Blastic plasmacytoid dendritic cell neoplasm: diagnostic criteria and therapeutical approaches

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Summary

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematological malignancy derived from the precursors of plamacytoid dendritic cells, with an aggressive clinical course and high frequency of cutaneous and bone marrow involvement. Neoplastic cells express CD4, CD43 (also termed SPN), CD45RA and CD56 (also termed NCAM1), as well as the plasmacytoid dendritic cell-associated antigens CD123 (also termed IL3RA), BDCA-2 (also termed CD303, CLEC4E) TCL1 and CTLA1 (also termed GZMB). The median survival is only a few months as the tumour exhibits a progressive course despite initial response to chemotherapy. The best modality of treatment remains to be defined. Generally, patients receive acute leukaemia-like induction, according to acute myeloid leukaemia (AML)-type or acute lymphoid leukaemia (ALL)-type regimens. The frequent neuromeningeal involvement indicates systematic pre-emptive intrathecal chemotherapy in addition to intensive chemotherapy. Allogeneic haematopoietic stem cell transplantation (HSCT), particularly when performed in first remission, may improve the survival. Preliminary data suggest a potential role for immunomodulatory agents and novel targeted drugs. Herein epidemiology, clinical manifestations, diagnosis and management of BPDCN will be presented. In detail, this review focuses on the therapeutic aspects of BPDCN, proposing a treatment algorithm for the management of the disease, including induction chemotherapy, allogeneic HSCT and intrathecal prophylaxis at different steps of treatment, according to compliance, biological and clinical characteristics of patients.

Keywords: blastic plasmacytoid dendritic cell neoplasm, acute leukaemia, chemotherapy, haematopoietic stem cell transplantation, intrathecal prophylaxis.

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive haematological malignancy derived from the precursors of plasmacytoid dendritic cells and characterized by co-expression of CD4 and CD56 (also termed NCAM1) without other lineage-specific markers (Chaperot *et al*, 2001; Petrella *et al*, 2002). The nomenclature used to describe this entity has evolved over the years as our understanding of the underlying biology has improved (Table I). It was initially described in 1994 as agranular $CD4^+$ natural killer cell leukaemia due to its unique agranular morphology and phenotype ($CD4^+$, $CD56^+$, $CD15^+$ and $CD3^-$) (Adachi *et al*, 1994; Brody *et al*, 1995). Based on the blastic appearance and CD56 expression, the term 'blastic NK cell lymphoma' was then used (Chan *et al*, 2001). Subsequently, the term 'agranular $CD4^+CD56^+$ haematodermic neoplasm/tumour' was coined based on the immunophenotype and the predilection for skin involvement (Petrella *et al*, 2002). The several synonyms and periodic name changes reflect the uncertainty of the cell origin. However, following the discovery and the confirmation that BPDCN derives from plasmacytoid dendritic cells (type 2 dendritic cells) (Willemze *et al*, 2002; Herling & Jones, 2007), the current nomenclature, blastic plasmacytoid dendritic cell neoplasm, was chosen to describe the entity in the 2008 World Health Organization (WHO) classification of tumours of the haematopoietic and lymphoid tissues, where it was recognized as a distinct disease and separately listed in the group of acute myeloid leukaemia (AML) and related precursor neoplasms (Facchetti *et al*, 2008) (Table I).

This review focuses on the clinical and, above all, the therapeutic aspects of BPDCN, and proposes a treatment algorithm for the management of the disease.

Epidemiology

There are no formal studies on the incidence of BPDCN in the general population. In addition, the exact prevalence of BPDCN is difficult to estimate due to the constantly changing nomenclature and lack of precise defining criteria prior to the 2008 WHO classification (Facchetti *et al*, 2008). The few available data reported that its overall incidence is extremely low, accounting from 0·44% of all haematological

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Table I. Evolution of the nomenclature used to describe 'Blastic plasmacytoid dendritic cell neoplasm'.

Nomenclature	References
$CD4^+/CD56^+$ acute monoblastic leukaemia	Tauchi *et al* (1990)
Acute agranular $CD4^+$ NK-cell leukaemia	Brody *et al* (1995)
Cutaneous agranular $CD2^-/CD4^+/CD56^+$ lymphoma	Kameoka *et al* (1998)
Primary cutaneous $CD4^+/CD56^+$ haematolymphoid neoplasm	Petrella *et al* (1999)
Agranular $CD4^+/CD56^+$ blastic NK leukaemia/lymphoma	Kimura *et al* (2001)
Blastic NK-cell lymphoma (WHO classification)	Chan *et al* (2001)
DC2 precursor acute leukaemia	Chaperot *et al* (2001)
$CD4^+/CD56^+$ acute leukaemia	Feuillard *et al* (2002)
Agranular $CD4^+/CD56^+$ haematodermic tumour	Petrella *et al* (2002)
Early plasmacytoid dendritic cell leukaemia/lymphoma	Jacob *et al* (2003)
$CD4^+/CD56^+$ haematodermic neoplasia (WHO-EORTC classification)	Willemze *et al* (2005)
DC2-related $CD4^+/CD56^+$ blastic tumour of skin	Herling and Jones (2007)
Blastic plasmacytoid dendritic cell neoplasm in: Acute myeloid leukaemia (AML) and related precursor neoplasms (WHO classification)	Facchetti *et al* (2008)

WHO, World Health Organization; EORTC, European Organization for Research and Treatment of Cancer.

malignancies (Bueno *et al*, 2004) to 0·7% of cutaneous lymphomas (Ng *et al*, 2006). However, cutaneous lymphoma registries probably underestimate the true incidence of BPDCN because a small but significant proportion of patients present without skin lesions. Furthermore the leukaemic form of disease is a rare phenomenon, representing <1% of acute leukaemia cases (Jacob *et al*, 2003).

BPDCN has been described in all races and all geographic locations. Predominantly males are affected, with a sex ratio of 2·5:1. The disease usually occurs in elderly patients, with a median age between 60 and 70 years (Feuillard *et al*, 2002; Petrella *et al*, 2005), however, it can present at any age; paediatric cases have also been reported, with a less aggressive clinical course (Garnache-Ottou *et al*, 2007; Facchetti *et al*, 2009, 2016; Jegalian *et al*, 2010).

The aetiology of BPDCN is unknown. There are no documented environmental or hereditary genetic factors predisposing to the development of disease. BPDCN can occur as an isolated disease or in the context of other haematological neoplasms. Approximately 10–20% of patients have a previous history of haematological malignancies including myelodysplastic syndrome (MDS), chronic myeloid leukaemia, chronic myelomonocytic leukaemia and AML (Feuillard *et al*, 2002; Julia *et al*, 2013; Pagano *et al*, 2013). A Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study described four patients with a prior history of MDS among a population of 43 cases (Pagano *et al*, 2013), and the French group described two cases of MDS among 23 patients (Feuillard *et al*, 2002). The Hellenic Dendritic Cell Leukaemia Study Group reported two cases of secondary BPDCN among 22 patients (Tsagarakis *et al*, 2010). The relationship between BPDCN and other myeloid malignancies is not clearly elucidated. However, the association with MDS and other myeloid neoplasms strengthens the myeloid origin of the neoplastic clone.

Clinical features

In most patients BPDCN usually presents with cutaneous lesions with or without bone marrow involvement (Feuillard *et al*, 2002; Julia *et al*, 2014). In fact, isolated skin lesions are frequently the first symptom leading patients to seek medical advice, and without therapy, they rapidly disseminate. Patients typically present with asymptomatic, solitary or multiple skin lesions that can be variable in size (from a few millimetres to 10 cm), shape and colour, and can appear as nodules, plaques or bruise-like infiltrates. The skin lesions can be associated with erythema, hyperpigmentation, purpura or ulceration (Julia *et al*, 2013). Lymphadenopathy, splenomegaly and cytopenias due to bone marrow involvement can be present at diagnosis or may occur at disease progression. When bone marrow is involved, the most common findings in the peripheral blood are thrombocytopenia (78%), anaemia (65%) and neutropenia (34%) (Pagano *et al*, 2013). Hyperleucocytosis is infrequent, but the presence of blasts in the blood is more commonly observed. Circulating malignant cells can be detected by morphological review or flow cytometric analysis of the peripheral blood. Morphologically, they appear as monomorphic, poorly differentiated, intermediate-sized blasts (Facchetti *et al*, 2008). Involvement of other sites, including liver, tonsils, soft tissues, paranasal cavities, lungs, eyes and central nervous system (CNS) have also been reported (Feuillard *et al*, 2002; Tsagarakis *et al*, 2010; Pagano *et al*, 2013; Feng *et al*, 2014; Martín-Martín *et al*, 2015). Of note, the incidence of neuromeningeal involvement is quite frequent, ranging in the major studies from 4% to 9% of patients at diagnosis and from 17% to 33% at relapse (Feuillard *et al*, 2002; Tsagarakis *et al*, 2010; Pagano *et al*, 2013; Martín-Martín *et al*, 2015).

Patients presenting with a leukaemic picture in the absence of cutaneous disease have also been described (Rauh *et al*, 2012; Wang *et al*, 2012; Pagano *et al*, 2013). The GIMEMA study described the largest number of patients affected by BPDCN with leukaemic presentation, among which 23% of cases had no cutaneous manifestations at diagnosis and only 2 patients developed skin lesions during the progression of disease (Pagano *et al*, 2013).

Immunophenotype and genetics

BPDCN usually exhibits a specific immunophenotype that must be confirmed by either immunohistochemistry or by flow cytometry, depending on the material available. The diagnosis relies on the demonstration of CD4 and CD56 positivity by tumour cells, together with markers more restricted to plasmacytoid dendritic cells [BDCA-2(also termed CD303, CLEC4E), CD123 (also termed IL3RA), TCL1 (also termed TCL1A)] and lack of expression of markers for B cells, T cells, myeloid or monocytic cells, and NK cells (Table II) (Facchetti, 2013; Facchetti *et al*, 2016). Exceptions include CD5, CD7 and CD33, which may be positive in some cases, and cytoplasmic CD3, which has been rarely reported using polyclonal antibodies (Facchetti *et al*, 2016).

The highly specific marker BDCA-2/CD303, as well as other plasmacytoid dendritic cell-associated antigens (CD2AP and above all TCL1), might be of great support to definitely establish the diagnosis and to exclude potential imitations of BPDCN (Petrella *et al*, 2004; Garnache-Ottou *et al*, 2007; Herling & Jones, 2007; Facchetti *et al*, 2008; Marafioti *et al*, 2008; Montes-Moreno *et al*, 2013). In particular, myeloid sarcoma/AML, T-cell lymphoblastic leukaemia/lymphoma (T-ALL/LBL), NK-cell lymphoma/leukaemia, and some mature T-cell lymphomas/leukaemia should be excluded through extensive immunophenotypic analysis (Table II). Despite that, in some cases the diagnosis still remains a challenge, probably because of the lack of recurrent and specific chromosomal abnormalities, its overlapping features with other entities, and its heterogeneous clinical presentation with multiple and variable tissue localizations. In particular, a clear diagnosis can be difficult to achieve when blast cells don't completely fit the typical $CD4^+CD56^+HLA\text{-}DR^{hi}CD123^+$lineage immunophenotypic profile. In fact, evidence exists regarding a broad range of atypical phenotypic profiles (Facchetti *et al*, 2003), including the absence of CD56 (Kawai, 2005; Martín-Martín *et al*, 2015) and CD4 (Montes-Moreno *et al*, 2013). In addition, atypical cases with aberrant expression of B, T or myeloid antigens have also been described (Garnache-Ottou *et al*, 2005; Cota *et al*, 2010). Garnache-Ottou *et al* (2009) proposed a diagnostic algorithm for establishing an immunophenotypic diagnosis of BPDCN. The coexpression of $CD4^+$, $CD56^{+/-}$, $CD123^+$, BDCA-2+ and/or BDAC-4+ and the absence of CD3-, CD11c-, MPO- and CD79a- were diagnostic for BPDCN. If CD123 expression is negative or when CD123 is positive but cells don't express BDCA-2 or BDCA-4, diagnosis of BPDCN should not be considered (Garnache-Ottou *et al*, 2009). Julia *et al* (2014) reported the immunohistochemical typing of 91 patients with BPDCN from the French Study Group on Cutaneous Lymphomas. They identified five of the most characteristic immunophenotypic markers, which included CD4, CD56, CD123, CD303 and TCL1. The contemporary expression of all markers was observed in only 46% of patients, but the expression of 4 markers was sufficient for reliable diagnosis (Julia *et al*, 2014). Finally, Facchetti (2013) reviewed the antigen expression on formalin-fixed, paraffin-embedded sections in a series of more than 300 published cases, suggesting that, in addition to CD4 and CD56, CD123 and TCL1 are the most reliable and useful markers to confirm or to exclude BPDCN diagnosis.

Recently, Martín-Martín *et al* (2015) described a series of 46 patients classified into three maturation-associated subgroups on immunophenotypic grounds, investigating whether the immunophenotypic features utilized for diagnosis can also correlate with the clinico-biological and prognostic characteristics of the disease. They showed that blasts from cases with an immature plasmacytoid dendritic cell phenotype exhibit an uncommon CD56- phenotype, coexisting with $CD34^+$ non-tumour cells, typically in the absence of extramedullary disease at presentation. Conversely, patients with a more mature blast cell phenotype more frequently displayed skin and extramedullary involvement and spread into secondary lymphoid tissues. The authors concluded that tumour cells from BPDCN might show a highly variable profile of maturation, which translates into a heterogeneous clinical behaviour ranging from that of acute leukaemia to peripheral mature lymphomas, which may also lead to variable diagnosis and treatment (Martín-Martín *et al*, 2015).

In conclusion, at present, although no consensus has been established with regard to a minimal phenotype to diagnose BPDCN, a confident diagnosis can be made when four antigens among CD4, CD56, CD123, TCL1 and BDCA-2/CD303 are expressed by neoplastic cells (Alayed *et al*, 2013; Boiocchi *et al*, 2013; Facchetti, 2013; Julia *et al*, 2014). According to the WHO, neoplasms which share some but not all immunophenotypic features of BPDCN may be better classified as 'acute leukaemia of ambiguous lineage' (Facchetti *et al*, 2008).

Most part of BPDCN present genetic abnormalities, even if there is no single cytogenetic change that is typical or diagnostic. A few studies have focused on BPDCN genetics, documenting a complex karyotype with deletions on chromosomes 5q21 or 5q34 (72%), 12p13 (64%), 13q13-q21 (64%), 6q23-qter (50%), 15q (43%) and 9 (28%) and sporadic genetic alterations affecting the *RB1*, *LATS2*, *CDKN1B*, *CDKN2A* and *TP53* genes (Leroux *et al*, 2002; Petrella *et al*, 2005; Facchetti *et al*, 2009). The biallelic loss of 9p21·3 was associated with a poor prognosis (Leroux *et al*, 2002). Molecular studies have also been performed; mutations in *TET2* and *TP53* were reported in 54% and 38% of cases among 13 patients analysed, respectively (Jardin *et al*, 2011). Moreover Dijkman *et al* (2007) identified overexpression of the oncogenes *HES6*, *RUNX2* and *FLT3* independently of genomic amplification. *NPM1* mutations have not been reported, while *FLT3*ITD internal tandem duplication (ITD) mutations can be present in a subset of patients (Pagano *et al*, 2013).

In addition to classical cytogenetic analysis, BPDCN has been assessed by array comparative genomic hybridization (CGH) analyses (Lucioni *et al*, 2011; Oiso *et al*, 2012;

Table II. Differential diagnosis among the main CD4 + CD56 + haematological malignancies.

	BPDCN	Extranodal (nasal-type) $CD56^+$ NK/T-cell lymphoma	Cutaneous T-cell lymphoma	$CD33^+$ AML $CD4^+/CD56^+$, undifferentiated AML or AML with myelomonocytic/monocytic differentiation or ambiguous lineage leukaemia
Age	Elderly (60–70 years)	Middle-aged	Young and middle-aged	Over 65 years
Sex predominance	Male predominance	Male predominance	Slight male predominance	Male predominance
Main localizations	BM, skin, CNS, LN, soft tissue	Nose, nasopharynx, palate, skin, soft tissue, GI tract, testis	Skin, LN, BM, blood	BM and LN (mainly), skin
Morphology	Diffuse monotonous infiltrate of medium-sized blast cells with fine chromatin, irregular nuclei and one to several small nucleoli	Polymorphic and pleomorphic lymphoid infiltrate that invades vascular walls, producing fibrinoid necrosis of vessel walls and coagulative necrosis of surrounding tissues	Epidermotropic lymphoid infiltrate of small- to intermediate-sized atypical lymphocytes with enlarged hyperchromatic, cerebriform nuclei and clear cytoplasm	Variable and pleomorphic monotonous medium-sized cells with fine chromatin
Phenotype	$CD2^{-/+}$, $sCD3^-$ $cCD3^{+/-}$, $CD4^+$, $CD56^+$, $CD43^+$,$CD45RA^+$, $TdT^{+/-}$, TIA-1^-, Granzyme B^-, $CD123^+$, BDCA-2/$CD303^+$, $TCL1^+$, $CTLA1^+$	$CD2^+$, $sCD3^-$, $cCD3^+$, $CD4^{-/+}$, $CD56^+$, TdT^-, TIA-1^+, Granzyme B^+, $perforin^+$	$CD3^+$, $CD4^+$, $CD56^{+/-}$, $CD2^+$, $CD5^+$, $CD7^+$, TIA-$1^{+/-}$, Granzyme $B^{+/-}$	$CD2^{-/+}$, $sCD3^-$, $cCD3^{+/-}$, $CD4^+$, $CD56^+$, $TdT^{+/-}$, TIA-1^-, Granzyme B^-, $CD33^+$, $MPO^{+/-}$, $CD13^+$, $CD15^+$, $CD117^+$, BDCA2/$CD303^-$, $TCL1^-$
Association with EBV	None	Strong	Strong	Extremely rare
Genetics	no specific single chromosomal aberrations, often 5q, 6q, 9, 12p, 13q, and 15q	No specific chromosomal aberrations, often del(6), inv(6)	No specific chromosomal aberrations	No specific single chromosomal aberration
T cell receptor gene	Germline	Germline	Monoclonal rearrangement	Germline
Clinical course	Aggressive with relapse	Locally destructive to aggressive	Locally destructive to aggressive	Aggressive

BPDCN, blastic plasmacytoid dendritic cell neoplasm; AML, acute myeloid leukaemia; BM, bone marrow; CNS, central nervous system; LN, lymph nodes; GI, gastro-intestinal; EBV, Epstein–Barr virus.

Stenzinger *et al*, 2014), which 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. Other frequently deleted regions include 13q13·1-q14·3 (*RB1*), 12p13·2-p13·1 (*CDKN1B*), 13q11-q12 (*LATS2*), and 7p12·2 (*IKZF1*) (Jardin *et al*, 2009; Lucioni *et al*, 2011).

More recently, Sapienza *et al* (2014) performed gene expression profiling in 27 samples of BPDCN, detecting an aberrant activation of the NF-kB pathway, concomitantly with the up-regulation of two NF-kB targets (BCL2 and IRF4).

Altogether, these molecular data demonstrate that BPDCN cells can carry multiple mutations that overlap with the genetic abnormalities of myeloid and lymphoid neoplasms, leading to the dysregulation of multiple pathways that may serve as targets for therapeutic agents.

Treatment

The clinical course of BPDCN is aggressive, with a reported median overall survival (OS) ranging from 12 to 16 months (Feuillard *et al*, 2002; Petrella *et al*, 2005). Because of its low incidence, prospective data are lacking and the few series published so far rarely exceed 15 cases (Feuillard *et al*, 2002; Dalle *et al*, 2010; Tsagarakis *et al*, 2010; Dietrich *et al*, 2011; Lucioni *et al*, 2011; Hashikawa *et al*, 2012; Pemmaraju *et al*, 2012; Pagano *et al*, 2013; Martín-Martín *et al*, 2015) (Table III). Moreover, no prognostic models are available to tailor therapy to individual cases. Consequently, no standardized therapeutic approach has been established yet and the optimal therapy remains to be defined.

Conventional chemotherapy

In patients with isolated cutaneous disease at the onset, the efficacy of skin-directed therapies, such as surgical excision, focal radiation therapy and systemic steroids, has been evaluated in several studies (Reimer *et al*, 2003; Dalle *et al*, 2010; Li *et al*, 2011; Pileri *et al*, 2012). These approaches can be initially effective and may lead to the complete resolution of cutaneous lesions, but do not appear to provide a long-term benefit. In fact, systemic relapse occurs within about 6–9 months (Suzuki *et al*, 2005; Dalle *et al*, 2010). However, the skin-directed therapeutic approach can be a reasonable palliative option for elderly patients or those who are not eligible for systemic intensive chemotherapy. Dalle *et al* (2010) compared the outcome of patients with exclusive cutaneous versus those with systemic involvement, showing no difference in terms of response and response duration. A more recent study found that prognosis is invariably severe in both presentations and systemic approaches are recommended (Rauh *et al*, 2012).

Regarding the best induction regimen, retrospective studies suggest that treatment with regimens commonly used in non-Hodgkin lymphoma yield complete remission (CR) rates of 40-–50%, but responses are short lived (Kharfan-Dabaja *et al*, 2013). Patients treated with regimens used in acute leukaemia, particularly ALL-type regimens, seem to obtain better responses (Reimer *et al*, 2003; Tsagarakis *et al*, 2010).

Feuillard *et al* (2002) reported the outcome of 23 patients treated with different chemotherapy regimens. CR was obtained in 86% of patients with a median follow-up of 15 months; however 83% of patients who obtained CR relapsed, and the median time of relapse was 9 months (range 3–18 months). The chemotherapy provided a high response rate, regardless of the type of regimen applied, but relapse was very frequent and rapid, suggesting the need for an intensive consolidation treatment (Feuillard *et al*, 2002). More recently, the Hellenic Group described 22 patients, of whom 19 were treated with different regimens: 47·4% received ALL-type therapy, 31·6% AML-type therapy and 21% lymphoma-type therapy (Tsagarakis *et al*, 2010). The median follow-up time was 15 months (range 6·6–23·4 months). A CR was reached in 78·9% of cases, 40% of who relapsed with an OS of 43·2% at 2 years. A relative superiority of ALL-type regimens was reported in terms of response and response duration (Tsagarakis *et al*, 2010). Moreover, Pemmaraju *et al* (2012) reported a CR of 90% in 10 patients treated with hyper-CVAD (hyper-fractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone/methotrexate, cytarabine), with a median duration of response of 19 months (range 4–39) and an OS of 29 months (range 1–44).

The largest study investigating treatment was a retrospective analysis of 43 patients diagnosed with BPDCN after a centralized histological revision at 28 Italian divisions (Pagano *et al*, 2013). The median OS was 8·7 months with estimated survival rates of 28% and 7% at 12 and 24 months, respectively. Forty-one patients received an induction therapy with an acute leukaemia-like regimen, consisting of AML-type therapy in 26 cases (60%) and ALL/lymphoma-type therapy in 15 (35%). Seventeen patients (41%) achieved a CR, 7 after AML-type regimens and 10 after ALL/lymphoma-type regimens, with a significant advantage for the ALL-type approach. However, six patients (35%) of the patients who achieved CR subsequently relapsed, at a median time of 9·1 months (range 5·8–19·8) after diagnosis (Pagano *et al*, 2013).

Finally, Martín-Martín *et al* (2015) recently described 25 patients aggressively-treated with intensive chemotherapy [ALL-type therapy (7/25), AML-type therapy (9/25) and lymphoma-type therapy (9/25)] and showed that cases treated with ALL-type protocols had a better outcome than the other patients, with lower rates of relapse and overall mortality.

The major studies reporting induction therapy in BPDCN that have included at least four patients are summarized in Table IV. No conclusive data concerning the best induction regimen can be drawn, even if ALL-type therapies appear more effective in many reports. It is also interesting to note that L-asparaginase and methotrexate, two drugs commonly used in ALL treatment, were reported to be active in some

Table III. Results of the main published series according to the induction chemotherapy utilized (selected studies with at least 4 cases): the complete remission rate and the median overall survival were higher in patients treated with ALL/lymphoma-type therapy.

	ALL/lymphoma-type therapy					AML-type therapy					Radiotherapy					Palliative therapy/no treatment		
Reference	N	CR *n* (%)	Relapse *n* (%)	Median relapse, months (range)	Median OS, months (range)	*N*	CR *n* (%)	Relapse *n* (%)	Median relapse, months (range)	Median OS, months (range)	N	CR *n* (%)	Relapse *n* (%)	Median relapse, months (range)	Median OS, months (range)	N	CR *n* (%)	Median OS, months, (range)
Feuillard *et al* (2002)	15	12 (80)	7 (58)	6 (4–12)	12 (4–98)	6	6 (100)	6 (100)	10·5 (3–18)	14·5 (5–37)	0	–	–			2	–	3 (3–3)
Dalle *et al* (2010)	26	14 (54)	n.r.	6 (2–42)	12 (3–42)	12	5 (41)	n.r.	12 (4–22)	19 (3–77)	5	4 (80)	n.r.	5·5 (2–9)	19 (8–36)	3	0 (0)	2 (1–12)
Tsagarakis *et al* (2010)	13	12 (92)	5 (42)	n.r.	n.r.	6	3 (50)	1 (33)	n.r.	n.r.	0	–	–	–	–	3	0 (0)	n.r.
Dietrich *et al* (2011)	4	4 (100)	3 (75)	11 (5–18)	21 (6–82)	2	1 (50)	1 (100)	7 (n.a.)	19 (13–25)	0	–	–	–	–	0	–	–
Lucioni *et al* (2011)	13	9 (69)	4 (44)	20·5 (11–36)	13 (8–72)	0	–	–	–	–	3	2 (67)	1 (50)	8 (n.a.)	14 (13–30)	3	0	3 (1–6)
Pemmaraju *et al* (2012)	12	10 (83)	n.r.	19 (4–39)	29 (1–44)	0	–	–	–	–	0	–	–	–	–	1	0 (0)	n.r.
Hashikawa *et al* (2012)	13	11 (85)	n.r.	n.r.	12 (4–21)	4	0 (0)	–	n.a.	5·5 (1–18)	4	3 (75)	n.r.	n.r.	6·5 (3–14)	0	–	–
Pagano *et al* (2013)	15	10 (67)	6 (60)	n.r.	12·3 (1–32·9)	26	7 (27)	0	n.r.	7·1 (0·2–9·5)	0	–	–	–	–	2	0 (0)	n.r.
Martín-Martín *et al* (2015)	16	14 (87·5)	10 (71)	n.r.	ALL-type: not reached; Lymphoma-type: 10 (4–16)	9	9 (100)	7 (78)	n.r.	11 (8–14)	0	–	–	–	–	0	–	–

OS, overall survival; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CR, complete remission; tp, therapy; n.r., not reported; n.a., not applicable.

Table IV. Results of the main published studies reporting high-dose chemotherapy and haematopoietic stem cell transplantation in BPDCN (selected studies with at least four cases). The highest percentage of patients alive in CR was observed after allogeneic HSCT in first CR.

References	Median age, years (range)	Transplantation procedure	Patients (*n*)	Outcome (alive in CR) *n* (%)	Median OS, months (range)
Reimer *et al* (2003)	28·5 (23–51)	Auto-HSCT in CR1	3	1 (25)	16·5 (n.r.)
		Auto-HSCT > CR1 or no CR	1		
	28 (6–35)	Allo-HSCT in CR1	4*	3 (43)	38·5 (n.r.)
		Allo-HSCT > CR1	3*		
Suzuki *et al* (2005)	35·5 (14–61)	Auto-HSCT in CR1	2	n.r.	13·5 (6–37)
		Auto-HSCT > CR1 or no CR	4		
Dalle *et al* (2010)	25	Auto-HSCT > CR1 or no CR	1	1 (100)	21 (12–77)
	38 (25–67)	Allo-HSCT in CR1	4*	3 (75)	
		Allo-HSCT > CR1	6*	2 (33)	
Dietrich *et al* (2011)	66 (56–70)	Allo-HSCT in CR1	1†	1 (100)	19 (n.r.)
		Allo-HSCT > CR1	3†	1 (33)	25 (23–82)
Tsagarakis *et al* (2010)	n.r.	Allo-HSCT in CR1	5‡	3 (60)	15 (6·6–23·4)
Pagano *et al* (2013)	n.r.	Allo-HSCT in CR1	3*	2 (67)	22·7 (12–32·9)
		Allo-HSCT > CR1 or no CR	3*	0	–
Roos-Weil *et al* (2013)	41 (10–70)	Allo-HSCT in CR1	19§	16 (47)	28 (4–77)
		Allo-HSCT > CR1	15§		
Unteregger *et al* (2013)	59 (38–64)	Allo-HSCT in CR1	3†	3 (100)	21 (18–30)
		Allo-HSCT > CR1 or no CR	2†	1 (50)	29·5 (20–39)
Heinicke *et al* (2015)	62 (22–66)	Allo-HSCT in CR1	2 (1*, 1†)	2 (100)	26·5 (18–35)
		Allo-HSCT > CR1	1 (1†)	1 (100)	41 (n.r.)
Aoki *et al* (2015)	57 (19–67)	Auto-HSCT in CR1	11	n.r.	53·5 (n.r)
	58 (17–64)	Allo-HSCT in CR1	10 (5*, 5†)		
		Allo-HSCT > CR1 or no CR	4 (3*, 1†)		

Auto-HSCT, autologous haematopoietic stem cell transplantation; allo-HSCT, allogeneic haematopoietic stem cell transplantation; CR, complete remission; CR1, first complete remission; OS, overall survival; n.r., not reported.
*Myeloablative conditioning (MAC).
†Reduced-intensity conditioning (RIC).
‡Type of conditioning not reported.
§Overall 25 MAC and 9 RIC.

experiences (Gilis *et al*, 2012; Gruson *et al*, 2013). Recently, preclinical studies by the French national network on BPDCN have shown that BPDCN cells are sensitive *in vitro* to idarubicin: culture with a combination of idarubicin, methotrexate, L-asparaginase and dexamethasone resulted in a synergistic effect because the viability of BPDCN primary cells decreased from $47 \pm 7{\cdot}5\%$ to $6{\cdot}1 \pm 1{\cdot}4\%$ ($n = 5$) (Angelot-Delettre *et al*, 2015). The authors studied nine patients receiving idarubicin in first-line therapy, obtaining a CR in seven cases and only one relapse after 10 months of response to therapy. However, the six patients in continuous CR without any relapse have been transplanted.

Conventional chemotherapy alone does not appear to be sufficient to ensure durable long-term remissions, with a relapse rate of about 60% of patients achieving a CR. The potential role of maintenance therapy deserves investigation in BPDCN.

CNS prophylaxis

As previously reported, CNS involvement has been observed both at presentation (Feng *et al*, 2014; Saeed *et al*, 2014) and, more often, during disease recurrence (Feuillard *et al*, 2002; Pagano *et al*, 2013). The outcome of three of the six patients who relapsed after achieving CR with a CNS involvement was reported by Pagano *et al* (2013); none of these patients had received intrathecal prophylaxis. From these observations, CNS prophylaxis, with intrathecal drug infusion of cytarabine or other drugs able to pass the blood-brain barrier, is strongly suggested in all patients, and must be routinely incorporated into induction treatment.

Haematopoietic stem cell transplantation (HSCT)

While the majority of adult patients with BPDCN will achieve a complete or partial response to induction therapy, most will relapse within two years, irrespective of the type of chemotherapy received (Table III). There are no published randomized controlled trials evaluating the role of autologous or allogeneic HSCT in patients with BPDCN, and most available information is derived from retrospective case reports and single-institution experiences on a limited number of patients, which, as such, suffer from several limitations. The little evidence provided by previous studies

suggests that the clinical course and the response to therapy differ between children and adults (Feuillard *et al*, 2002; Dalle *et al*, 2010; Jegalian *et al*, 2010; Hashikawa *et al*, 2012). BPDCN occurring in childhood is clinically less aggressive, and children (<18 years) appear to benefit from treatment similar to that given for high-risk ALL, reserving allogeneic HSCT for patients who relapse and achieve a second CR (Jegalian *et al*, 2010). On the contrary, as the disease is more aggressive in adults, there is emerging evidence suggesting that adults may benefit from allogeneic HSCT in first CR, achieving long-term survival (Dietrich *et al*, 2011; Pagano *et al*, 2013; Roos-Weil *et al*, 2013). Adults with comorbidities may be considered for reduced intensity conditioning. The role of autologous HSCT is still debated.

The response rates and survival of patients undergoing autologous and allogeneic HSCT in the main studies are reported in Table IV.

Autologous HSCT

Few cases of autologous HSCT are available in literature (Table IV). Reimer *et al* (2003) described four patients receiving autologous HSCT; only one of them obtained a CR, with a median survival of 13 months. Suzuki *et al* (2005) reported the experience of autologous HSCT performed in six patients: three were alive and in CR after 11, 22 and 37 months, respectively. Other single cases of successful treatment with autologous HSCT have been reported (Dalle *et al*, 2010; Goren Sahin *et al*, 2013).

Recently, Aoki *et al* (2015) demonstrated, for the first time, the clinical advantage of performing autologous HSCT in first CR on a reasonably large number of BPDCN. The authors reported the outcome of 11 patients (median age 57 years, range 19–67) from registry data of the Japan Society for Haematopoietic Cell Transplantation: all of them underwent autologous HSCT in first CR and, after a median follow-up of 53·5 months, they achieved an advantage both on OS (4 year-OS 82%) and on progression free survival (4-year PFS 73%), regardless of the type of induction regimen. This is the largest study to analyse the role of autologous HSCT in BPDCN, suggesting that high-dose chemotherapy may play an important role in curing BPDCN independent of a graft-versus-tumour effect of allogeneic HSCT and that the disease status at autologous HSCT is crucial for a better outcome (Aoki *et al*, 2015).

The small number of published studies precludes the identification of a particular subset of BPDCN likely to benefit from high-dose therapy and autologous HSCT. It appears, however, that patients with active and chemorefractory disease are not likely to achieve durable remissions after autologous HSCT (Reimer *et al*, 2003; Aoki *et al*, 2015). These cases should ideally be considered for enrolment in clinical trials, while autologous HSCT might be offered to patients with chemosensitive disease, preferably early in the disease course, and to older patients in good clinical condition.

Finally, considering the great heterogeneity of conditioning regimens employed in autologous HSCT, the limited number of treated patients and the variations in survival reported in the few published studies, it is difficult to recommend a specific high-dose regimen before autologous transplantation. However, bearing in mind the high rate of CNS involvement both at diagnosis and above all at relapse, thiotepa-based conditioning regimens should be preferred to standard lymphoma regimens, given the appreciable blood-brain barrier penetration of thiotepa and its active metabolite tepa, also used in the treatment of high-grade lymphoid malignancies (Heideman *et al*, 1989; Ferreri *et al*, 2008).

Allogeneic HSCT

Data regarding the outcomes following allogeneic HSCT come from retrospective analyses of small series of patients and single case reports showing that myeloablative treatment with allogeneic HSCT during the first remission resulted in the chance of a significant improvement of survival, especially in young patients (Feuillard *et al*, 2002; Reimer *et al*, 2003; Tsagarakis *et al*, 2010) (Table IV). Reimer *et al* (2003) described four patients treated with allogeneic HSCT in first CR, three of who remained in CR at the time of reporting. Three more patients received allogeneic HSCT in second or subsequent remission and all of them died from disease recurrence or toxicity (Reimer *et al*, 2003).

In the French analysis (Dalle *et al*, 2010), 10 of the 47 patients with BPDCN were transplanted during the management of the disease (nine allogeneic transplants, one autologous transplant, median age 38 years); the transplanted patients had a significantly longer survival (31·3 months) than that of the non-transplanted patients (12 months) (Dalle *et al*, 2010). Dietrich *et al* (2011) demonstrated the feasibility of allogeneic HSCT in older patients with the use of a reduced intensity conditioning regimen. They described four patients (median age 67 years) who underwent allogeneic HSCT, of which two were allografted in remission and were alive and disease-free at 57 and 16 months post-transplant. Interestingly, one of the patients in CR suffered from extensive chronic graft-versus-host-disease (GVHD), which suggests a clinically significant graft-versus-leukaemia (GVL) effect operating in BPDCN (Dietrich *et al*, 2011).

The European Group for Blood and Marrow Transplantation have performed the largest retrospective study, analysing 34 patients with a median age of 41 years, receiving allogeneic HSCT from sibling ($n = 11$) or unrelated donors ($n = 23$). Myeloablative conditioning (MAC) was used in 25 (74%) patients. Nineteen patients (56%) were transplanted in first CR. The 3-year cumulative incidence of relapse, disease-free survival (DFS) and OS was 32%, 33% and 41%, respectively (Roos-Weil *et al*, 2013). Univariate analysis indicated that receiving a transplant in first CR was associated with a significantly favourable outcome, whereas age, donor source and presence of chronic GVHD had no impact on

survival. Noteworthy, analysing only the patients who underwent MAC in first CR, produced a three-year DFS of 45% and an OS of 60%. No relapses were observed after 27 months post-HSCT, suggesting that high-dose therapy followed by allogeneic HSCT can provide durable disease control even in elderly patients with BPDCN. It remains to be shown if the efficacy of allogeneic HSCT can be attributed to an eventual graft-versus-leukaemia effect or if is just a matter of high-dose intensity conferred with MAC regimens (Roos-Weil *et al*, 2013). In this study, having chronic GVHD was not associated with improved disease control. However, the reduced-intensity conditioning (RIC) group comprised only nine patients, and failure in this group of patients was mainly due to non-relapse mortality rather than relapse. Therefore, the contribution of the GVL effect and the role of RIC allogeneic HSCT cannot be defined based on this study (Roos-Weil *et al*, 2013).

Interestingly, two groups have recently presented strong evidence for the existence of a potent GVL effect in BPDCN (Kaloyannidis *et al*, 2010; Unteregger *et al*, 2013). Kaloyannidis *et al* (2010) reported a BPDCN patient whose relapse, 26 months after allogeneic HSCT while on prolonged immunosuppression, was successfully treated with donor-lymphocyte infusions combined with injections of interleukin-2 and interferon alpha (Kaloyannidis *et al*, 2010). Unteregger *et al* (2013) treated five patients with allogeneic HSCT during the first or subsequent remission. Two patients received RIC, 1 MAC and 2 umbilical cord blood (UCB) transplantations. No GVHD was observed in patients who received UCB HSCT, but both of these patients developed post-transplantation lymphoproliferative disease. Four patients were in CR at the time of the report, with PFS and OS rates of 17 and 21 months, respectively. One experienced relapse; in this patient, a strong GVL effect was induced by four escalating doses of donor lymphocyte infusions leading to a second CR (Unteregger *et al*, 2013). Thus, it is likely that this GVL effect may substantially contribute to the success of allogeneic HSCT in BPDCN patients. Regarding the use of cord blood stem cells, Ramanathan *et al* (2013) described the case of BPDCN onset in a young woman as a leukaemia who successfully underwent UCB HSCT in first CR. The authors demonstrated for the first time that UCB HSCT could be a feasible and effective therapeutic strategy for this rare and aggressive leukaemia. The advantages of using UCB as source of stem cells include, among others, the increased ability to find a donor and the reduced incidence of life threatening grade 3 or 4 acute GVHD (Ramanathan *et al*, 2013).

Finally, Heinicke *et al* (2015) reported three patients that were treated with acute leukaemia-type induction therapy followed by allogeneic HSCT (one after standard MAC and two after RIC) who achieved sustained remissions with a follow-up of 8, 35 and 41 months, respectively, whereas median survival in the non-allogeneic HSCT group was only 9·5 months and only one patient survived beyond 1 year. Lokare *et al* (2014) reported a patient treated with alemtuzumab-based T cell-deplete conditioned allogeneic transplant, who is currently alive and in remission 4 years post-transplant.

The encouraging results reported above suggest that allogeneic HSCT may result in prolonged remissions and represents the best therapeutic choice, especially in younger patients achieving a CR, who comprise the minority of cases. RIC regimens should be considered for patients in CR who are not fit to undergo myeloablative transplantation due to advanced age or medical comorbidities.

Notably, interpreting the beneficial role of allogeneic HSCT in this aggressive neoplasm, the possibility of inherent biases must be taken in account. First of all, allogeneic transplantation may appear superior just by virtue of patient selection, as the efficacy of this procedure has been always reported in younger patients in CR, who represent a better population from a biological point of view (selection bias in relation to age). In addition, the small number of published cases may suggest the existence of a reporting bias.

Ultimately, collaborative prospective clinical trials are needed to thoroughly define the role of allogeneic HSCT in BPDCN.

Palliative therapy

Few data are available for the management of older patients or relapsed patients unfit for HSCT. Hatano *et al* (2007) described a 72-year-old patient treated with low-dose etoposide oral therapy, obtaining a long-term remission after isolated cutaneous relapse. A single report of Pralatrexate in relapsed BDPCN with skin lesions suggests a possible role for this agent. Pralatrexate shows greater antitumour effects, with particular activity in methotrexate-resistant T-cell lymphomas and in cutaneous lymphomas. The authors described a durable response in an elderly patient with prevalent skin disease resistant to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) treatment. This encouraging experience should be confirmed with further studies (Leitenberger *et al*, 2008). It is conceivable that less intensive regimens and monochemotherapy may be used in relapsed elderly patients that are not eligible for HSCT.

On the contrary, for those elderly patients with a low performance status or characterized by the presence of relevant co-morbidities (i.e., cardiopathy, chronic obstructive pulmonary disease) the best supportive care is the only option that must be considered.

Future perspectives and new targeted drugs

No targeted agents are currently approved for patients with BPDCN, even if the results of early clinical studies have revealed novel targets and potentially effective agents.

Agliano *et al* (2011) developed a xenograft mouse model of human BPDCN, on which the effect of lenalidomide was

tested. The drug showed a relevant cytotoxic and proapoptotic activity on the murine model, which was also supported by molecular analysis of cytokine levels and enzymatic activity; however these data have not been confirmed clinically (Agliano *et al*, 2011).

Another promising potential therapeutic option comes from a recent analysis of gene expression profile which discovered aberrant activation of the NF-kB pathway, indicating it as a suitable therapeutic target (Sapienza *et al*, 2014). Moreover, the authors showed that the BPDCN cell line, CAL-1, was highly sensitive to bortezomib treatment both in terms of proliferation inhibition and cell death induction (Sapienza *et al*, 2014).

The recently discovery of recurrent mutations of genes involved in DNA methylation, mainly *TET2* and *IDH1/2* (Alayed *et al*, 2013; Menezes *et al*, 2014; Rakheja *et al*, 2015) provide a strong rationale for the use of epigenetic therapies for BPDCN treatment. A clear and sustained activity on skin lesions and systemic manifestation of BPDCN has been recently reported in two elderly patients, who underwent frontline therapy with 5-azacytidine and achieved resolution of their skin lesions and stabilization of their haematological parameters (Laribi *et al*, 2014).

In addition, Pagano *et al* (2013) described three cases of BDPCN with *FLT3*-ITD mutations, suggesting a potential role of FMS-like tyrosine kinase-3 inhibitors.

Among the new drugs, the most promising is SL-401, a recombinant human interleukin 3α (IL3A) protein conjugated with truncated diphtheria α-toxin, a potent inhibitor of protein synthesis (Frankel *et al*, 2000, 2014; FitzGerald, 2014; Angelot-Delettre *et al*, 2015). The IL3 receptor (IL3R) is a heterodimer combining an α chain (CD123) and a β chain (CD131); CD123 is highly expressed in BPDCN. The binding of SL-401 with IL3R causes the internalization and, consequently, the translocation of the diphtheria toxin into the cytosol that binds to ADP-ribosylated elongation factor 2, leading to inactivation of protein synthesis and cell death. The cytotoxicity of SL-401 was assessed in a preclinical study in patient-derived BPDCN cell lines (CAL-1 and GEN2·2). This compound exhibited a strong cytotoxicity in a dose dependent and more efficient way than other tested chemotherapeutic drugs. Mice inoculated with a BPDCN cell line and treated with a single cycle of SL-401 survived significantly longer than untreated controls (Angelot-Delettre *et al*, 2015). Frankel *et al* (2014) reported data from a phase 1/2 study in which 11 patients (7 relapsed and 4 untreated) with BPDCN received a single daily course of SL-401 at 12·5 μg/kg for 5 d. Seven of the 9 BPDCN patients evaluable for response had objective responses (78%, 5 CR and 2 PR). The median duration of response was 5 months. Grade 3 or 4 toxicities observed were thrombocytopenia, neutropenia, transaminase elevations, hypoalbuminaemia and hyponatraemia. Fever, chills and nausea were usually experienced within the first several hours after infusion, mitigated by premedication. All adverse events were brief and resolved completely and no treatment-related deaths were observed (Frankel *et al*, 2014). Recently, the lead-in stage results of a pivotal trial on the use of SL-401 in 9 patients with relapsed/refractory BPDCN have been published (Sweet *et al*, 2015). Five (71%) of 7 evaluable BPDCN patients had major objective responses, including CR with normalization to ≤5% blasts in the bone marrow involvement in 4 patients. The resolution of extensive symptomatic skin lesions, lymphadenopathy and soft tissue disease has also been noted, often within days of starting treatment with an acceptable safety profile (Sweet *et al*, 2015).

These encouraging results suggest that target therapy has the potential for improving patient outcomes. SL-401 could be used to consolidate the effects of first-line chemotherapy and/or to reduce minimal residual disease before allogeneic HSCT. An on-going prospective study is expected to confirm these results (NCT02113982).

Conclusions

BPDCN is a rare disease, with a dismal prognosis, behaving like acute leukaemia with high-risk features, and arising from precursors of plasmacytoid dendritic cells. Accurate diagnosis, which requires expert physicians, both clinicians and histopathologists, is essential in order to provide prompt treatment, especially considering that the clinical presentation is often indolent. BPDCN may be suspected from a set of converging features from the clinical presentation to histological findings, but overlap with other haematological neoplasms is considerable. The final diagnosis relies on a compatible immunophenotype, which must be confirmed by accurate immunohistochemical and cytofluorimetric analysis with extended panels. The tumour cells typically express CD4 and CD56, combined with the expression of one or more plasmacytoid dendritic cell specific antigens (CD123, BDCA-2/CD303, TCL1, CTLA1 [also termed GZMB]). There are few data regarding the best treatment, which remains to be defined. Moreover, clinical practise generally varies based on institutional preference. Similarly to Riaz *et al* (2014), we suggest a tailored therapeutic approach according to the age and the clinical condition of the patients (Fig 1). While patients aged >75 years or >65 with medical comorbidities can be treated with low dose monochemotherapy in order to resolve the disease, for adults <65 years and/or without comorbidities with newly diagnosed BPDCN, we suggest induction chemotherapy with a regimen similar to that used for ALL treatment, including intrathecal prophylaxis. On the other hand, due to the relatively short-lived remissions after frontline therapies and the myeloid lineage derivation of blastic dendritic cells, accordingly to our previous experience (Pagano *et al*, 2013), we suggest the addition of more myeloid-focussed strategies, such as consolidation with high or intermediate doses of cytarabine, which represents the backbone of therapy for AML (Löwenberg *et al*, 2011; Büchner

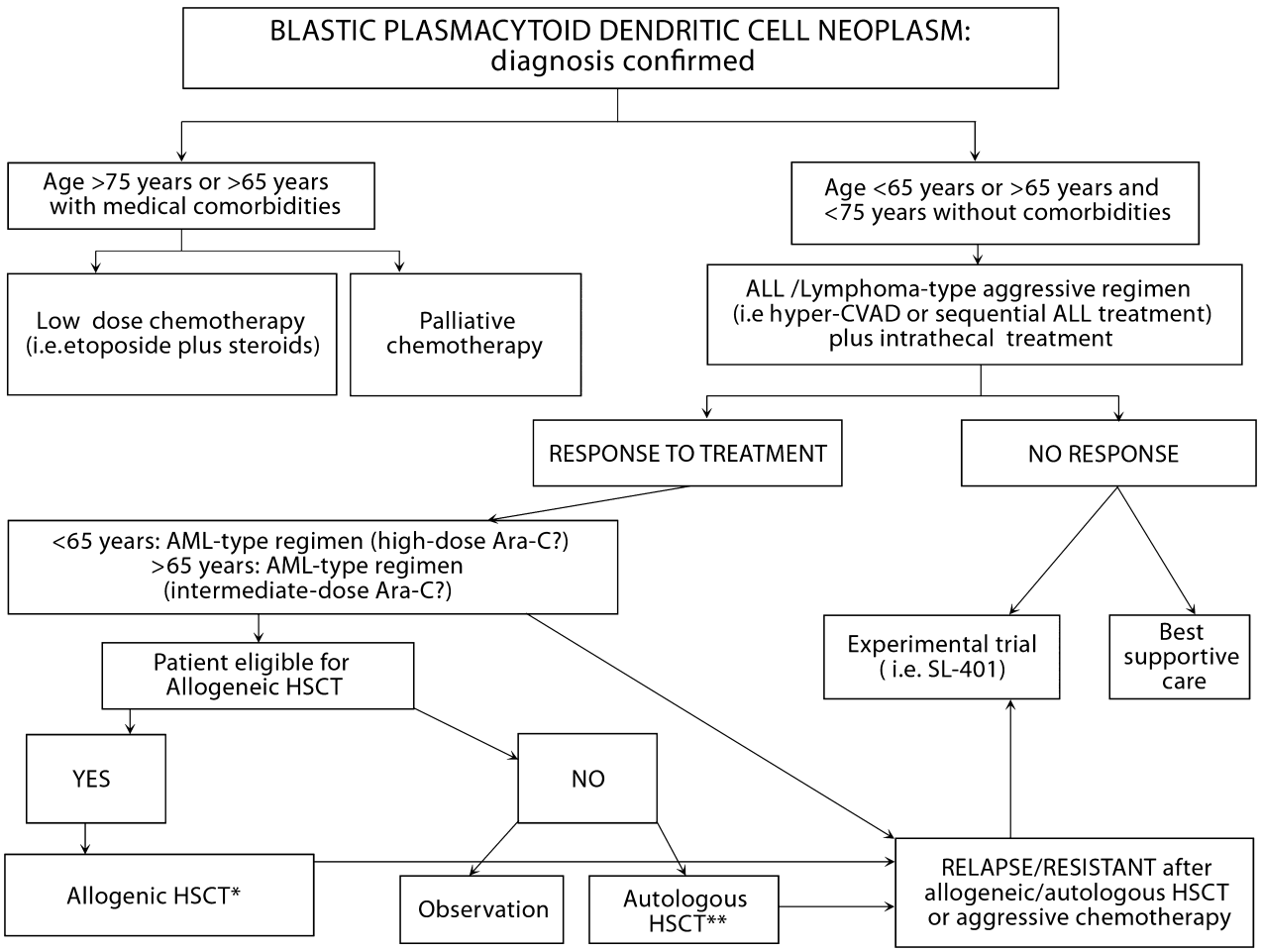

Fig 1. Algorithm to guide the therapeutic strategy in patients with BPDCN.*Adults not eligible for myeloablative allogeneic HSCT may be considered for reduced-intensity conditioning regimens. **For autologous HSCT conditioning, high-dose regimens including drugs with an appreciable blood-brain barrier penetration like thiotepa should be preferred, considering the high rate of CNS involvement. AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; Ara-C, cytarabine; HSCT, haematopoietic stem cell transplantation; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, adriamycin, and dexamethasone/methotrexate and cytarabine.

et al, 2012) and could be useful for reducing minimal residual disease, even if no data exist about this therapeutic possibility in BPDCN. Given that effective second-line therapies remain elusive, for adults who achieve a CR, we recommend allogeneic HSCT in first remission; adults in CR who are not candidates for myeloablative HSCT may be considered for RIC. Autologous HSCT may be reserved for patients who are not eligible for allogeneic procedures or if a suitable donor is not available, as 'consolidation' therapy, early in the disease course. A valid therapeutic approach can be to offer a patient enrolment into a well-designed, scientifically valid clinical trial (Fig 1).

Future new insights for such a rare and severe disease can only derive from cooperative, eventually prospective, studies. For elderly or unfit patients, considering the high probability of early relapse even after a successful induction, the role of a maintenance treatment needs to be explored. Preclinical studies support the efficacy of lenalidomide, a drug successfully used as maintenance in other diseases. From other preclinical studies a possible role for other agents active in diseases with aberrant NF-KB activation, as well as epigenetic treatments could be explored. At the present time, the only really promising new agent has been elegantly created, conjugating IL3 to diphtheria toxin; very encouraging results have been obtained with this drug in pre-treated patients, a group with very bad prognosis in this disease. Special and cooperative efforts should be made for continuing the evaluation of this drug earlier in the course of the disease or in combination with other agents.

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Author contributions

All the authors (LP, CGV, SG and AP) have contributed to the concept, literature review, writing and final approval of the manuscript.

Conflict of interest

The authors declare no competing financial interests.

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