapies with focal radiation therapy, systemic glucocorticosteroids, or nonintensive chemotherapy regimens can be initially effective and may lead to the complete resolution of cutaneous lesions, but such approaches do not appear to provide a long-term benefit.33-35 Nearly all patients relapse within several months after such treatment; however, because patients with isolated cutaneous lesions may have better prognoses, the skin-directed therapeutic approach can be a reasonable palliative option for patients who have a poor performance status due to underlying comorbidities and who are unable to tolerate systemic intensive chemotherapy.35

Standard frontline therapy has not been established for patients with advanced-stage BPDCN; thus, participation in a clinical trial should be encouraged (Fig 5). Clinical practice varies based on institutional preference. Patients with BPDCN may have been treated with regimens derived from the management of more common hematological malignancies, including non-Hodgkin lymphoma (cyclophosphamide/hydroxydaunomycin/vincristine/prednisone [CHOP] or CHOP-like), acute lymphoblastic leukemia (ALL; hyperfractionated/cyclophosphamide/vincristine/doxorubicin/dexamethasone [hyper-CVAD] alternating with methotrexate and cytarabine), and AML.51-55 Feuillard et al51 treated 23 patients with CHOP-like regimens and reported a complete response (CR) rate of 86%; however, responses were short lived, with a median time to relapse of 9 months. Three patients had isolated cutaneous lesions at diagnosis and demonstrated bone marrow involvement at relapse, and 5 patients had central nervous system relapse. Overall survival was 25% after 24 months of follow-up.51 More intensive, ALL-like treatment regimes (eg, hyper-CVAD) yielded higher response rates. Pemmaraju et al52 reported a CR of 90% in 10 patients treated with hyper-CVAD, reporting a median duration of response of 20 months and a median overall survival rate of 29 months.

AML-like treatment regimens have also been used as initial therapy. Dietrich et al53 reported a CR rate of 83% in 6 patients treated with an AML-like regimen. An et al54 reported a single institutional experience with 6 patients treated with multiagent chemotherapy as first-line treatment and 1 patient treated with radiation therapy. The median progression-free survival rate was 8.6 months (range, 2.6–28.9 months) and the overall survival rate was 15 months (range, 4.4–60.0 months), with a median follow-up of 13.8 months (range, 1.9–29.9).54 Four patients with cutaneous involvement survived, which is in contrast to the patient without skin involvement who died of disease.54 Gills et al55 treated 11 patients with BPDCN, with 6 receiving high-dose methotrexate followed by L-asparaginase. All 6 patients (55%) who received the combination therapy achieved CR, while 5 patients treated with an alkylating agent as frontline therapy achieved only a partial response (PR). Nine patients (82%) died of disease progression (median survival, 9 months).55

Pagano et al56 reported the outcomes of 43 patients with BPDCN who were diagnosed in Italy between 2005 and 2011. Forty-one of these patients received induction therapy, with 26 and 15 receiving AML-like and ALL-like regimens, respectively. Seventeen (41%) patients achieved a CR (7 in the AML-like group and 10 in the ALL-like group), with a statistically significant advantage for ALL-like chemotherapy (P = .02). Of the 17 patients who achieved a CR, 6 (35%) subsequently relapsed. Three patients had a central nervous system relapse. None received central nervous system prophylaxis.6 Although prospective, randomized studies have not compared ALL-like with AML-like induction regimens, data from retrospective studies have suggested a higher response rate with ALL-like regimens.8,55 Due to a high risk of central nervous system involvement, particularly among patients who have relapsed, central nervous system prophylaxis should be considered, as the incidence of central nervous system involvement is between 9% and 26%.8
Relapse Management and Maintenance Therapy
Gruson et al. treated 7 patients with an L-asparaginase–containing regimen (L-asparaginase/methotrexate/dexamethasone) and reported good tolerance in both the untreated and relapsed patients. The objective response rate was 71% (4 CR and 1 PR), and overall survival rates ranged from 6 to 34 months. However, only patients who received consolidation with allogeneic stem cell transplantation were alive at the time of the report. Leitenberger et al. reported on a patient with relapsed BPDCN following 2 cycles of CHOP who demonstrated a regression of skin tumors after being treated with weekly prednimustine. Using low-dose etoposide therapy, Hatano et al. maintained a long-term remission in a patient with relapsed BPDCN. These data suggest that less intensive regimens containing L-asparaginase and monochemotherapy may be used in relapsed disease or as maintenance in patients not eligible for hematopoietic stem cell transplantation (HSCT).

Hematopoietic Stem Cell Transplantation
Despite a favorable response to initial induction therapy in most patients, responses are typically short-

![Flowchart](https://via.placeholder.com/150)

Fig 5. — Treatment algorithm for blastic plasmacytoid dendritic cell neoplasm.

*Selected patients may be considered for consolidation with reduced-intensity conditioning allogeneic stem cell transplantation during the first remission.

lived, suggesting that induction therapy alone is not sufficient to maintain durable remissions. The role of maintenance or consolidation therapy has not been well defined, and no randomized controlled trials define the role of HSCT. In most HSCT reports, because of the small number of patients, statistical power could not be shown regarding whether a difference could be seen among patients undergoing transplantation and those who did not. In a literature review of HSCT in patients with BPDCN, 76 patients were identified who underwent consolidation with allogeneic HSCT and 13 patients with autologous HSCT. Because younger patients typically have a better performance status and a good response to induction chemotherapy than older patients, younger people are typically selected for HSCT; therefore, the better outcomes seen in some reports among patients undergoing HSCT could be due to a selection bias.

Autologous HSCT has been utilized as consolidative therapy in patients with BPDCN. Suzuki et al reported on the outcomes of 6 patients who received high-dose chemotherapy followed by autologous HSCT. Two patients had a CR, 1 patient had a PR, another patient had a second PR, 1 patient was treated at the time of the first relapse, and 1 patient had primary refractory disease. Three patients died after disease progression and 3 patients were alive at 11, 22, and 37 months following autologous HSCT. Reimer et al reported disease relapse in 3 of 4 patients studied following autologous HSCT; the median survival rate was 13 months. Due to limited data and a high relapse rate, only selected patients with chemosensitive disease and no available donor for allogeneic HSCT should be referred for autologous HSCT.

Allogeneic HSCT offers durable disease control and possible cure, particularly if it is performed during the first complete remission. Roos-Weil et al analyzed 34 patients (median age, 41 years) in the European Group for Blood and Marrow Transplantation registry who underwent allogeneic HSCT between 2003 and 2009. Eleven patients received a transplant from siblings, 23 patients received a transplant from unrelated donors, and 19 (56%) patients underwent transplantation during their first remission. The 3-year cumulative incidences of relapse, disease-free survival, and overall survival rates were 32%, 33%, and 41%, respectively. In a univariate analysis, allogeneic HSCT at first remission was associated with improved survival rates. In a single institutional report, 6 of the 19 patients (32%) studied underwent consolidation with autologous (3 patients), allogeneic (2 patients), and cord blood (1 patient) transplantation. The median overall survival rate for patients undergoing transplantation was 31 months vs 29 months for those not receiving transplantation (n = 13; \( P = .82 \)). The results of this study suggested no statistically significant improvement in survival among patients treated with HSCT compared with conventional therapy. However, the numbers of patients were too small to draw any definitive conclusions. Unteregger et al treated 5 patients with allogeneic HSCT during the first or subsequent remission. Four patients received reduced intensity conditioning and 2 umbilical cord blood transplantations. No graft-vs-host disease was observed in patients who received umbilical cord blood transplantation, but both of these patients developed post-transplantation lymphoproliferative disease. Four patients were in complete remission at the time of the report, with progression-free survival and overall survival rates of 17 and 21 months, respectively.

Jegalian et al retrospectively reviewed the cases of 25 pediatric patients with BPDCN who underwent induction therapy with intensive high-risk, ALL-type chemotherapy regimens. The event-free survival rate was 64%, and 9 of the 25 patients (36%) were alive 5 years after diagnosis. Three patients underwent HSCT. Among those who did not manifest cutaneous involvement, the survival rate was 100%; by contrast, the survival rate was 61% in patients with cutaneous disease. The overall survival rate was 72% with a median follow-up of 30 months. This study suggested that a prognosis of BPDCN might be better in pediatric patients; thus, consolidation with HSCT should be reserved for pediatric patients in cases of relapse during complete remission.

**Targeted Therapy**

No specifically targeted agents are currently approved for patients with BPDCN. However, advances in the understanding of the pathobiology of BPDCN, as well as the results of early clinical studies, have revealed novel targets and potentially effective agents. FLT3-ITD mutations were detected in 3 patients among 14 examined cases of BPDCN; none of these 3 patients had previous MDS or myeloproliferative neoplasm. If these results are confirmed in a larger cohort of patients, then these findings could lead to a potential novel therapy with FMS-like tyrosine kinase-3 inhibitors.

Agliano et al demonstrated the ex vivo efficacy of lenalidomide against BPDCN cells in a xenograft mouse model; thus, the activity of lenalidomide should be further explored in clinical studies of patients with BPDCN. Laribi et al reported on 2 patients with BPDCN who underwent frontline therapy with 5-azacytidine and achieved a resolution of their skin lesions and a stabilization of their hematological parameters. This therapy could be effective, particularly among patients with BPDCN and concurrent myelodysplastic changes or myeloid malignancy (eg, MDS, AML).

Several groups of investigators have reported the results of preclinical and early clinical data with SL-401, a recombinant human interleukin 3α protein
conjugated with truncated diphtheria α-toxin, a potent inhibitor of protein synthesis. In a preclinical study, SL-401 revealed antitumor activity against BPDCN cell lines with the half maximal inhibitory concentration in the femtomolar range. Frankel et al reported on data from a phase 1/2 study in which 11 patients with BPDCN received a single daily course of SL-401 at 12.5 mcg/kg for 5 days. Of those patients, 2 were not evaluable for a response; however, 7 patients (78%) achieved major responses (5 CRs, 2 PRs). Complete remissions included the elimination of malignant cells from all compartments, including the skin, bone marrow, peripheral blood, spleen, and lymph nodes. The median duration of response was 5 months (range, 1–20+ months). The most common adverse events seen in these patients were fever, chills, hypotension, hypoalbuminemia, peripheral edema, thrombocytopenia, and the transient elevation of liver transaminases. These encouraging results suggest that targeted therapy has the potential for improving patient outcomes.

**Prognosis**

The long-term prognosis of patients with BPDCN is poor due to the aggressive behavior of the disease, the advanced age of most patients, and an absence of effective targeted therapy with low toxicity rates. Due to the limited number of patients in retrospective reports, validated prognostic and predictive markers are lacking. Analyses of small case series suggest that adult patients with skin involvement at presentation have better prognoses than their counterparts. By contrast, in 1 study, patients with the leukemic form of BPDCN had a median survival rate of 8.7 months, which is shorter than the 12 months reported for all patients together.

In a large, retrospective, national registry study, the expression levels of CD303 and high Ki-67 proliferative index were significantly associated with longer survival rates. The biallelic loss of 9p21.3 and the mutation in the methylation pathway genes have been associated with an unfavorable prognosis. Pediatric patients with BPDCN treated with high-risk, ALL-like induction regimens had better prognoses than their adult counterparts, and most of these patients did not require consolidation with allogeneic HSCT during their first remission.

**Conclusions**

Blastic plasmacytoid dendritic cell neoplasm is a rare but aggressive hematological malignancy with a poor prognosis. Prognosis for pediatric patients appears to be better than for adults. No established standard frontline treatment regimen exists for patients with blastic plasmacytoid dendritic cell neoplasm. Acute lymphoblastic leukemia–like and acute myeloid leukemia–like induction chemotherapy regimens are associated with relatively high response rates, although with a short duration in adult patients. Available data suggest that allogeneic hematopoietic stem cell transplantation, particularly if performed during the first complete response, offers the best chance of durable remission. Although it is difficult to conduct randomized trials in this rare disease entity, prospective studies using novel targeted agents could establish more effective and tolerable therapies in the near future.

**References**

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