Blastic plasmacytoid dendritic cell neoplasm: a short review and update

Cesare Massone,[1] Giulia Rivoli,[2] Simona Sola,[3] Emanuele Angelucci[2]

[1]Dermatology Unit and Scientific Directorate, Galliera Hospital, Genoa; [2]Hematology and Cellular Therapies Operational Unit, IRCCS San Martino Polyclinic Hospital, Genoa; [3]Department of Surgical Pathology, Galliera Hospital, Genoa, Italy

Abstract

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm (less than 1% of primary cutaneous lymphomas and acute leukemia) with a highly aggressive clinical course and frequent skin, bone marrow and central nervous system involvement. Even though there is often an early response to chemotherapy, leukemic dissemination relapses are very common and result in poor outcomes, with a median overall survival of 8 to 14 months in the first-line setting using standard combination chemotherapy regimens. Almost 90% of patients experience skin involvement as their initial site of infection, where BPDCN may stay restricted for weeks or even months until a swift secondary phase involving multiple organs takes place. Consequently, it is crucial to suspect and identify early skin lesions, as well as to conduct and report a skin biopsy as soon as possible. In order to diagnose and treat BPDCN, a multidisciplinary strategy involving collaboration between pathologists, hematologists, and dermatologists is unquestionably essential.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematologic neoplasm with a highly aggressive clinical course and frequent skin, bone marrow and central nervous system (CNS) involvement.[1] Despite a frequent initial response to chemotherapy, relapses with eventual leukemic dissemination are extremely common, leading to poor outcomes and median overall survival (OS) ranging from 8 to 14 months in first-line setting, with standard combination chemotherapy regimens.[1] BPDCN arises from precursors of type 2 or plasmacytoid dendritic cells (pDCs) that account for less than 1 percent of mononuclear cells. Two types of dendritic cells are now recognized: myeloid DCs and pDCs. pDCs are produced in the bone marrow, circulate in blood and accumulate in mucosal sites.[2] pDCs were first identified by Lennert in 1958 and are type I interferon-producing cells that modulate innate and adaptative immune responses; particularly, pDCs produce high amounts of type I interferons (α/β) in response to viruses or virus-derived nucleic acids.[3,4] pDCs are also the benign counterpart of other hematologic malignancies, namely the mature pDC proliferation (MPDCP) associated with myeloid neoplasms, mainly chronic myelomonocytic leukemia, myelodysplastic syndrome and acute myeloid leukemia (AML). MPDCP is associated with a poor outcome.[5] Beyond myeloid neoplasms, pDCs are also present in the reactive lymph nodes and skin of patients with Kikuchi lymphadenitis, Castleman hyaline vascular disease and lupus erythematosus.[5]

Epidemiology, pathogenesis and genetic features

BPDCN represents less than 1% of primary cutaneous lymphomas and acute leukemia;[6] however, the real incidence is probably underestimated. The majority of patients are older adults of all races and worldwide, with a median age at diagnosis of 65 to 67 years and a male-to-female ratio of approximately 2.5:1. Pediatric cases have been reported. Approximately 10 to 20 percent of patients present a previous history of myelodysplastic syndrome, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, and acute myeloid leukemia.[2,7,8] Even if a viral trigger may be plausible, a causative viral agent has not been identified yet. No environmental or hereditary genetic factors predisposing to the development of BPDCN are known.[2,6] Many genetic alterations have been described, but none is really distinctive of the BPDCN because the abnormalities found in BPDCN are seen in both myeloid and lymphoid malignancies. A variety of cytogenetic abnormalities has been described, including a complex karyotype

with alterations concerning chromosomes 5, 12, 13, 6, 7, 15 and 9, mostly represented by deletions; cytogenetic abnormalities may affect genes implicated in cancer development including RB1 (13q14), ETV6, CDKN1B; IKZF1 (7p12), TP53 (17p13), NR3C1 (5q31), rearrangements of MYB (6q23) and KMT2A.[1,6] Currently, no cytogenetic abnormalities are known to impact survival with the exception of monoallelic deletion of the NR3C1 locus at 5q31, described in 28% of patients with BPDCN and associated with a poor clinical outcome and biallelic deletion of CDKN2A/CDKN2B on 9p21.3. It should be noted, though, how all evaluations were performed on a limited number of cases.[1,9] Molecular studies have also been performed, although in a small number of cases: most common aberrations include ASXL1, IDH1-2, IKZF1-3, NPM1, NRAS, TET1-2, TP53, U2AF1, ZEB2.[1,10]

Nomenclature and classification

The actual and definitive definition of BPDCN was finally given in the 2008 edition of the World Health Organization (WHO) classification of Tumors of Hematopoietic and Lymphoid Tissues.[11-13] Since its first report in 1990 by Tauchi *et al.*, BPDCN

Figure 1. Bruise-like patches on the chest.

Figure 2. Erythematous nodule on the forehead.

Figure 3. Subcutaneous plaque mimicking erythema nodosum.

Figure 4. Abscess-like nodule on the back.

has been many times renamed and classified as CD4+/CD56+ acute monoblastic leukemia, acute agranular CD4+ natural killer (NK)-cell leukemia,[14] primary cutaneous CD4+/CD56+ hematolymphoid neoplasm,[15] Blastic NK-cell lymphoma in the 2001 edition of the WHO classification of Tumors of Hematopoietic and Lymphoid Tissues and CD4+/CD56+ hematodermic neoplasm in the 2005 WHO-EORTC classification.[16-18]

BPDCN and pDCs neoplasms have been placed in the category of myeloid and histiocytic/dendritic neoplasms in the 2022 5th edition of the WHO classification.[5]

Clinical features, diagnosis and staging investigations

Since its first description, it was clear that in the natural history of the disease, the skin is the first affected site (in almost 90% of patients) where BPDCN may remain confined for weeks or even months (sanctuary?) until a rapid second step with multiorgan involvement occurs. Only a minority of cases present with leukemia without skin involvement.[2,19-22] Many reports confirm that almost half of the patients have at the time of diagnosis generalized cutaneous lesions, about 18% of patients present multiple skin lesions at 1 body site and about one-third of patients have only solitary tumors. All body sites, including the CNS, and even mucosae may be involved.[13,15,19] Early skin lesions are usually "bruise-like" brown to violaceous infiltrated patches single or multiple, of different dimension, mainly on the skin, rarely on mucosae. With progression, the hue becomes darker, patches evolve in tumors and within a few weeks or months, new skin lesions occur, predominantly with hemorrhagic appearance. Single subcutaneous nodules mimicking erythema nodosum or abscess-like tumors have been rarely reported. Less hemorrhagic but erythematous single or multiple tumors are also possible.[7,19] Clinical differential diagnosis includes leukemia cutis, particularly secondary skin involvement by AML and other myeloid neoplasm, intravascular NK/T cell lymphoma and other aggressive primary cutaneous T-cell lymphoma and B-cell lymphomas. Sweet syndrome may also clinically simulate BPDCN.

Skin biopsy is the first diagnostic mandatory step that must be urgently performed when BPDCN is suspected, particularly when only single or few lesions are present, therefore most probably when a systemic dissemination has not occurred yet.[8]

In fact, at the time of diagnosis and after complete staging investigations with complete blood count, peripheral blood cytofluorimetric analysis, bone marrow biopsy, total body computed tomography (CT) scan and positron emission tomography (PET)-CT, the involvement of bone marrow and lymph nodes involvement is observed in 60-90% of patients (mainly with disseminated and multiple skin lesions) and 40-50% of patients, respectively.[5] It must be stressed that it is of uppermost importance to suspect and recognize early skin lesions and to perform and report a skin biopsy as soon as possible (Figures 1-4).[2,5,8]

A multidisciplinary approach with coordination among dermatologists, pathologists and hematologists is definitively crucial in the diagnosis and management of BPDCN.[2,5,8]

Histopathology

The pathology of skin lesions of BPDCN shows a diffuse dermal and subcutaneous infiltrate constituted by monomorphous medium-sized atypical cells with a blastic morphology. There is no epidermotropism and a grenze zone between the epidermis and the infiltrate is usually observed. The involvement of the subcutaneous fat is very common and, in a few cases, may be predominant. Contrarily, a granulomatous reaction, angiocentricity and/or angiodestruction or areas of tissue necrosis are uncommon. Hemorrhages are typically observed and explain why the clinical appearance of the lesions is bruise-like.[3,5-8,12,13,15,20] BPDCN cells express CD4, CD56 and CD123 (Figure 5); terminal deoxynucleotidyl transferase is positive in 30-60% of the neoplastic cells as well as Ki67 (20 to 90% of the cells) and CD68 while NK-cell markers, cytotoxic markers (granzyme B), myeloperoxidase, lysozyme, myeloid cell nuclear differentiation marker are negative. Other important positive markers of BPDCN are T-cell leukemia/lymphoma (TCL)-1, blood dendritic cell antigen (BDCA-2, CD303), CD304, transcription factor TCF4.[3,5-8,12,13,15,20] It must be underlined that cases of BPDCN negative for CD4 and/or CD56 and in rare cases even CD123 have been reported.[23]

Immunophenotypic diagnostic criteria

The 5th edition of the WHO classification proposes as immunophenotypic diagnostic criteria for BPDCN: i) expression for CD123 plus one other pDCs marker (TCF4, TCL-1, CD303, CD304) in addition to CD4 and/or CD56 and negativity for CD3, CD14, CD19, CD34; ii) expression of any 3 pDCs markers and absent expression of all expected negative markers – particularly myeloperoxidase and lysozyme. Markers for B, T or NK lineage are typically not expressed.[1,5,24,25]

Differential diagnosis on skin biopsy

A complete panel of immunohistochemistry markers must be performed because many pitfalls may occur.

CD123 is expressed clusters of cells in lymphocytic infiltration (Jessner-Kanof)/lupus tumidus, therefore early lesions of BPDCN with only perivascular infiltrate must be differentiated by these entities.

BCL-6 and multiple myeloma oncogene may result positive in a few cells sometimes also in BPDCN, and reactive germinal centers may be present as well, becoming a source of another diagnostic pitfall.

CD4, but also CD56 and in some cases, even CD123 may be positive also in myeloid leukemia.

Several other markers may result positive in a different proportion of cells in BPDCN: CD2, CD5, CD7, CD10, CD13, CD38, CD79a, CD117, CD2AP, BCL-2, CD43, CD45RA, CD36, BCL11a, SPIB, HLA-DR.[3,5-8,12,13,15,20]

Treatment

Isolated cutaneous disease

A systemic approach is preferred in all cases when feasible, even when a clinical presentation is exclusively cutaneous. When compared, the outcomes of patients with exclusive cutaneous versus those with systemic involvement did not differ in terms of response and response duration. Prognosis is invariably severe in both presentations.[1,26] Skin-directed local therapies such as

surgery or radiation may lead to initial responses but are not able to provide a long-term benefit and the disease almost invariably relapses within generally 6-9 months. These local therapies may be considered as options in a palliative setting, for patients not eligible for more intensive approaches.[1,10]

Optimal induction in patients eligible for intensive treatment

Historically, prospective data regarding BPDCN treatment are lacking, and traditional approaches were based on conventional combination chemotherapy.[24]

Patients eligible for intensive remission induction therapy have been historically treated with combination chemotherapy, with a wide range of multi-agent schemes used, followed by allogeneic stem cell transplant. Multi-drug combinations used were derived from associations used in acute lymphoblastic leukemia (ALL) treatment [such as hyper-central venous access device (CVAD)-cyclophosphamide, vincristine, doxorubicin and dexamethasone/methotrexate and cytarabine – or Aspa-MTX – high-dose methotrexate with asparaginase], in AML treatment (standard-dose cytarabine by continuous infusion for 7 days in combination with daunorubicin or idarubicin for 3 to 5 days) or in non-Hodgkin lymphomas (NHL) treatments (CHOP cyclophosphamide, doxorubicin, vincristine, and prednisone – or CHOP-like regimens or platinum-based schemes).[9] Although these various regimens have never been prospectively compared, treatment combinations used in acute leukemia, particularly ALL-type regimens, seem to yield better responses in various case series and retrospective studies.[1]

In an Italian retrospective observational study of 43 patients, most patients (41/43, 95%) received induction therapy with an acute leukemia-like regimen: AML-like in 26 cases (60%); ALL/lymphoma-type therapy in 15 (35%). Overall, 41% of treated patients achieved a complete response (CR), 7 after AML-type regimen, 10 after ALL/lymphoma-type, with a reported advantage for the ALL-type approach. Median OS was 8,7 months, with estimated survival rates of 28% and 7% at 12 and 24 months. Among patients in CR, 6 (35%) subsequently relapsed at a median time of
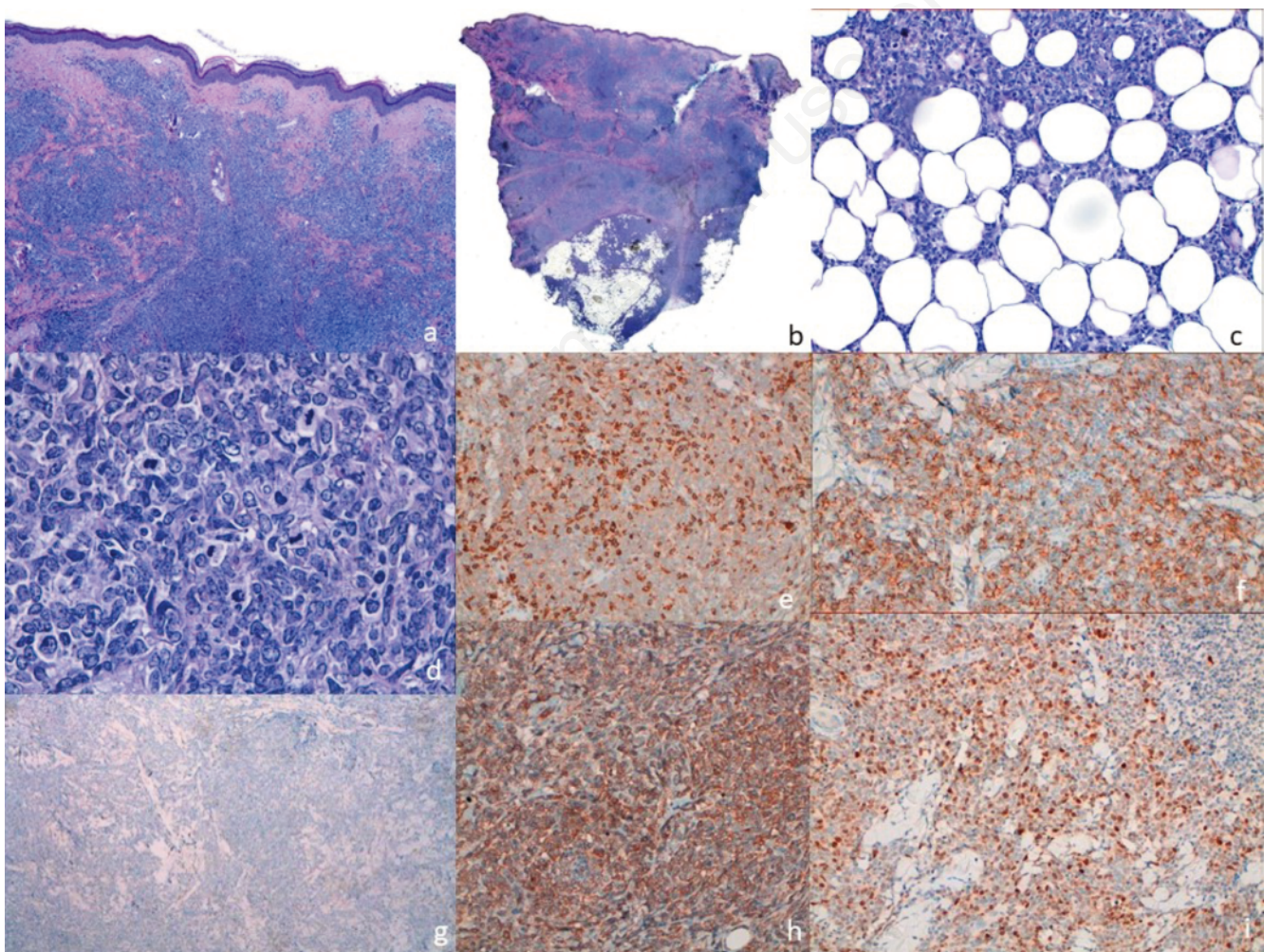
Figure 5. a) Non epidermotropic atypical dense lymphoid infiltrate in the dermis with grenze zone (original magnification 40x); **b)** atypical dense lymphoid infiltrate in the dermis and in the subcutis (original magnification 20x); **c)** atypical dense lymphoid infiltrate in the subcutis (original magnification 100x); **d)** atypical lymphocytes with blastic morphology and mitotic figures (original magnification 400x); **e)** positivity for CD4 (original magnification 400x); **f)** positivity for CD56 (original magnification 400x); **g)** negativity for myeloperoxidase (original magnification 400x); **h)** positivity for CD123 (original magnification 400x); **i)** positivity for terminal deoxynucleotidyl transferase (original magnification 400x).

9,1 months.[27] A French report including 86 patients undergoing BPDCN treatment, did not show statistically significant differences in terms of CR rates and remission duration among patients treated with AML-like, ALL-like and Aspa-MTX regimens. CR was obtained in 47 patients (60.2%) and relapse occurred in 17 patients at a median of 19.2 months.[25]

Overall, the median duration of remission was longer in the AML-like/ALL-like/Aspa-MTX group than in the CHOP-like/NOS group (47 months *vs.* 7 months respectively).[25]

The largest report to date is a retrospective multi-center analysis of 398 patients in 75 centers. The median overall OS reported was 18 months. Patients were treated with a variety of combination chemotherapy, with the best survival outcomes obtained with NHL/AL-like regimens followed by allogeneic stem cell transplant (SCT): in this last group median OS was not reached.

In patients undergoing autologous SCT, OS was 65 months. Patients treated with AL-like and NHL-like regimens without consolidation had inferior survival outcomes, with OS of 18 months and 14 months, respectively. Overall survival was significantly shorter (4 months) for patients receiving palliative care.[6]

Tagraxofusp (formerly SL-401) is a CD-123 directed cytotoxin consisting of human interleukin-3 fused to truncated diphtheria toxin (8), approved in December 2018 by the Food and Drug Administration for first-line treatment of BPDCN in adults and children 2 years of age and older. Tagraxofusp received "orphan-drug" designation in the European Union (EU) and authorization for the first-line treatment of adult patients with BPDCN in January 2021.[28] Approval was based on phase I/II clinical trial data involving 47 patients with BPDCN, 32 treatment naïve and 15 relapsed/refractory (R/R). Among previously untreated patients, the overall response rate (ORR) was 90%, and of these patients, 45% (13/29) proceeded SCT while in remission.

In the R/R group of 15 patients, ORR was 67%, with a median overall survival of 8.5 months.[29,30] Overall, these data represent an improvement both in terms of ORR and survival rates, when compared to a historical cohort, and led to approval of tagraxofusp in the United States and EU.

A recent update for long-term results of the largest prospective study evaluating Cd123-targeted therapy in BPDCN has shown an ORR of 75% in first-line (1L) and 58% in R/R patients.

In untreated patients, CR + clinical CR (CRc; CR with residual skin abnormality not indicative of active disease) rate was 57%, with 51% of these patients bridging to hematopoietic SCT (HSCT). The median duration of CR+CRc was 25 months after 3 years of follow-up. In R/R patients, CR+CRc rate was 16% and 5% of patients bridged to HSCT.[31] Data from the European expanded access program (EAP) of tagraxofusp showed, in a group of 32 evaluable patients of 40 treated, high ORR rates (88% in 1L, 67% in R/R), CR rates (71% 1L, 40% R/R) and successful bridging to allo-SCT (45% in 1L, 39% in R/R).[21] It is likely that survival rates after tagraxofusp induction are positively affected by the relatively high rate of SCT performed in the first remission and a generally good performance status (ECOG 0-1) of patients enrolled in clinical trials.[32] Nevertheless, it is currently recommended that tagraxofusp should be considered as the preferred induction in patients fit for intensive chemotherapy and transplant.[10] Other induction options include AML-type induction chemotherapy, ALL-type induction chemotherapy such as hyper-CVAD and lymphoma induction such as CHOP-like regimens.[10]

Role of stem cell transplantation in blastic plasmacytoid dendritic cell neoplasm

Eligible patients should be referred to allogeneic or autologous SCT in first remission.[10,33] BPDCN has an aggressive clinical course, especially in adults, and most patients, although experiencing high rates of initial response to induction treatment, will relapse within two years.

In historical cohorts, survival outcomes between transplanted (autologous or allogeneic SCT) and not-transplanted patients showed a significant advantage for the first group.[1,25,34]

The largest retrospective report to date, including 398 patients, reported 61 allogeneic SCT (15.5%) and 16 autologous SCT (4.1%). In this study, patients receiving NHL/AL-like regimens, followed by allogeneic HSCT, had the best outcome; median OS was not reached.[9]

The reported OS for patients undergoing autologous HSCT was 65 months *vs.* 18 months and 14 months, respectively, for those treated with AL-like and NHL-like regimens without transplant. Consolidation with allogeneic HSCT, in eligible patients, appeared superior to autologous HSCT in this study.[9]

A possible survival advantage for autologous SCT was also pointed out in a small cohort of 11 patients, where it was associated with a significant improvement in OS and progression-free survival (PFS) (at 4 years 82% and 73% respectively), regardless of the type of induction regimen used.[1,9,35]

A systematic review and metanalysis on allogeneic SCT in BPDCN showed pooled OS and PFS/disease-free survival (DFS) rates of 50% and 44%), regardless of remission status at the time of transplant.[32] Not surprisingly, patients undergoing allo-SCT in first CR had higher pooled rates of OS (67% *vs.* 7%) and PFS/DFS (53% *vs.* 7%). The pooled non-relapse mortality rate for allogeneic hematopoietic cell transplantation, regardless of regimen intensity, was 27%.[32]

Treatment with tagraxofusp monotherapy enabled 51% of 1L patients who achieved remission to bridge to SCT; an ORR of 58% has been reported in R/R patients, with a sCR+CRc rate of 16% and 5% of patients bridged to HSCT.[31]

Data regarding tagraxofusp as induction therapy in the European EAP, including 40 patients, showed improved survival outcomes in the transplant group: at a median follow-up of 10.1 and 8.4 months, respectively, the median OS rates were 16.7 months and not reached among the 1L and R/R group. Survival rates among non-tranplanted patients were 9.5 and 6.2 months among the 1L and R/R groups.[21] At present, there are no published randomized trials assessing the role of autologous or allogeneic SCT in BPDCN; with these limitations, data from retrospective cohorts and from a systematic review and metanalysis of 128 patients suggest that consolidation with allogeneic HSCT, when feasible, appears superior to autologous HSCT allogeneic SCT in first CR.[1,9,32] Allogeneic SCT is considered feasible with reduce-intensity conditioning (RIC) regimens in those patients not fit for age or comorbidities to undergo myeloablative conditioning (MAC) allo-SCT.[1]

The use of allo-SCT MAC regimens (*vs.* RIC), however, resulted in lower relapse rates (18% *vs.* 40%), which may suggest a benefit of using more intense conditioning regimens in BPDCN.[32] The role of autologous SCT in BPDCN is yet to be defined. The systematic review and metanalysis exploring the role of SCT in BPDCN could not offer a clear recommendation due to reported contradicting outcomes in two limited series of patients.[32]

More recent retrospective data derived from the analysis of a large multi-centric cohort of 398 patients suggest that autologous HSCT could offer a clinical advantage when compared to chemotherapy combinations without consolidation strategy and may have a role in patients deemed ineligible for allo-SCT.[1,9,35]

Available data do not allow recommending a specific conditioning regimen before auto-SCT. It could be reasonable to regi-

mens active on the CNS, when considering the high rates of neuro-meningeal involvement and relapses.[1]

How should we manage intrathecal prophylaxis/treatment in blastic plasmacytoid dendritic cell neoplasm?

The exact incidence of BPDCN CNS involvement, in particular of cerebrospinal fluid (CSF) positivity from lumbar puncture (LP) analysis, is unknown in the modern targeted-therapy era.[36] A LP is now recommended in the initial work-up of the disease, to rule out CNS localization,[26] but historically, it has not been included as a standard of care at the time of diagnosis; also, in most clinical trials, CNS disease has been excluded, or prophylactic intratecal chemotherapy have not been systematically performed (including trials with CD123 target therapy).[26,36]

The observation of better outcomes for patients treated with regimens, including CNS prophylaxis and HSCT, led to hypothesizing that CNS involvement may occur more often than previously suspected. In historical cohorts, the involvement of CNS in BPDCN is quite variable, ranging from 4 to 9% at diagnosis and from 17 to 33% at relapse.[1] One study, performed before the use of targeted agents, demonstrated flow cytometric identification of CSF positivity in 60% of patients with BPDCN at diagnosis and in 100% of patients at the time of relapse.[37] A recent case series on 103 patients, collected from 1999 through 2020, showed how only 29 (28%) had undergone LP analysis. 23 patients (22%) had had 1 diagnosis during their BPDCN disease course: 57% were routinely discovered with frontline LP, with the remaining 43% discovered in the relapsed setting after presenting with neurologic symptoms. The six remaining patients with negative LPs were asymptomatic. The CSF status of the remaining 74 patients in this cohort is unknown.[37] In two recent small case series, including patients treated with CD123 targeted therapy, CNS involvement ranged from 54 to 60%, including cases of occult CNS disease.[38,39] These findings suggest a possible underestimation of CNS involvement, particularly CSF positivity without neurological symptoms, defined as occult CNS disease. Due to high rates of CNS relapse, intrathecal (IT) prophylaxis or therapy has been historically recommended in association with combination chemotherapy regimens.[34,38,39] Published data leading to tagraxofusp approval did not provide evidence regarding its activity against CNS disease. Patients with known CNS disease were excluded from the study and a LP was not routinely performed to assess occult CNS disease (which could occur in up to 10% of cases).[29] It appears therefore reasonable to perform a diagnostic LP in all patients diagnosed with BPDCN.

Management of capillary leak syndrome occurring with tagraxofusp administration

Capillary leak syndrome (CLS) is a potentially serious/fatal toxicity associated with tagraxofusp administration.

CLS consists of an endothelitis, with fluid leakage from the intravascular compartment and it was reported in about 1 in 3 patients treated with tagraxofusp, with variable severity.

CLS-related symptoms may consist of hypoalbuminemia, onset or worsening of edema, including pulmonary edema or hypotension, weight gain, hemodynamic instability. It is a potentially life-threatening complication, prompting the need for immediate recognition and management; a box warning regarding CLS was issued upon the approval of tagraxofusp.

CLS occurs most commonly during or immediately after the first course of treatment, with a median time of onset of 5 days (range 4-51) and a median duration of 4 days (range 3-19).[10,29,30]

A consistent predictor of CLS appeared to be a low pre-treatment level of serum albumin;[29] management recommendations include a baseline serum albumin requirement (≥3.2 g/dl), albumin intravenous replacements as needed in case of reduction from baseline, a baseline assessment of cardiac functions and the administration of the first course of treatment in an inpatient setting.[10]

It is recommended to administer premedication of the drug with a H1-histamine antagonist, acetaminophen, corticosteroids and H2-histamine antagonist before each infusion.[10]

During treatment, regular monitoring of serum albumin levels, vital signs, weight changes, and of any sign/symptom of CLS is required.

Management of CLS includes intravenous albumin replacement, delaying or withholding of additional tagraxofusp doses, use of corticosteroids and close management of volume status and fluid balance (with diuretics or intravenous fluids depending on the clinical presentation).[10,29]

Notably, after the three fatal CLS events documented in the registration trial, no other fatal CLS event was registered documenting the manageability of this possible complication.

Assessment of response to treatment in blastic plasmacytoid dendritic cell neoplasm

Historically, no consensus guidelines to assess and measure treatment response were available for patients with BPDCN.

A comprehensive set of response criteria, including the evaluation of the most commonly involved disease compartments, was developed to evaluate response in the phase II trial assessing the efficacy of tagraxofusp.[29]

CR in BPDCN has the same hematologic criteria of AML on bone marrow and peripheral blood assessments, but it is also important to document response in any known extramedullary site of disease, including CNS and skin.[10,29]

Cutaneous measurements were performed by skin biopsy and the Modified Severity Weighted Assessment Tool; lymph nodes and viscera were evaluated by standard criteria based on computed tomography.[29]

Complete response was defined as the disappearance of disease in each site of the initial disease.

A new category of response, named clinical complete response (CRc) was identified to include all patients presenting a complete response in all non-skin disease, marked clearance of all skin lesions from baseline, but persistence of skin abnormalities – such as hyperpigmentation or microscopic abnormalities – not indicative of active BPDCN.[29]

In cases of CRc where the skin still shows microscopic disease, it is advisable to consider continuing additional cycles (at least 4) of therapy before proceeding to consolidation strategies or managing the disease as R/R.[10]

Pediatric, adolescent and young adult patients

BPDCN is rare in pediatric and young adult patients. Recently a case series of eight patients treated with tagraxofusp has been reported. Seven patients (88%) were bridged to HSCT. Five patients remained alive at the last follow-up. These cases highlight the efficacy and safety of Tagraxofusp in this category of patients.[40]

Treatment of relapsed/refractory disease

Treatment of R/R BPDCN can be challenging as consensus regarding the optimal management and data deriving from

prospective data are lacking. Enrolment in a clinical trial, when available, should therefore always be considered. Patients eligible for intensive regimens should be treated with combination chemotherapy (see options listed as induction treatments) or tagraxofusp, depending on what has been used in first line, with preference for an alternative regimen. All patients should be screened at relapse for CNS disease and evaluated for IT therapy or prophylaxis (CNS involvement at relapse can be documented in up to one-third of patients). If an allogeneic transplant has not yet been performed and the patient is eligible, donor search should be initiated promptly at first relapse. Other options include local radiation to isolated lesions or areas or systemic steroids. Overexpression of BCL2 represents a hallmark of tumoral vs normal pasmacytoid dendritic cells, thus indicating a possible therapeutic target in this neoplasm.[25,41-43] Venetoclax-based therapy is listed as a possible option in R/R disease.[10] Data regarding the use of venetoclax-based therapies in R/R BPDCN are limited to case reports and to a small number of patients treated with venetoclax-based combination therapy (with azacytidine or with low-dose cytarabine) in the context of a trial involving AMLs and related myeloid malignancies.[41-44] Overall, two patients treated off-label with venetoclax experienced significant clinical benefits; while clinical experience with venetoclax combination therapy in 2 BPDCN R/R patients showed no response by formal criteria but highlighted one case of PET/CT major response + >50% blast reduction and improvement in skin lesions and 1 major response in skin lesions. Further data are awaited and venetoclax is currently being explored in BPDCN in an ongoing phase 1 clinical trial (NCT03485547). Other investigational therapies currently under evaluation include new agents targeting CD123. IMGN632 is an antibody-drug conjugate consisting of a humanized anti-123 antibody G4723A fused to an indolino-benzodiazepine cytotoxic agent (IGN). The compound can alkylate DNA without crosslinking and it is able to kill target cells expressing CD123.[24,45] IMGN632 has shown potent activity in both CD-123 expressing AML samples and in multiple AML xenograft models. The *in vitro* activity was established at concentrations well below levels impacting normal bone marrow progenitors, a finding suggesting the potential for efficacy with limited myelosuppression.[45] A phase 1 trial of IMGN632 in CD-123 expressing hematological malignancies is ongoing (NCT03386513). Other investigational treatments include a phase 1 study with CD123-directed CAR-T cells in patients with AML and BPDCN (NCT02159495) and a phase 1 trial of XmAb14045, a bispecific antibody that binds CD123 and CD3 in patients with CD123- expressing hematologic malignancies, including AML, B-cell ALL, BPDCN, and CML (NCT02730312).[24]

The use of hypomethylating agents in BPDCN is limited to a few case reports, showing in 2 patients (ages 78 and 81) with BPDCN and myelodysplastic syndrome evidence of skin response and hematologic stability after azacytdine.[26,44] An additional case report of 3 additional elder patients, (age range 75-80 years) treated with azacytidine with or without localized radiotherapy showed a PFS of 6, 7, and 24 months, respectively.[26,46] Another case series (3 patients) investigated the use of bortezomib/lenalidomide/dexamethasone combination in BPDCN patients with treatment-refractory disease or in whom chemotherapy is contraindicated showed encouraging results, with CR for all three patients after two or three treatment cycles.[47]

References

1. Pagano L, Valentini CG, Grammatico S, Pulsoni A. Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches. Br J Haematol 2016;174:188-202.
2. Pileri A, Delfino C, Grandi V, et al. Blastic plasmacytoid dendritic cell neoplasm (BPDCN): the cutaneous sanctuary. G Ital Dermatol Venereol 2012;147:603-8.
3. Lennert K, Remmele W. Karyometrische untersuchungen an lymphknotenzellen des menschen. Acta Haematol 1958; 19:99-113.
4. Reizis B, Bunin A, Ghosh HS, et al. Plasmacytoid dendritic cells: recent progress and open questions. Annu Rev Immunol 2011;29:163.
5. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36: 1703-19.
6. Pagano L, Zinzani PL, Pileri S, et al. Unmet clinical needs and management recommendations for blastic plasmacytoid dendritic cell neoplasm: a consensus-based position paper from an ad hoc international expert panel. Hemasphere 2023;7:e841.
7. Massone C, Chott A, Metze D, et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic, and molecular study of 50 patients. Am J Surg Pathol 2004;28: 719-35.
8. Massone C, Raiola AM, Dominietto A, et al. Blastic Plasmacytoid Dendritic Cell Neoplasm: Underlining the importance of an early diagnosis and the use of tagraxofusp therapy before wide dissemination. Australas J Dermatol 2021;62:e316-e318.
9. Laribi K, Baugier de Materre A, Sobh M, et al. Blastic plasmacytoid dendritic cell neoplasms: results of an international survey on 398 adult patients. Blood Adv 2020;4:4838-48.
10. NCCN guidelines, version 3.2021. Blastic plasmacytoid dendritic cell neoplasm (Age ≥18 years)
11. Facchetti F, Cigognetti M, Fisogni S, et al. Neoplasms derived from plasmacytoid dendritic cells. Mod Pathol 2016;29:98-111.
12. Facchetti F, Jones D, Petrella T. Blastic plasmacytoid dendritic cell neoplasm. In: WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H., Thiele, J. & Vardiman, J.W. (eds.), IARC press, Lyon, France; 2008:145-7.
13. Facchetti F, Pileri SA, Lorenzi L, et al. Histiocytic and dendritic cell neoplasms: what have we learnt by studying 67 cases. Virchows Arch 2017;471:467-89.
14. Brody JP, Allen S, Schulman P, et al. Acute agranular CD4-positive natural killer cell leukemia: comprehensive clinico-pathologic studies including virologic and in vitro culture with inducing agents. Cancer 1995;75:2474-83.
15. Petrella T, Dalac S, Maynadie M, et al. CD4+ CD56+ cutaneous neoplasms: a distinct hematological entity? Groupe Francais d'Etude des Lymphomes Cutanes (GFELC). Am J Surg Pathol 1999;23:137-46.
16. Chan JKC, Jaffe ES, Ralfkiaer E. Blastic NK-cell lymphoma. In: WHO Classification. Tumors of Haematopoietic and Lymphoid Tissues. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds.), IARC Press, Lyon, France; 2001;214-5.
17. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768-85.

18. Willemze R, Jansen PM, Cerroni L, et al. EORTC cutaneous lymphoma group. subcutaneous panniculitis-like T-cell lymphoma: definition, classification, and prognostic factors: an EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838-45.

19. Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. Am J Surg Pathol 2010;34:75-87.

20. Massone C, Lozzi GP, Egberts F, et al. The protean spectrum of non-Hodgkin lymphomas with prominent involvement of subcutaneous fat. J Cutan Pathol 2006;33:418-25.

21. Sapienza MR, Pileri A, Derenzini E, et al. Blastic plasmacytoid dendritic cell neoplasm: state of the art and prospects. Cancers (Basel) 2019;11:595.

22. Valentini CG, Piciocchi A, Facchetti F, et al. Blastic plasmocitoid dendritic cell neoplasm with leukemic spread: a GIMEMA survey. Blood Adv 2021;5:5608-11.

23. Ascani S, Massone C, Ferrara G, et al. CD4-negative variant of CD4+/CD56+ hematodermic neoplasm: description of three cases. J Cutan Pathol 2008;35:911-5.

24. Leukemia & Lymphoma Society. Facts about Blastic Plasmacytoid Dendritic Cell Neoplasm. 2019. Available from: https://www.lls.org/sites/default/files/2021-05/FSHP2_BPDCN_FINAL_2019.pdf

25. Garnache-Ottou F, Vidal C, Biichlé S, et al. How should we diagnose and treat blastic plasmacytoid dendritic cell neoplasm patients? Blood Adv 2019;3:4238-51.

26. Kharfan-Dabaja MA, Pemmaraju N, Mohty M, et al Therapeutic Approaches for Blastic Plasmacytoid Dendritic Cell Neoplasm: Allogeneic Hematopoietic Cell Transplantation and Novel Therapies. Clin Hematol Int 2019;1:2-9.

27. Pagano L, Valentini CG Pulsoni, A, et al. Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study. Haematologica 2013;98:239-46.

28. Elzonris® (tagraxofusp). CHMP Assessment Report. 2020.

29. Pemmaraju N, Lane A, Sweet KL, et al. Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm, N Engl J Med 2019;380:1628-37.

30. Alfayez M, Konopleva M, Pemmaraju N. Role of tagraxofusp in treating blastic plasmacytoid dendritic cell neoplasm (BPDCN). Expert Opin Biol Ther 2020;20:115-23.

31. Pemmaraju N, Sweet KL, Stein AS, et al. Long-term benefits of tagraxofusp for patients with blastic plasmacytoid dendritic cell neoplasm. Lane J Clin Oncol 2022;26:3032-6.

32. Kharfan-Dabaja MA, Reljic T, Murthy HS, et al. Allogeneic hematopoietic cell transplantation is an effective treatment for blastic plasmacytoid dendritic cell neoplasm in first complete remission: systematic review and meta-analysis. Clin Lymphoma Myeloma Leuk 2018;18.

33. Dalle S, Beylot-Barry M, Bagot M, et al. Blastic plasmacytoid dendritic cell neoplasm: is transplantation the treatment of choice? Br J Dermatol 2010;162:74-9.

34. Sullivan JM, Rizzieri DA. Treatment of blastic plasmacytoid dendritic cell neoplasm. Hematology Am Soc Hematol Educ Program 2016;2016:16-23.

35. Aoki T, Suzuki R, Kuwatsuka Y, et al. Long-term survival following autologous and allogeneic stem cell transplantation for blastic plasmacytoid dendritic cell neoplasm. Blood 2015;125:3559-62.

36. Pemmaraju N, Wilson NR, Khoury JD, et al. Central nervous system involvement in blastic plasmacytoid dendritic cell neoplasm. Blood 2021;138:1373-7.

37. Martın-Martın L, Almeida J, Pomares H, et al. Blastic plasmacytoid dendritic cell neoplasm frequently shows occult central nervous system involvement at diagnosis and benefits from intrathecal therapy. Oncotarget. 2016;7:10174-81.

38. Greenwell IB, Davis J, Li H, et al. Outcomes of CNS involvement in blastic plasmacytoid dendritic cell neoplasm (BPDCN). J Clin Oncol 2021;39:e19043-e19043.

39. Rivoli G, Beltrami G, Raiola A, et al. P:530: Tagraxofusp in blastic plasmacytoid dendritic cell neoplasm with/without central nervous system involvement and intrathecal chemotherapy as primary treatment or prophylaxis: an Italian experience. HemaSphere 2022;6:429-30.

40. Pemmaraju N, Cuglievan B, Lasky J, et al. Efficacy and manageable safety of tagraxofusp in pediatric and adolescent/young adult patients with blastic plasmacytoid dendritic cell neoplasm. Br J Haematol 2023;5:61-9.

41. Montero J, Stephansky J, Cal T, et al. Blastic plasmacytoid dendritic cell neoplasm is dependent on BCL-2 and sensitive to venetoclax. Cancer Discov 2017;7:156-64.

42. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL-2 inhibitor venetoclax in combination therapy for relapsed and refractory AML and related myeloid malignancies. AM J Hematol 2018;93:401-7.

43. Sapienza MR, Pileri A, Derenzini E, et al. Blastic plasmacytoid dendritic cell neoplasm: state of the art and prospects. Cancers (Basel) 2019;11:595.

44. Laribi K, Denizon N, Ghnaya H, et al. Blastic plasmacytoid dendritic cell neoplasm: the first report of two cases treated by 5-azacytidine. Eur J Haematol 2014;93:81-5.

45. Kovtun Y, Jones GE, Adams S, et al. A CD123-targeting antibody-drug conjugate, IMGN632, designed to eradicate AML while sparing normal bone marrow cells. Blood Adv 2018;2:848-58.

46. Khwaja R, Daly A, Wong M, et al. Azacitidine in the treatment of blastic plasmacytoid dendritic cell neoplasm: a report of 3 cases. Leuk Lumphoma 2016;57:2720-2.

47. Marmouset V, Joris M, Merlusca L, et al. The lenalidomide/bortezomib/dexamethasone regimen for the treatment of blastic plasmacytoid dendritic cell neoplasm. Hematol Oncol 2019;37:487-89.