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Unmet Clinical Needs and Management Recommendations for Blastic Plasmacytoid Dendritic Cell Neoplasm: A Consensus-based Position Paper From an Ad Hoc International Expert Panel

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ABSTRACT

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a hematological malignancy characterized by recurrent skin nodules, an aggressive clinical course with rapid involvement of hematological organs, and a poor prognosis with overall survival. The rarity of the disease results in a few large-scale studies, a lack of controlled clinical trials for its management, and a lack of evidence-based guidelines. Here, we present a review of unmet clinical needs on the management of BPDCN by a panel of eleven experts involved in the research and clinical practice of BPDCN. Recommendations and proposals were achieved by multiple-step formalized procedures to reach a consensus after a comprehensive analysis of the scientific literature. The panel analyzed the critical issues of diagnostic pathway, prognostic stratification, therapy for young and fit patients and elderly and unfit patients, indication for allotransplant and for autotransplant, indication for central nervous system prophylaxis, and management of pediatric BPDCN patients. For each of these issues, consensus opinions were provided and, when appropriate, proposals for advancement in clinical practice were addressed. The hope is that this comprehensive overview will serve to improve the practice of BPDCN and inform the design and implementation of new studies in the field.

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a hematological malignancy characterized by an aggressive clinical course with a poor prognosis and overall survival. The current edition of the World Health Organization (WHO) includes BPDCN as a distinct form of acute myeloid leukemia (AML).¹ The overall incidence of the disease is extremely low, accounting for 0.44% of all hematologic malignancies and 0.7% of cutaneous lymphomas.²

The rarity of the disease and the physiopathological uncertainties result in a few large-scale studies, a lack of controlled clinical trials for its management, and a lack of evidence-based guidelines. As a consequence, many clinical issues in the management of the disease are controversial. In particular, diagnosis of BPDCN itself is challenging due to biological and phenotypic heterogeneity, with an overlap in morphologic and immunophenotypic features with various cutaneous, lymphatic, or hemato-poietic tumors. In front of this platform, no recommendations

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on therapy have been issued by scientific societies or health authorities.

The objectives of this project are to identify the most clinically relevant unmet clinical needs (UCNs) in the management of patients with BPDCN and to produce recommendations on the appropriateness of the clinical decisions concerning the identified clinical needs.

METHODS

Experts with extensive experience in BPDCN convened to develop this position paper. Throughout the project, the methodology of group discussion (questionnaires and consensus meetings) was followed as a consensus-based project. This means that we intended to produce recommendations that do not derive from a systematic review and grading of the evidence. Consensus-based recommendations assume that the experts have an implicit and comprehensive mastery of scientific and practical information that would yield the most appropriate decisions.

Three chairmen (LP, PLZ, and SP) appointed an Expert Panel (hereafter referred to as the Panel) of 11 members. The Panel comprised an international group of BPDCN experts across disciplines, who hailed from both Europe and the United States, to provide various perspectives on treatment approaches for patients with BPDCN. A clinician with expertise in clinical epidemiology (GB) assured the methodological consistency of the process. During an initial meeting in June 2021, the outline of the project was discussed and the topics that form the structure of the present document were decided. The key UCNs were selected through a series of questionnaires according to the Delphi technique.³ Members of the Panel reviewed the evidence on selected UCNs by PubMed searches of English-language literature (2007 to December 2021). Additionally, the proceedings of the latest international annual meetings were searched for relevant unpublished evidence. Afterward, panelists drafted statements that addressed one identified UCN, while the remaining panelists scored their agreement with those statements and provided suggestions for modifications. Finally, the Panel convened for a virtual consensus conference in May 2022. In this conference, participants were first asked to comment in a round-robin fashion on their disagreements with the proposed issues and to vote for final statements.

UNMET CLINICAL NEEDS

Although numerous UCNs in the domain of BPDCN were issued by the Panel (Table 1), this review focuses only on some

of the major outstanding challenges voted as the most relevant and urgent by the panelists.

UCN 1. Optimization of the diagnostic pathway

The diagnosis of BPDCN is usually based on a pathological biopsy, more often of the skin that represents the commonest site of disease presentation, followed by the lymph node, bone marrow (BM), and peripheral blood.⁴ Kerr et al showed tumor cells invading the dermis and adipose tissue of the skin, with no tumor cells in the epidermis.⁵ When the lesion involves the BM, it may present as an interstitial infiltration or as a mass of tumor cells, such as infiltrating leukemia, often accompanied by hematopoietic tissue dysplasia.⁵ On cytological grounds, BPDCN can mimic either acute leukemia or immunoblastic lymphoma.⁶ In the latter condition, the tumor carries *MYC* rearrangement.⁷ BPDCN should be distinguished from the condition termed by Xiao et al as pDC-AML, consisting in the plasmacytoid dendritic cell (DC) expansion in the context of AML.⁸ pDC-AML was reported to frequently carry *RUNX1* mutations, which are indeed rare in BPDCN.⁸

Immunophenotyping in tissue sections relies on the search for CD4, CD56, CD123, CD303, TCL1, and TCF4 in the absence of other myeloid, histiocytic, DC, and lymphoid lineage-specific markers.^{4,6} The co-expression of all the above mentioned molecules produces a distinctive phenotypic profile. However, most of them are not exclusive to BPDCN (eg, CD4, CD56, CD123, and TCL1) and—even when pathognomonic (eg, CD303)—are not detected in all instances. Julia et al described that the co-expression of the 5 most common markers, CD4, CD56, CD123, CD303, and TCL1, only occurred in 46% of patients with BPDCN.⁹ TCF4, which was discovered by an RNA interference screening study of the CAL-1 BPDCN cell line and might represent the rational for the therapeutic usage of BET-inhibitors, represents a highly specific nuclear marker that so far has not been extensively studied.¹⁰

Flow cytometry can assist in diagnosing BPDCN in cases with involvement of the blood and/or BM, which is often detected during staging procedures. A recent survey showed that half of the Italian hematologists applied a panel including CD123, CD303, and TCL1 only in selected cases, after the exclusion of other forms of acute leukemia.¹¹ Regrettably, the limitations in the composition and usage of phenotypic panels lead to delay in diagnosis and subsequent treatment.

Garnache-Ottou et al developed a scoring system for the diagnosis of BPDCN by applying a large series of markers to 20 BPDCN cases and 113 acute lymphoid leukemia (ALL) and AML cases. They identified that the expression of CD4 (CD56±) and lack of CD11c, cCD3, cCD79a, and MPO scored 1 point; CD123 high and BDCA4/CD303+ scored 1 point each, and the expression of BDCA2/CD303 scored 2 points.¹² Accordingly, the diagnosis of BPDCN was trustworthy when the total score was >2 points, which is applicable for typical or atypical BPDCN immunophenotype.

Gene mutations in BPDCN affect several functional classes of genes, mainly DNA methylation, histone modification, signal transduction, transcription factors, cell-cycle regulation, and splicing factors.^{13–20} However, the reported frequency of each mutation varies widely. In a study performing the mutation profile in 50 BPDCN cases evaluated by next-generation sequencing (NGS) using targeted panels for genes commonly mutated in hematologic neoplasms, Yin et al detected mutations in the interrogated genes in 84% of the cases, and 66% of patients had >1 mutation.¹⁹ In keeping with previous studies, an Italian study showed that *TET2* and *ASXL1* were the most frequently mutated genes, seen in 56% and 46% of cases, respectively.¹⁸ They were representative of the common alteration of genes involved in chromatin remodeling and methylation.¹⁸ Gene expression profiling studies evidenced that the signature of BPDCN is closer to the one of resting plasmacytoid DCs and

Table 1
List of UCNs Proposed by the Panel

- 1. Optimization of subclassification: pediatric vs adult
- 2. Optimization of the prognostic stratification
- 3. Indication to allotransplant
- 4. Indication to autotransplant
- 5. Optimization of the staging pathway
- 6. Optimization of the diagnostic pathway
- 7. CNS prophylaxis
- 8. Multidisciplinary management coordination
- 9. Making the pediatric groups more aware of the disease
- 10. Optimization of subclassification: plasmacytoid vs AXL+ dendritic cell neoplasms.
- 11. Therapeutic recommendations for young (and fit) patients
- 12. Mechanism of drug resistance
- 13. Therapeutic recommendations for elderly or unfit patients

CNS = central nervous system; UCN = unmet clinical need.

myeloid precursors. In addition, they revealed constitutive overexpression of *BCL2* and activation of the NF- κ B pathway. The former corresponds to strong *BCL2* positivity on immunohistochemistry, a finding which allows the easy differentiation of BPDCN elements from normal plasmacytoid DCs, which turn regularly negative.¹⁴

Patients with BPDCN carry heterogeneous karyotypic aberrations. It has been reported that approximately 60% of patients have a complex karyotype, with imbalanced chromosomal losses being the most common.²¹ On FISH analysis, *MYC* rearrangement is observed in about 40% of cases by heralding a worse prognosis and possible sensitivity to ALL-based therapies.⁶ By conventional cytogenetics and a-CGH, the biallelic deletion of *CDKN1B* seems to predict a worse outcome, while the aberrations of *IKZF1*, which is involved in the DC hematopoiesis, have still a controversial impact on prognostic grounds.⁶

Recommendations and proposals

The final diagnosis of BPDCN should be made either by tumor skin biopsy immunohistochemistry or by BM cell flow cytometry.

The close collaboration of the clinician with the pathologist is essential in the diagnostic process. A description of the macroscopic characteristics of cutaneous lesions should always be followed by a detailed description of the morphologic and molecular features of the tumor.

Whenever possible, the immunohistochemical description should be integrated with the FACS analysis data, since there is not always total equivalence between the phenotypic profile on tissue sections and peripheral blood.

The results of the case series do not allow to trace of a diagnostic immune-histochemical algorithm based on the presence/absence of key markers.

The panel of biomarkers listed by WHO diagnostic criteria should be initially used with additional biomarkers that are useful for excluding differential diagnosis in the case of non-standard results including peripheral T/NK-cell lymphomas, myeloid sarcoma, and cutaneous involvement by AML.

For this endeavor, the search for CD303 and TCF4 is worthy because of their high specificity.

Molecular analysis of the malignant cells is not necessary for the diagnosis.

UCN2. Optimization of the prognostic stratification

BPDCN patients show a dismal prognosis, with overall survival (OS) of <1 year in most patients treated by conventional therapies.¹⁸ Due to the rarity of this condition and the challenges in the nosologic definition and diagnosis, no standardized prognostic factor has been identified to be used in clinical practice. Some studies, however, reported significant differences in terms of disease outcome according to specific clinical, as well as phenotypic and molecular parameters.

In the largest series reporting a total of 398 patients from 75 centers, a significant negative impact on OS was found for age, ECOG score, disseminated disease with or without skin involvement, and extranodal disease.²² Also a CD4+CD56+CD123+TCL1+BDCA2+ phenotype revealed a negative impact on prognosis, while high expression of terminal deoxynucleotidyl transferase (TdT) was associated with better prognosis.²² Other studies confirmed the favorable prognostic role of high levels of TdT expression (>50%).⁹ Survival analyses showed also that CD303 expression and high Ki67 index are associated with better OS, while 9p21.3 deletion was associated with a shorter one.^{9,23}

On clinical background, reports document that patients with isolated cutaneous lesions display a better clinical outcome than those with widespread lesions (progression free survival: 23 versus 9 months, respectively).²⁴ However, not all studies agree that limited cutaneous involvement correlates with better OS. In

a French retrospective study of 86 patients, the variables with a significant impact on OS were treatment with acute leukemia-like versus CHOP-like, ECOG, and age.²⁵ In a retrospective group of 49 patients treated at 3 US centers, a worse outcome was associated with age (>60 years old), abnormal karyotype (in particular with 3 or more abnormalities), and TdT negativity.²⁶ Similarly, in a series of 50 BPDCN cases, patients <65 years old showed a better OS, while the presence of ≥ 3 mutations or mutations in DNA methylation pathway genes was associated with shorter OS.¹⁹ In a series of 49 consecutive patients treated with either conventional chemotherapy or the new anti-CD123 tagraxofusp targeted therapy, there was no difference according to the extent of the disease (skin versus BM versus both) or younger age (<60 years old).²⁷

Recommendations and proposals

Based on the currently available data, young age, high TdT expression, and the absence of karyotype abnormalities are associated with a better OS.

Multicenter studies are needed to define prognostic/predictive factors associated with disease outcome and therapy response, which at the time of writing are unavailable.

UCN 3. Therapeutic recommendations for young and fit patients with BPDCN

BPDCN has generally been regarded as a disease of older adults, with median age closer to 65–70 years.²⁸ However, as diagnostic accuracy and overall disease awareness have increased over time, we are seeing a greater population of younger adults in our clinics. Notably, the only approved therapy to date in all of the rare disease fields of BPDCN remains the novel CD123-based targeted therapy known as tagraxofusp (U.S. Food and Drug Administration approved, December 2018, for patients with BPDCN aged 2 years and older; as well as European Medicines Agency approved in first-line adults, January 2021).

The therapy recommendations in younger adults will vary based on geographic location, availability of actual chemotherapy agents themselves, physician preference, and personal experience.

If available, one of the frontline approaches remains referral to a major academic center for consideration of BPDCN-dedicated clinical trials for all patients with BPDCN, whether frontline or beyond. We emphasize this point as not only little is known about this rare malignancy but patient samples are rare and we advocate if/when possible for patients to be enrolled in clinical/translational studies for novel agents and opportunity for laboratory collection for exploratory correlative analysis so that we may as a field learn as much as we can from every single patient case.

Of note, active clinical trials are ongoing in the United States for combination triplet therapies, including for frontline patients with BPDCN (eg, tagraxofusp/azacytidine/venetoclax and tagraxofusp/HCVAD/venetoclax) on clinical trials (*ClinicalTrials.gov* Identifiers: NCT03113643 and NCT04216524).

With tagraxofusp, incidence of capillary leak syndrome (CLS) is well-known from prior studies with this agent.^{29,30} Importantly in the recently published updated dataset by Pemmaraju et al,³¹ at approximately 3-year follow-up, CLS occurrence was still as expected at 21% (similar to previous experience) with 7% grade 3 or higher events. Precautions include patient and provider education, healthcare multidisciplinary coordination, especially during inpatient hospitalization, monitoring and replacing of albumin, measurement of daily weights, albumin levels, vital signs (Body Temperature, Pulse Rate, Respiration Rate, Blood Pressure) during infusion days; hospitalization during cycle 1 for optimal administration; and appropriate use of diuretics when indicated, and employment of measures such as high-dose steroids for active treatment, in addition to other

standard practices evaluating for infection/sepsis, other cardiac/pulmonary events during the suspected time of CLS.

Beyond frontline therapy, moving into the relapsed/refractory (R/R) setting, it is notable that patients with BPDCN experience quite poor outcomes, despite modern therapy approaches. For example, among 15 R/R BPDCN patients treated with tagraxofusp in the original pivotal trial, even with an overall response rate (ORR) of 67%, the median OS was only 8.5 months.²⁹ In longer, approximately 3-year follow-up of the original tagraxofusp study, Pemmaraju et al then described in later publication update that among 65 frontline-treated patients with BPDCN, the ORR was 75% with 57% CR/Cr rate, and no new/unexpected safety signals were uncovered.³¹ Median OS with this longer follow-up was 15.8 months with survival probability at 24 months of 40%.

The other most developed CD123-targeted program is that of IMGN 632 clinical trial, which enrolled 29 patients with R/R BPDCN and demonstrated a 31% ORR among prior tagraxofusp-treated patients; this program has received FDA *Breakthrough Therapy Designation* and is now actively enrolling patients in frontline BPDCN setting in both USA and European sites.^{32,33} Other active clinical trial approaches in the R/R setting include Chimeric Antigen Receptor (CAR-T) therapy, bispecific molecules, immunotherapy approaches, and combination therapy approaches including hypomethylating agents, and BCL2 antagonists (venetoclax), and cytotoxic chemotherapy regimens not yet used in the frontline approach.³⁴

RECOMMENDATIONS AND PROPOSALS

Among young and fit patients with BPDCN, there remains a great area for debate and discussion on the optimal frontline approach, as there are still to date no randomized, head-to-head comparison clinical trials comparing directly targeted therapy approaches versus cytotoxic chemotherapy approaches.

Therapeutic options include clinical trials (including combination approaches); CD123-targeted regimens (including tagraxofusp, and Immunogen (IMGN632) clinical trial actively enrolling frontline patients); and cytotoxic-based chemotherapy regimens, most commonly ALL-based such as the HCVAD regimen.

Regardless of regimen choice or clinical trial availability, the Panel agreed on 2 mainstays of young and fit BPDCN management: all younger/fit patients should be considered for allogeneic stem cell transplant (alloSCT) optimally in first complete remission (CR) (if not, then in second CR and beyond); and central nervous system (CNS)-directed therapy should be offered to all patients, preferably via intrathecal chemotherapy as in high-risk ALL/Burkitt's leukemia paradigm.

UCN 4. Therapeutic recommendations for elderly and unfit patients with BPDCN

There are several guiding principles in the treatment of older/unfit patients with BPDCN that differ from the younger/fit patient approach. One must first determine alloSCT fitness or not; by definition, most, if not all, in this category will not be able to go for curative alloSCT. However, a subset of patients might be considered for autologous stem cell transplant (autoSCT), a practice that has been documented in prior experiences with BPDCN around the world.^{35,36} Therefore, consideration of autoSCT may still apply to selected patients.

In the absence of a consensus on treatment in frontline older/unfit settings, several active programs were put forward by the Panel for consideration: clinical trials if available; CD123-targeted agents if available; strong consideration for hypomethylating agents (HMA) plus venetoclax approach.

Both decitabine and azacitidine^{22,37,38} have been utilized in the treatment of older/unfit BPDCN historically; additionally, several groups have demonstrated the feasibility of a combination approach with both HMA and venetoclax; in a series of 10

older patients treated at Mayo Clinic and MDACC in the United States, with all 10 having older age and major comorbidities, all patients had some form of response, although most transient; but several patients were able to proceed to alloSCT indicating improved performance status after treatment with HMA plus venetoclax.³⁹

With cytotoxic agents and venetoclax+HMA, incidence of neutropenia and neutropenic fever is expected as is the case with treatment of older AML. We recommend all patients receive prophylactic antibiotics based on local practices similar to older AML for our patients with BPDCN receiving these myelosuppressive regimens, and early intervention, hospitalization, infection/sepsis work-up and endovenous antibiotics and higher level care if/as needed in the case of infections/neutropenic fevers during venetoclax+HMA or cytotoxic chemo regimens across the world.

Still a role for cytotoxic chemotherapy, but the key is to use markedly reduced doses, omit highly toxic and/or myelosuppressive agents, watch renal, hepatic, and immune system function carefully. Examples of cytotoxic programs used by experts in older/unfit BPDCN include mini-cyclophosphamide, vincristine, and prednisone (CVD) regimen (HCVAD minus the anthracycline; reduction of doses of all agents with particular focus on creatinine and myelosuppression/infection/sepsis risk); cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) lymphoma-based regimen; dose reduced AML-based regimens.^{22,26,29,40,41}

The emergence of venetoclax is a most important development in the treatment of BPDCN, particularly for older/unfit patients, especially as its availability is increasing worldwide following its approval and use in multiple other hematologic malignancy settings as both monotherapies and as a combination partner with other chemotherapeutic drugs.⁴² First approved as a single oral agent in chronic lymphocytic leukemia (CLL) and later in older AML patients in combination with either HMA or low-dose cytarabine, venetoclax is now being actively investigated in clinical trials for BPDCN either alone or in combination.³⁹ Furthermore, several reports across the world have demonstrated the safety and efficacy of combinations of venetoclax either with chemotherapy (HCVAD plus VEN) or combinations with CD123-based agents, providing a novel approach to older/unfit patients or even for younger patients or those with resistant to disease to frontline approaches.^{34,40}

As relapse rates remain high in BPDCN and OS still needs improvement for vast majority of patients, we need to still keep searching for novel approaches. In particular, one approach that has been hypothesized is a more multiple myeloma (MM)-based cytotoxic chemotherapy approach with proteasome inhibitors such as bortezomib. Originally postulated by Sapienza et al with targeting NF-κB activity,⁴³ the agent known as bortezomib has already been used in context of myeloma and lymphoma. Several groups have begun to investigate bortezomib either alone or in combination with several other agents as combination feasibility with this agent has been demonstrated in MM field.⁴⁴⁻⁴⁶

RECOMMENDATIONS AND PROPOSALS

No worldwide consensus on guiding principles for the treatment of older/unfit patients with BPDCN has been yet reached.

Several active programs were put forward by the Panel for consideration: (a) clinical trials, if available; (b) CD123-targeted agents, if available; (c) strong consideration for venetoclax in combination with hypomethylating agents approach; and (d) cytotoxic chemotherapy.

The Panel agreed on recommending the use of markedly reduced doses of cytotoxic chemotherapy, omitting highly toxic and/or myelosuppressive agents, watch renal, hepatic, and immune system function carefully.

Examples of cytotoxic programs used by experts in older/unfit BPDCN include mini-CVD regimen; CHOP lymphoma based regimen; dose-reduced AML-based regimens.

UCN 5. Indication for allotransplant in BPDCN

Despite the high frequency of CR following first-line chemotherapy treatment, the majority of patients with BPDCN experience drug-resistant relapse in a brief time, resulting in an overall median survival <2 years.⁴⁰ AlloSCT has been consistently reported to confer a longer survival benefit in comparison to other consolidation strategies, including autoSCT, suggesting a valuable allo-immune graft-versus-neoplasia effect.²⁶ AlloSCT, however, is burdened by a high risk of morbidity and mortality, and it is limited to patients <70 years, without major comorbidities, with an available donor.³⁴ Reduced-intensity conditioning may be used in frail and older patients to reduce complications, even though at the cost of a greater posttransplant risk of disease relapse.^{47,48}

RECOMMENDATIONS/PROPOSALS

Indication for alloSCT in BPDCN is independent of the stage of disease at diagnosis, as hematological organs involvement with extremely aggressive clinical course occurs in almost all relapsing patients.

Because the longest disease-free relapse has been reported among patients allografted in first CR, patients <70 years should undergo human leukocyte antigen (HLA)-typing at the time of diagnosis, together with family members who may become donor candidates for an alloSCT. Exceptionally, patients >70 with good performance status and no major comorbidities may also be referred for possible evaluation in experienced BMT centers.

On the other hand, it should be emphasized that in patients >70 years with single lesions limited to the skin local radiotherapy may be followed by durable CR with no relapse.

Activation of a registry search for HLA-matching donors should also be considered promptly for patients without HLA-identical siblings eligible for hematopoietic cell donation.

In younger and fit patients who achieve CR following an acute leukemia-like induction chemotherapy treatment, alloSCT is recommended within 3 months if a donor is identified, to minimize the risk of early on-treatment relapse.

As far as the type of alternative donor (in patients lacking HLA-identical sibling donor) is concerned, even though no data are available in support of matched unrelated versus mismatched unrelated versus family haploidentical, due to the rarity of the disease in a minority of patients eligible for alloSCT, anyone would be a reasonable choice on the base of the few cases reports currently available in the literature.

Likewise, no data are available concerning specific conditioning regimens (total body irradiation [TBI]-based vs. chemotherapy [CT]-based) and the stem cell source (BM versus PB versus cord blood). However, most patients undergoing alloSCT reported in the literature received CT-based conditioning including fludarabine in association with an alkylating agent such as busulfan, melphalan, or cyclophosphamide, or TBI-based conditioning including ≥10 Gy TBI plus cyclophosphamide (in MAC) or 2 Gy TBI plus fludarabine (in RIC).

UCN 6. Indication for autotransplant in BPDCN

Although consolidation with alloSCT appears superior to autoSCT, especially in patients undergoing transplantation in the first CR, this strategy is vastly limited by the median age of diagnosis in BPDCN (around 70 years), making many patients not eligible for allotransplant.

RECOMMENDATIONS AND PROPOSALS

For patients with CT sensitive extra-hematological disease, in first CR but with age-related and/or comorbidity-related high

risk of transplant-related mortality, as well as for patients lacking HLA-suitable hemopoietic cell donor, autoSCT may represent another consolidation strategy, even though limited data are available in the literature.

To minimize the risk of collecting and cryopreserving neoplastic cells, mobilization and collection of peripheral blood stem cells should be accomplished within the course of induction chemotherapy, as soon as evidence of a Positron Emission Tomography (PET)-documented CR is achieved and possibly with a documented measurable residual disease (MRD) negative flow cytometry test both in BM and blood/apheresis.

Due to the well-known skin localization of the disease and its not unfrequent CNS involvement, myeloablative TBI-based or chemotherapy-based conditioning should be preferred.

UCN 7. Indication for CNS prophylaxis

CNS involvement is a serious complication observed in various hematological malignancies. The incidence of CNS localization and its clinical impact is well known in pediatric and adult patients affected by ALL and in lymphomas, on the contrary, it is rarely reported in myeloproliferative disorders (ie, AML, MDS).⁴⁹

Although BPDCN is classified in the context of AML, the onset of CNS involvement at diagnosis or during BPDCN is high^{9,22,27,41,50–55} (Table 2).

Various hypotheses can be considered to justify this higher incidence of CNS disease in BPDCN. DCs are ubiquitous but generally produced at the BM level and once matured they migrate to the lymphoid system. A small part is present in the epithelial (skin). These cells may lose the adhesion molecules and increase the expression of migration molecules such as CLA and CD56, therefore increasing their ability to infiltrate other parenchyma including the skin and CNS. Another possible explanation may be the local availability of chemokines binding cognate receptors expressed by the neoplastic cells such as CXCR3, CXCR4, CXCR6, CXCR7.²⁹ Another hypothesis, as reported in a recent study by Sapienza and co-workers, based on the microRNA expression profile, suggests possible neurogenesis of the neoplastic process.⁵⁶

The incidence of CNS involvement in BPDCN, considering the forms observed at the onset of the disease and those observed at relapse, is not well defined and it ranges from 2.5% to 69%. This marked variability is due to many factors. On the one hand, there is the problem that many epidemiological studies in the past, given the rarity of the disease, are retrospective and due to the classification of BPDCN in myeloid diseases, a diagnostic lumbar puncture was not performed, so frequently CNS was undiagnosed. In other cases, where clinicians have focused on the CNS problem, the cases of clinically asymptomatic forms

Table 2
Incidence of CNS Involvement in BPDCN Patients

References	BPDCN Cases	CNS Involvement		
		At Diagnosis	At Relapse	Overall
Pagano et al ⁴¹	43	4 (9%)	3 (7%)	7 (16%)
Julia et al ⁵²	90	nr	nr	9 (10%)
Martin-Martin et al ⁵³	13	6 (46%)	3 (23%)	9 (69%)
Yun et al ²⁷	49	0	0	0
Cernan et al ⁵⁴	14	1	1	1 (7%)
Laribi et al ²²	398	NR	NR	10 (2.5%)
Ozdemir et al ⁵⁵	9	2	0	2 (22%)
Pemmaraju et al ⁴⁴	103	13 (13%)	10 (10%)	23 (22%)
Valentini et al ¹¹	68	4	2	6 (12.5%)

BPDCN = blastic plasmacytoid dendritic cell neoplasm; CNS = central nervous system; NR = not reported.

(occult forms) have been identified, which seem to be a significant number, resulting in an increase in the rate of localizations to the CNS.

Regarding a CNS prophylaxis, there are no precise indications in the literature, neither if it is to be performed nor on the type of prophylaxis (chemotherapy or radiotherapy) to be performed. Although some authors underline the need to carry out serial cerebro-spinal fluid (CSF) examinations, at the moment, the only indication is the one suggested to us by Pemmaraju and co-workers, with the addition of medicated lumbar punctures alternating methotrexate with cytarabine during induction therapy.⁵⁰

RECOMMENDATIONS AND PROPOSALS

The Panel agreed that a diagnostic and medicated lumbar puncture should be mandatory performed in patients with leukemia presentation of the disease at diagnosis and in all patients at the time of relapse, regardless of hematological involvement.

A diagnostic lumbar puncture is highly recommended in all patients at the diagnosis.

The use of high-sensitivity flow testing of CSF involvement should be encouraged.

Medicated lumbar puncture program should be performed during the induction phase (at least 6–8) by combining cytarabine, methotrexate, and steroid.

In the case of CNS involvement, we do recommend consideration for consultation with Radiation oncology team for possible chemo-XRT or XRT-based approaches.

UCN 8. Pediatric BPDCN: categorization and management issues

The incidence of BPDCN in children is extremely low, with fewer than 80 cases reported: thus, many pediatric institutions are not familiar with the disease. Clinical findings (skin, CNS, etc.) in children might be different in adults. For example, in a systematic review of 74 pediatric patients, 24% presented without skin lesions.⁵⁷ No other clinical findings, laboratories, or radiology images have been related to either a favorable or unfavorable prognosis. Treatment of newly diagnosed BPDCN in pediatrics is different from in adults, and the role of alloSCT in first remission is unclear. High-risk ALL-based treatment, including CNS prophylaxis, has led to encouraging outcomes and alloSCT is reserved for a group of pediatric BPDCN patients with multiorgan involvement, minimal residual disease positivity, and/or persistent illness.⁵⁸ Many new strategies such as venetoclax and CD123-targeted therapies are being employed for this subset of patients.⁵⁹ Of note, a pediatric patient with BPDCN who was treated initially with the ALL-based regimen followed by alloSCT and salvaged with Hyper-CVAD combined with venetoclax after testicular relapse 11 months post alloSCT was recently reported.⁶⁰ Tagraxofusp was FDA-approved in 2018 in the United States for pediatric patients (2 years and older) and was recently approved in the EU as monotherapy for first-line treatment in adults. Recently, 6 pediatric patients treated with this agent led to promising efficacy, including half of the patients with responses that allowed for bridging to alloSCT.

Proposals

Efforts should be made by the scientific community to highlight the differences in clinical presentation, pathology phenotype, and prognosis of pediatric patients with BPDCN concerning adults.

The Panel agreed on the need for recommendations for staging and management of pediatric patients.

Generating clinical trials in cooperative groups for pediatric BPDCN patients in frontline and relapsed settings are urgently needed.

CONCLUSIONS

The main aim of this endeavor is to optimize the care of patients with BPDCN. Despite the paucity of high-level evidence on several important clinical issues, the panel of experts was able to reach a high degree of consensus. This consensus is a valid basis for clinical implementation of the recommendations given and for the design of new studies that may guide therapeutic decisions.

AUTHOR CONTRIBUTIONS

LP, SP, and PLZ coordinated the study. GB was responsible for the methodology. All authors contributed equally to the paper.

DISCLOSURES

LP was Board member of Gilead Science, MSD, Pfizer, Stemline, Basilea, Janssen-Cilag, Novartis, Jazz Pharmaceutical, Cidara and has been speaker for Gilead Sciences, Kiowa Kirin, MSD, Pfizer Pharmaceuticals, Astellas Pharma, Novartis, Jazz Pharmaceutical. Consultant for Menarini. PLZ Board member for Secura Bio, Celltrion, Gilead, Janssen-Cilag, BMS, Servier, Sandoz, MSD, TG therapeutics, Takeda, Roche, EUSapharma, Kiowa Kirin, Novartis, ADC therapeutics, Incyte, Beigene and Speakers bureau for Celltrion, Gilead, Janssen-Cilag, BMS, Servier, MSD, TG therapeutics, Takeda, Roche, EUSapharma, Kiowa Kirin, Novartis, Incyte, Beigene. Consultant for MSD, EUSapharma, Novartis. SP Advisory Board for Takeda, Beigene, Diatch, Speakers bureau for Menarini, Roche. FO Speakers bureau for Menarini-Stemline. PQ Advisory boards and Speakers bureau for Takeda, Kyowa Kirin, Therakos, Cellgene, Recordati Rare Diseases, 4sc, Menarini, Roche. EB Advisory boards and Speakers bureau for Leo Pharma, Novartis, Abbvie, Takeda, Recordati Rare Disease, Kyowa Kirin, Almirall, Sanofi. NP Scientific/Advisory Committee Member for Cancer.Net, CareDx, CTI BioPharma, EUSA Pharma, Inc., Novartis Pharmaceuticals Corp, Pacylex, PharmaEssentia; Speaker/Preceptorship: AbbVie, Aplastic Anemia & MDS International Foundation, Curio Science LLC, Dava Oncology, Imedex, Magdalen Medical Publishing, Medscape, Neopharm, PeerView Institute for Medical Education, Physician Education Resource, Physicians Education Resource, Postgraduate Institute for Medicine, Stemline Therapeutics, Inc. Consultant for AbbVie, Aptitude Health, Astellas Pharma US, Inc., Blueprint Medicines, Bristol-Myers Squibb, Celgene Corp, Cimeio Therapeutics AG, ClearView Healthcare Partners, CTI BioPharma, Dava Oncology, Immunogen, Incyte, Intellisphera, LLC., Novartis AG, Novartis Pharmaceuticals Corp, OncoLive (Owned by Intellisphera, LLC), Patient Power, PharmaEssentia, Protagonist Therapeutics, Sanofi-aventis, Stemline Therapeutics, Inc., Total CME. AO Advisory board for Cytognos, Blueprint Medicines, Amgen. Speakers bureau for Amgen, MSD, Alexion. Research support Cytognos, Becton/Dickinson Biosciences, 300K Solutions. All the other authors have no conflicts of interest to disclose.

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