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INTRODUCTION — Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematologic malignancy that most commonly manifests as cutaneous lesions with or without bone marrow involvement and leukemic dissemination.

The nomenclature used to describe this entity has evolved over the years as understanding of the underlying biology has improved. The tumor was initially described in 1995 as an acute agranular CD4-positive natural killer (NK) cell leukemia [1]. Based on the blastic appearance and CD56 expression, the term "blastic NK cell lymphoma" was used. Subsequently, the term "agranular CD4+CD56+ hematodermic neoplasm/tumor" was coined based on the immunophenotype and a predilection for skin involvement. However, following the discovery and confirmation that BPDCN is derived from plasmacytoid dendritic cells (type 2 dendritic cells), the current nomenclature, blastic plasmacytoid dendritic cell neoplasm, was chosen to describe the entity in the 2008 World Health Organization classification of tumors of the hematopoietic and lymphoid tissues and is expected to remain in the 2016 revision [2,3].

The epidemiology, clinical manifestations, pathologic features, diagnosis, and management of BPDCN will be presented here. Chronic NK cell lymphocytosis and NK cell large granular lymphocyte leukemia are described separately. (See "Natural killer (NK) cell large granular lymphocyte leukemia".)

EPIDEMIOLOGY — Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm and the exact incidence is unknown. The precise incidence of BPDCN is difficult to estimate due to constantly changing nomenclature and lack of precise defining criteria prior to the 2008 World Health Organization classification system. BPDCN represent 0.7 percent of primary cutaneous skin lymphomas [4]. However, cutaneous lymphoma registries likely underestimate the true incidence of BPDCN because a small but significant proportion of patients present without skin lesions [5].

BPDCN occurs in all races and all geographic locations; however, there are few data regarding whether the incidence varies by ethnicity or geography. BPDCN has been described in all age groups but is most common in adults [4,6,7]; the majority of patients are older adults, and the median age at diagnosis is 65 to 67 years. There is a modest male predominance with a male to female ratio of approximately 2.5:1.

There are no known environmental or hereditary genetic factors predisposing to the development of BPDCN. BPDCN can occur as an isolated disease or in the context of other hematologic neoplasms. Approximately 10 to 20 percent of patients have antecedent history of hematologic malignancies including myelodysplastic syndrome, chronic myeloid leukemia, chronic myelomonocytic leukemia, and acute myeloid leukemia [5-7]. The relationship between BPDCN and other myeloid malignancies is not clearly elucidated. However, BPDCN should be distinguished from proliferations of mature CD56-negative plasmacytoid dendritic cells that can be seen in association with myeloid leukemias, most notably chronic myelomonocytic leukemias [8]. (See "Chronic myelomonocytic leukemia".)

PATHOGENESIS — Blastic plasmacytoid dendritic cell neoplasm (BPDCN) arises from the precursors of myeloid-derived resting plasmacytoid dendritic cells (type 2 dendritic cells) [9-13]. Classical dendritic cells are

the most potent antigen presenting cells. They play a critical role in the initiation of the immune response by capturing and processing antigens and presenting the processed antigens to other immune cells.

Unlike the classical dendritic cells, the plasmacytoid dendritic cells are capable of producing copious amounts of type I interferons (IFN-α/β) in response to viruses or virus-derived nucleic acids [14]. While it is biologically plausible that viral exposure may play a role in the pathogenesis, to date no association has been reported between BPDCN and a viral pathogen, including the Epstein-Barr virus.

Genetic studies have offered little insight into the pathogenesis of BPDCN (see 'Genetic features' below):

- While several recurrent cytogenetic abnormalities have been reported, none is unique to BPDCN.
- Array comparative genomic hybridization (CGH) studies have reported loss of genomic DNA copy numbers for several genes that affect cell cycle progression, including *p18*, *p16*, *p27*, and *RB1* [15,16].
- Molecular studies have also reported mutations in *TET2* and *TP53* genes [17]. *NPM1* mutations have not been reported; in contrast, *FLT3-ITD* mutations can be present in a subset of patients [5].
- A study using gene expression profiling and immunohistochemistry identified aberrant NF-kB pathway activation in these tumors and explored the possibility of therapeutic targeting of the pathway to treat BPDCN [13].

Given the rarity of BPDCN, these observations come from relatively small numbers of patients. In addition, it is not clear whether these genetic alterations contribute to malignant transformation or if they merely represent a consequence of malignant transformation.

CLINICAL MANIFESTATIONS — Most patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) present with cutaneous lesions with or without bone marrow involvement and leukemic dissemination [6]. A minority of cases present with leukemia without skin involvement [18]. The skin lesions can be brown to violaceous bruise-like lesions, plaques, or tumors, and may be solitary or widespread [7]. Cytopenias, lymphadenopathy, and/or splenomegaly are present in a significant majority of patients [5,6]. Involvement of liver has been reported and appears to be more frequent in patients with extensive bone marrow involvement [5]. Involvement of the tonsils, paranasal cavities, lungs, eyes, central nervous system (CNS), and paravertebral involvement have also been reported [5,6].

A retrospective series of 90 patients presenting with cutaneous involvement reported that the clinical presentation varied from one or two skin nodules or tumors to disseminated cutaneous spread [7]. Most patients could be classified as having one of three cutaneous presentations:

- Brown or purple nodular lesions (73 percent)
- "Bruise-like" brown to violaceous infiltrated patches (12 percent)
- Disseminated and mixed lesions (14 percent)

Approximately half of patients initially presented with localized nodular disease consisting of one or two nodules, while 27 percent had multiple nodules affecting one or two areas [7]. The most common areas of localized involvement were the face or scalp (20 percent), lower limb (11 percent), trunk (9 percent), and upper limb (7 percent). Mucosal involvement was seen in five patients. Further evaluation revealed involvement of the bone marrow, lymph nodes, or blood in 61 percent of cases [7]. CNS involvement was demonstrated in 11 percent. Approximately one-third had no evidence of disease beyond the skin.

Case reports have also described patients presenting with a leukemic picture in the absence of cutaneous disease [18]. Such patients present with abnormal circulating "lymphoid/monocytoid" cells with or without leukocytosis, anemia, thrombocytopenia, hepatosplenomegaly, and lymphadenopathy.

PATHOLOGIC FEATURES

Morphology

Skin biopsy — Skin biopsies of involved areas demonstrate an infiltrate of medium-sized cells that spare the epidermis but can extend to the subcutaneous fat (picture 1) [19]. There is no coagulative necrosis, angioinvasion, or inflammatory cells within the infiltrate. When the subcutis is infiltrated, "rimming" of adipocytes can be seen.

The tumor cells are usually monomorphic, poorly differentiated, intermediate-sized blasts with fine chromatin and 2 to 3 nucleoli [4,6,20,21]. The nuclei are most commonly round or oval, but may be irregular (notched, folded, bilobed). The cells typically have scant blue-gray, agranular cytoplasm on Giemsa stained preparations. Mitotic activity is usually infrequent. On touch imprints, the tumor cells may show microvacuoles along the cell membrane ("pearl necklace" appearance) and pseudopod-like extensions.

Lymph nodes — Lymph node involvement usually displays a leukemic pattern with infiltration of monomorphic cells that resemble those seen in the skin [19]. While initial involvement may be confined to the interfollicular areas, eventually, involvement becomes diffuse. Coagulative necrosis and angioinvasion are not present.

Peripheral blood and bone marrow — The most common findings in the peripheral blood are thrombocytopenia (78 percent), anemia (65 percent), and neutropenia (34 percent) [6]. Circulating malignant cells can be detected by morphologic review or flow cytometry of the peripheral blood. Morphologically, they are monomorphic, poorly differentiated, intermediate-sized blasts, resembling those seen in the skin (picture 2). While malignant cells can be detected in the peripheral blood of approximately 60 percent of cases, the number of circulating malignant cells is extremely variable.

Bone marrow involvement is present in over 80 percent of the patients and diffuse involvement is common. However, just as in the peripheral blood, the number of malignant cells in the bone marrow varies and special studies may be required to identify these cells. The tumor cells may show microvacuoles along the cell membrane ("pearl necklace" appearance) and pseudopod-like extensions.

Immunophenotype — The immunophenotype of blastic plasmacytoid dendritic cell neoplasm (BPDCN) can be confirmed by either immunohistochemistry or using flow cytometry, depending on the material available. The tumor cells express CD4 and CD56 [19]. In addition, several plasmacytoid dendritic cell associated markers have been evaluated for expression in normal and malignant plasmacytoid dendritic cells. The expression of one or more of these antigens needs to be demonstrated to establish a definitive diagnosis of BPDCN. These markers include CD123 (interleukin-3 alpha-chain), BDCA-2/CD303 (blood dendritic cell antigen-2), TCL1, and SPIB [12,22-25]. At our institution, we rely on CD123 and TCL1 in addition to CD4 and CD56 for making this diagnosis.

Terminal deoxynucleotidyl transferase (TdT) expression is observed in up to 40 percent of cases [22]. When present, TdT expression is variable and can be seen in 10 to 80 percent of cells in the tumor. CD68 expression can be seen in up to 50 percent of cases. However, CD68 expression may be weak and represented by a dot-like positivity in the Golgi zone [4].

CD7 (a T cell antigen) and CD33 (a myeloid antigen) are also expressed relatively frequently. However, expression of CD19, CD20, CD79a (all B cell antigens), and CD3 or CD5 (T cell antigens) is usually not

observed. Similarly, myeloperoxidase, CD117, lysozyme, CD13, and CD16 are not expressed. CD34 expression is also not present, and no Epstein-Barr virus encoded RNA (EBER) is detected in BPDCN.

Of note, rare cases that do not express CD56 have been reported, and the diagnosis of BPDCN can be made if the tumor cells express CD4, CD123, and TCL1. In addition, atypical cases with aberrant expression of B, T, or myeloid antigens have also been described. In order to retain specificity without being too restrictive, a scoring system has been proposed and is likely to be of great utility in establishing immunophenotypic diagnosis of BPDCN [21].

Genetic features — The majority of BPDCN cases have genetic abnormalities, but there is no single cytogenetic change that is typical or diagnostic. The T cell receptor (TCR) genes are usually germline.

Abnormal karyotype has been reported in 50 to 66 percent of patients [5,26]. While not specific, the karyotype is significant for presence of gross genomic imbalances represented mostly by loss of genetic material [26]. Certain chromosomes are preferentially targeted. These are 5q, 12p, 13q, 6q, 15q, and 9 [26]. These represent abnormalities seen in both myeloid and lymphoid malignancies. Molecular cytogenetic studies have identified monoallelic deletion of the NR3C1 locus at 5q31 as a recurrent abnormality in 28 percent of patients and this finding is associated with a poor clinical outcome [27].

In addition to classical cytogenetic analysis, BPDCN has also been assessed by array comparative genomic hybridization (CGH) analyses [15,16]. The array-CGH studies also confirm that loss of genetic material is much more frequent than presence of additional genetic material. Furthermore, proteins that regulate cell cycle are preferentially targeted. *CDKN2A/CDKN2B* on 9p21.3 is frequently lost; when biallelic, this deletion is associated with a poor outcome. Other frequently deleted regions include 13q13.1-q14.3 (*RB1*), 12p13.2-p13.1 (*CDKN1B*), 13q11-q12 (*LATS2*), and 7p12.2 (*IKZF1*) [15].

In addition, gene expression studies have identified overexpression of *FLT3*, *HES6*, and *RUNX2* independently of genomic amplification [28]. More recently, mutations in *TET2* and *TP53* were seen in 53 and 38 percent of cases analyzed [17].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS — The diagnosis of blastic plasmacytoid dendritic cell neoplasm (BPDCN) is usually suspected in patients who present with brown to violaceous bruise-like lesions, plaques, or tumors. Skin biopsy with routine histology and immunophenotype is the single most important laboratory tool that will assist the clinician in establishing the diagnosis. However, an absence of skin lesions does not rule out the diagnosis since a minority of cases present with leukemia without skin involvement. As such, a diagnosis of BPDCN should also be suspected in a patient presenting with a poorly differentiated leukemia with an ambiguous immunophenotype. In either case, the diagnosis of BPDCN requires biopsy and morphologic assessment of the involved tissue, along with appropriate immunophenotypic studies by either multicolor flow cytometry or immunohistochemistry.

Importantly, accumulations of mature plasmacytoid dendritic cells seen in association with some reactive conditions, such as Kikuchi's disease, and myeloid malignancies, such as chronic myelomonocytic leukemia, are CD56 negative and should not be diagnosed as BPDCN.

Cutaneous presentation — Almost 80 percent of patients with BPDCN present with skin lesions. A biopsy of the involved area is required for diagnosis. In addition to morphologic review, the evaluation should include an assessment of the expression of BPDCN-associated antigens by a panel of antibodies. To avoid misclassifying BPDCN, tumors that express CD4 and do not express CD11c, MPO, cytoplasmic CD3, and cytoplasmic CD79a should be evaluated for CD123 expression, regardless of CD56 expression [21]. In such tumors, expression of CD123 plus either BDCA2 or TCL1 suggests the diagnosis of BPDCN. BDCA4 expression, while not entirely specific, is helpful in making the diagnosis of BPDCN in conjunction with the other markers.

The differential diagnosis includes other malignancies with cutaneous manifestations, such as [22]:

- **CD56+ acute myeloid leukemias (AMLs)** – Both CD56+ AML and BPDCN can present with skin lesions and circulating blasts and some cases of BPDCN express the myeloid antigen CD33, which is common to AML. However, unlike BPDCN, most cases of AML demonstrate positivity for myeloperoxidase and express other myeloid antigens such as CD13, CD15, and CD117. (See "Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia".)

- **Nasal-type extranodal NK/T cell lymphoma** – Both nasal-type extranodal NK/T cell lymphoma and BPDCN can present as cutaneous lesions that express CD56 and CD4. Unlike BPDCN, the histology of nasal-type extranodal NK/T cell lymphoma is characterized by a polymorphous lymphoid infiltrate that invades the vascular walls, producing fibrinoid necrosis of vessel walls and coagulative necrosis of surrounding tissues. Unlike in BPDCN, NK/T cell lymphomas are associated with Epstein-Barr virus that can be demonstrated by in situ hybridization for Epstein-Barr virus encoded RNA (EBER). (See "Clinical manifestations, pathologic features, and diagnosis of extranodal NK/T cell lymphoma, nasal type".)

- **Subcutaneous panniculitis-like T cell lymphoma (SPTCL)** – Patients with SPTCL typically present with one or more usually painless subcutaneous nodules or poorly circumscribed indurated plaques. BPDCN can be differentiated from SPTCL based upon the immunophenotype and molecular studies. Unlike SPTCL, T cell receptor genes are usually germline and the tumor cells express CD56 but not cytotoxic molecules (TIA-1, granzyme B, and/or perforin). (See "Clinical manifestations, pathologic features, and diagnosis of subcutaneous panniculitis-like T cell lymphoma".)

- **Cutaneous T cell lymphoma** – Like BPDCN, cutaneous T cell lymphoma may express CD4 and cutaneous lymphocyte associated antigen (CLA). However, unlike BPDCN, cutaneous T cell lymphomas do not express CD56, CD123, and BDCA2. (See "Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides".)

Leukemic presentation — A minority of patients with BPDCN will present with circulating blasts without skin lesions. Leukemic manifestation without skin involvement should be distinguished from other myeloid and lymphoid leukemia, and the distinction relies heavily on demonstration of the appropriate immunophenotype. Presence of leukemic blasts with an undifferentiated or ambiguous immunophenotype should raise the possibility of leukemic presentation of BPDCN. Of note, all of the antigens expressed on BPDCN malignant cells, including CD4, CD56, and even CD123, can be expressed individually on myeloid or lymphoid leukemia. Therefore, the diagnosis of BPDCN should be established after evaluation for expression of multiple antigens [21]. (See "Clinical manifestations, pathologic features, and diagnosis of acute myeloid leukemia" and "Clinical manifestations, pathologic features, and diagnosis of precursor T cell acute lymphoblastic leukemia/lymphoma" and "Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma".)

PRETREATMENT EVALUATION — The initial evaluation of a patient with blastic plasmacytoid dendritic cell neoplasm (BPDCN) must establish the extent and sites of disease and provide information about the individual's comorbidities that are likely to have an impact on treatment. There are no formal guidelines for staging BPDCN. Patients who present even with localized disease have an aggressive disease course and poor outcome.

In addition to a history and physical examination, it is our practice to perform the following pretreatment studies in patients with BPDCN:

- Laboratory studies include a complete blood count with differential, chemistries with liver and renal function and electrolytes, lactate dehydrogenase (LDH), hepatitis B, HIV, and uric acid. Human leukocyte antigen

(HLA) typing should be performed for younger patients who are candidates for hematopoietic cell transplantation.

- The peripheral smear is reviewed morphologically and a sample is assessed with flow cytometry.
- Unilateral bone marrow aspiration with trephine biopsy is recommended for all patients. This sample should be sent for pathologic review, immunophenotyping, cytochemistry, and metaphase cytogenetics.
- A contrast-enhanced computed tomography (CT) scan of the chest, abdomen, and pelvis should be performed.
- Patients with neurologic signs or symptoms should undergo imaging studies to evaluate for meningeal disease or central nervous system bleeding. We perform a lumbar puncture in all patients given the high incidence of occult cerebrospinal fluid (CSF) involvement (eg, in one study 6 of 10 patients at diagnosis and 3 of 3 patients at relapse had occult CSF involvement) [29]. CSF should be sent for both cytology (examination of stained cytospin slides) and flow cytometry.
- A study of cardiac ejection fraction (eg, echocardiogram or MUGA) should be performed if anthracyclines are used.
- Men and women of childbearing potential should receive counseling about the potential effect of treatment on their fertility and options for fertility-preserving measures. Given the urgent need for treatment, options for women are limited, but men can often participate in sperm banking.

MANAGEMENT — The optimal treatment for blastic plasmacytoid dendritic cell neoplasm (BPDCN) is unknown, due to a paucity of data regarding therapy. Based on retrospective studies, the clinical course and response to therapy appear to differ between children and adults. A survey of 356 patients (283 adults over 19 years old and 74 children) reported that pediatric patients had better response to initial therapy, more favorable overall survival (OS), and lower rate of relapse [30].

Children — For children (<18 years) with newly diagnosed BPDCN, we suggest induction chemotherapy with a regimen similar to that used for high-risk acute lymphoblastic leukemia (ALL). For children who achieve a complete remission (CR), we suggest observation rather than hematopoietic cell transplantation (HCT) in first remission. Allogeneic HCT is offered to patients who relapse and achieve a second remission. (See "Overview of the treatment of acute lymphoblastic leukemia in children and adolescents", section on 'Induction therapy'.)

The largest study of pediatric BPDCN was a retrospective analysis of 29 children (<18 years old) from the National Cancer Institute, which included 20 cases published in the literature [31]. With a median follow-up 30 months, OS and event-free survival (EFS) rates were 72 and 64 percent, respectively. Among 14 children treated with ALL-like therapy, 12 achieved CR and 2 achieved partial response (PR). In contrast, four of six children who received non-Hodgkin lymphoma (NHL)-like therapy (eg, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP) achieved CR, while all five children treated with acute myeloid leukemia (AML)-like therapy died from progressive disease or therapy-related complications.

Adults — For adults with newly diagnosed BPDCN, we suggest induction chemotherapy with a regimen similar to that used for ALL, including central nervous system (CNS) prophylaxis or treatment. For adults who achieve a CR, we suggest allogeneic HCT in first remission rather than observation with plans for HCT in second remission. (See "Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults" and "Post-remission therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults".)

Remission induction — The preferred induction chemotherapy regimen for adults with BPDCN is unknown and clinical practice varies. Outcomes appear to be most favorable for patients treated with ALL-like regimens, based on small retrospective studies. The specific choice of regimen is often dictated by clinician/institutional experience. While the majority of patients will achieve a response to induction therapy, most will relapse within two years [6].

We suggest treatment with an ALL-like regimen, rather than protocols used for treatment of NHL or AML. Because CNS involvement is common, patients should receive treatment of detectable CNS disease or prophylaxis, if no disease is detected. As an example, flow cytometry detected disease in 6 of 10 asymptomatic patients at the time of diagnosis and in all 3 patients evaluated at the time of relapse [29]. Induction therapy and management of CNS involvement is described separately. (See "Induction therapy for Philadelphia chromosome negative acute lymphoblastic leukemia in adults".)

The largest study investigating treatment of BPDCN was a retrospective analysis of 43 adults (median age 68 years) diagnosed at 28 Italian centers [5]. Median OS was 9 months, with 28 and 7 percent survival at 12 and 24 months, respectively. Patients who received ALL/aggressive NHL-like therapy (eg, hyper-CVAD, CHOP) were more likely to achieve a CR and had significantly longer OS compared with patients who received AML-like therapy. Among 15 patients treated with ALL-like regimens, 10 achieved CR (6 of whom later relapsed), 1 had a PR, and 3 died during induction. Among 26 patients treated with AML-like regimens, 7 achieved CR, 5 had PR, and 4 died during induction.

Hematopoietic cell transplantation (HCT) — Most adults with BPDCN who achieve CR or PR following induction therapy will relapse within two years, irrespective of the type of initial therapy [6]. In contrast to children, adults with BPDCN may benefit from allogeneic HCT in first CR [5,32,33].

We prefer myeloablative allogeneic HCT given the greater experience with this approach. Patients who achieve CR, but are not candidates for myeloablative HCT, may be considered for reduced intensity conditioning or autologous transplantation. Eligibility for allogeneic and autologous HCT differs by country and institution. Further details regarding eligibility for HCT are presented separately. (See "Determining eligibility for allogeneic hematopoietic cell transplantation" and "Determining eligibility for autologous hematopoietic cell transplantation".)

Data regarding the outcomes following HCT come from retrospective analyses [32-36]. As examples:

- The largest retrospective study included 34 patients (median 41 years) who received allogeneic HCT and were registered in the European Group for Blood and Bone Marrow Transplantation database [33]. The OS was 41 percent at three years, and no relapses were observed after 27 months past HCT. A majority of patients received myeloablative conditioning and stem cells from either siblings or matched unrelated donors. In a univariate analysis, receiving transplant in first CR was associated with a significantly favorable outcome, whereas age, donor, source, and presence of chronic graft-versus-host disease had no impact on survival. Of note, when the analysis was restricted to patients who underwent myeloablative conditioning in first CR, there was a three-year disease-free survival of 45 percent and an OS of 60 percent.

- A smaller case series demonstrated the feasibility of allogeneic HCT in older patients with the use of a reduced intensity conditioning regimen [32]. In a single institution case series of six adults with BPDCN (median age of 67 years, range 55 to 80 years), four underwent reduced intensity allogeneic HCT. Two were transplanted in CR and had sustained remissions at 57 months and 16 months. The other two patients transplanted with active disease relapsed at 6 and 18 months after transplantation.

- A retrospective analysis from Japan included 25 patients (median 58 years) who received allogeneic HCT after myeloablative (8 patients) or reduced intensity (6 patients) conditioning or underwent high dose

therapy with autologous HCT [34]. The 11 patients who underwent autologous HCT were in first CR. In contrast, patients who underwent allogeneic HCT were in first CR (10 patients), second CR (2 patients), or had refractory disease (2 patients). After a median follow-up of 53 months, estimated rates of OS and progression-free survival (PFS) at four years after allogeneic HCT were 53 and 48 percent, respectively, for the group as a whole. Among the 10 patients undergoing allogeneic HCT in first CR, the estimated OS at four years was 69 percent. All patients not in first CR at the time of HCT relapsed. Estimated four-year OS and PFS rates for autologous HCT were 82 and 73 percent.

Relapsed/Refractory disease — Optimal treatment of relapsed or refractory BPDCN is poorly defined. Ideally, treatment should take place in the context of a clinical trial.

Allogeneic HCT should be offered, if not previously performed, to appropriate candidates. (See 'Hematopoietic cell transplantation (HCT)' above.)

Examples of other therapeutic approaches that have been reported in this setting include:

- The BCL2 inhibitor, venetoclax, achieved significant response in two patients with relapsed BPDCN [37].
- Bendamustine achieved a CR in one of five patients, and the remission was maintained for at least seven months [38].
- Biweekly CHOP chemotherapy achieved a CR that lasted 16 months [39].

CLINICAL TRIALS — Often there is no better therapy to offer a patient than enrollment onto a well-designed, scientifically valid, peer-reviewed clinical trial. Additional information and instructions for referring a patient to an appropriate research center can be obtained from the United States National Institutes of Health (www.clinicaltrials.gov).

Tagraxofusp (SL-401) is a novel targeted therapy directed against interleukin-3 receptor alpha (CD123), which is comprised of recombinant IL-3 linked to truncated diphtheria toxin [40]. In a phase I/II study (NCT02113982), 29 previously untreated patients with BPDCN had a 90 percent overall response rate (ORR; 72 percent CR); 45 percent were bridged to allogeneic hematopoietic cell transplantation. In 13 patients with relapsed or refractory BPDCN, ORR and CR were 69 and 38 percent, respectively. The most common treatment-related adverse events were elevated liver transaminases, hypoalbuminemia, and thrombocytopenia; capillary leak syndrome was noted in 19 percent of patients, and was fatal for one patient. Tagraxofusp has been granted breakthrough therapy designation (BTD) for the treatment of patients with BPDCN by the US Food and Drug Administration.

PROGNOSIS — Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare disease that is treated based on institutional preferences. In the absence of large prospective trials, it is challenging to comment on features that might be predictive of prognosis. Younger age is predictive of better outcome [6]. Other smaller series that have included patients with only cutaneous disease have reported somewhat better complete remission rates and a comparable advantage for acute lymphoblastic leukemia-like induction therapy [41,42]. Finally, there appears to be some correlation between the maturity of the tumor cells and response to therapy with the more immature cells being more responsive to therapy in comparison to the less mature tumors [43]. Owing to the rarity of the disease, optimized therapy and prognostic factors are still only poorly defined. These data will hopefully emerge from future prospective trials.

SUMMARY AND RECOMMENDATIONS

- Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive neoplasm arising from precursors of the type 2 or plasmacytoid dendritic cells. (See 'Epidemiology' above and 'Pathogenesis' above.)

- Most patients with BPDCN present with cutaneous lesions with or without bone marrow involvement and leukemic dissemination. The skin lesions can be brown to violaceous bruise-like lesions, plaques, or tumors and may be solitary or widespread. Cytopenias, lymphadenopathy, and/or splenomegaly are present in a significant majority of patients. A minority of cases present with leukemia without skin involvement. (See 'Clinical manifestations' above.)

- Skin biopsies of involved areas demonstrate an infiltrate of monomorphic, medium-sized, poorly differentiated cells that spare the epidermis but can extend to the subcutaneous fat. Circulating malignant cells can often be detected by morphologic review or flow cytometry of the peripheral blood. Involvement of the bone marrow and lymph nodes is common. (See 'Morphology' above.)

- The tumor cells typically express CD4 and CD56. In addition, expression of one or more plasmacytoid dendritic cell specific antigens (CD123, BDCA-2, TCL1, SPIB) is present. (See 'Immunophenotype' above.)

- The diagnosis of BPDCN requires biopsy and morphologic assessment of the involved tissue (usually skin), along with appropriate immunophenotypic studies by either multicolor flow cytometry or immunohistochemistry. The differential diagnosis includes other hematologic malignancies with cutaneous manifestations. (See 'Diagnosis and differential diagnosis' above.)

- There is a paucity of data to guide the treatment of patients with BPDCN and the optimal treatment is unknown. Small retrospective analyses suggest that the clinical course and response to therapy differ between children and adults.

- For children (<18 years) with newly diagnosed BPDCN, we suggest induction chemotherapy with a regimen similar to that used for high-risk acute lymphoblastic leukemia (ALL) rather than regimens used for non-Hodgkin lymphoma (NHL) or for acute myeloid leukemia (AML) (**Grade 2C**). (See 'Children' above.)

  For children who achieve a complete remission (CR), we suggest observation rather than allogeneic hematopoietic cell transplantation (HCT) in first remission (**Grade 2C**).

  Allogeneic HCT is offered to children who relapse and achieve a second remission. (See 'Children' above.)

- For adults with newly diagnosed BPDCN, we suggest induction chemotherapy with an ALL-like regimen that includes central nervous system (CNS) prophylaxis or therapy, rather than a regimen for NHL or AML (**Grade 2C**). (See 'Adults' above.)

  For adults who achieve a CR, we suggest allogeneic HCT in first remission rather than observation followed by HCT in second remission (**Grade 2C**). (See 'Hematopoietic cell transplantation (HCT)' above.)

  For adult patients who achieve CR, but are not candidates for myeloablative HCT, options include allogeneic HCT with reduced intensity conditioning or autologous transplantation.

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