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Review

Diagnostic and Therapeutic Advances in Blastic Plasmacytoid Dendritic Cell Neoplasm: A Focus on Hematopoietic Cell Transplantation

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A B S T R A C T

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an exceedingly rare disorder categorized under acute myeloid leukemia by the World Health Organization. Phenotypically, malignant cells coexpress $CD4^+$ and $CD56^+$ without coexpressing common lymphoid or myeloid lineage markers. BPDCN frequently expresses CD123, TCL1, BDCA-2, and CD2AP. Restriction of CD2AP expression to plasmacytoid dendritic cells makes it a useful tool to help confirm diagnosis. Clonal complex chromosome aberrations are described in two-thirds of cases. Eighty percent of BPDCN cases present with nonspecific dermatological manifestations, prompting inclusion in the differential diagnosis of atypical skin rashes refractory to standard treatment. Prognosis is poor, with a median survival of less than 18 months. No prospective randomized data exist to define the most optimal frontline chemotherapy. Current practice considers acute myeloid leukemia-like or acute lymphoblastic leukemia–like regimens acceptable for induction treatment. Unfortunately, responses are short-lived, with second remissions difficult to achieve, underscoring the need to consider hematopoietic cell transplantation early in the disease course. Allografting, especially if offered in first remission, can result in long-term remissions. Preclinical data suggest a potential role for immunomodulatory agents in BPCDN. However, further research efforts are needed to better understand BPDCN biology and to establish evidence-based treatment algorithms that might ultimately improve overall prognosis of this disease.

INTRODUCTION

Blastic plasmacytoid dendritic cell neoplasm (BPDCN), previously known as blastic natural killer (NK) cell lymphoma or $CD4^+/CD56^+$ hematodermic neoplasm, is an exceedingly rare hematological disorder currently categorized under acute myeloid leukemia (AML) and related precursor neoplasms in the 2008 World Health Organization classification [1-4]. Limited amounts of literature are available on BPDCN for disease biology and treatment options. There is no established standard of care for BPDCN, and the prognosis remains generally poor with a median survival of typically less than 18 months using conventional chemotherapy regimens [5,6]. Hematopoietic cell transplantation (HCT) appears to be an attractive treatment option for patients with BPDCN, although experience is mostly anecdotal, supported by small case series.

Here, we provide a comprehensive review of BPDCN. We summarize the published medical literature regarding disease biology and treatment outcomes after conventional chemotherapy and HCT, autologous or allogeneic. We also present suggested treatment strategies and explore future therapeutic options.

LITERATURE SEARCH

A comprehensive literature search was performed using PubMed (1966 to November 30, 2012), with the following search strategy: ((“Dendritic Cells”[Mesh] AND “Antigen-Presenting Cells”[Mesh]) AND “Neoplasms”[Mesh]) AND “Leukemia”[Mesh]. We identified 677 publications (not relevant to BPDCN = 437, relevant to BPDCN = 240).

Clinical, Morphological, Biological, and Genetic Characteristics

BPCDN represents 0.27% of cases presenting as non-Hodgkin lymphoma and 0.76% of cases presenting as AML in the Western hemisphere [7]. A Japanese study reported a 6.3% incidence among NK cell lineage neoplasms [8]. Median age at presentation was 60 to 70 years with a male predominance (3:1) [9]. BPDCN has also been described in children and younger adults, who appear to have a less aggressive clinical course [10]. The disease has a proclivity to involve the skin, bone marrow, and lymph nodes [2,11]. Organomegaly is also frequently described [1]. More than 80% of cases present with skin lesions without specific morphological features or pattern of distribution and are often asymptomatic or might be associated with pain and pruritus [2,11].

Typically, the malignant cell in BPDCN has abundant cytoplasm with a medium or low nucleus-to-cytoplasmic ratio and displays faint basophilia without granulation. However, microvacuoles are commonly seen, most likely made of glycogen, arranged in a way to adopt a “pearl

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necklace" aspect beneath the nuclear membrane and characteristic pseudopod-like cytoplasmic expansions [2]. Malignant cells of BPDCN generally coexpress $CD4^+$ and $CD56^+$ without coexpressing common lymphoid or myeloid lineage markers (Figure 1A, B, C) [1,10,12]. Garnache-Ottou et al. demonstrated, however, that some cases of BPDCN express myeloid markers (CD33), suggesting that CD33 expression on $CD4^+CD56^+$ cells should not exclude such diagnoses [12]. Differential diagnosis of $CD4^+CD56^+$ malignancy includes aggressive NK cell lymphoma/leukemia, nasal and nasal-type NK cell lymphoma, and AML (especially cases with aberrant expression of CD4 and/or CD56 and cutaneous involvement) [13]. Several cases of BPDCN showed coexpression of CD2, CD7, CD33, and/or CD117 [9,12]. Identified key markers include CD123, the interleukin-3 receptor α-chain, T cell leukemia/lymphoma 1 (TCL1), blood dendritic cell antigen-2 (CD303/BDCA-2), and CD2-associated protein (CD2AP) [1,3,4,10]. CD2AP is an 80-kDa molecule identified through its binding to the terminal 20 amino acids in the cytoplasmic domain of the T cell–associated molecule CD2 [14]. CD2AP appears to be restricted to plasmacytoid dendritic cells, potentially making it a useful tool to confirm the diagnosis of BPDCN [15].

Clonal, generally complex, chromosome aberrations have been described in 66% of cases [16]. Leroux et al. defined 6 major recurrent chromosomal targets, 5q, 12p, 13q, 6q, 15q, and monosomy 9, implicated in 72% (5q), 64% (12p and 13q), 50% (6q), 43% (15q), and 28% (monosomy 9) of cases [16]. Lucioni et al. demonstrated that complete or partial chromosomal losses are more frequent than gains, with common deleted regions including 9p21.3 (*CDKN2A/CDKN2B*), 13q13.1-q14.3 (*RB1*), 12p13.2-p13.1 (*CDKN1B*), 13q11-q12 (*LATS2*), and 7p12.2 (*IKZF1*) [17]. Worse outcomes were apparently described in the presence of biallelic loss of locus 9p21.3 [17].

Conventional Therapy

Because of the rarity of BPDCN, no prospective data are available to define the most optimal frontline therapy. Limited cutaneous disease at presentation, without obvious nodal, bone marrow, and/or peripheral blood involvement, is not uncommon. However, even in such cases, local therapies (eg, surgical excision or involved field radiation therapy) are ineffective, with systemic relapse anticipated in almost all cases, typically within 6 months [18].

Frontline treatment with regimens commonly used in non-Hodgkin lymphoma (eg, cyclophosphamide, doxorubicin, vincristine, prednisone [CHOP]; CHOP-like regimens; or ifosfamide/etoposide-based regimens) yield complete remission (CR) rates of 40% to 50%, but responses are short-lived [2,13,18]. Recent literature, albeit limited by small sample size, described more intense regimens, such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine), offered as frontline therapy for BPDCN with more encouraging responses [19]. Pemmaraju et al. reported a CR rate of 90% in 10 patients, with a median age of 62 years (range, 20 to 86), treated with hyper-CVAD. However, responses were relatively short-lived at a median of 20 months (range, 4 to 39), and median overall survival (OS) was 29 months (range, 1 to 44) [19].

Dietrich et al. reported a CR rate of 83% in 6 patients treated with daunorubicin plus cytarabine followed by high-dose cytarabine (AML-like, n = 3) or an acute

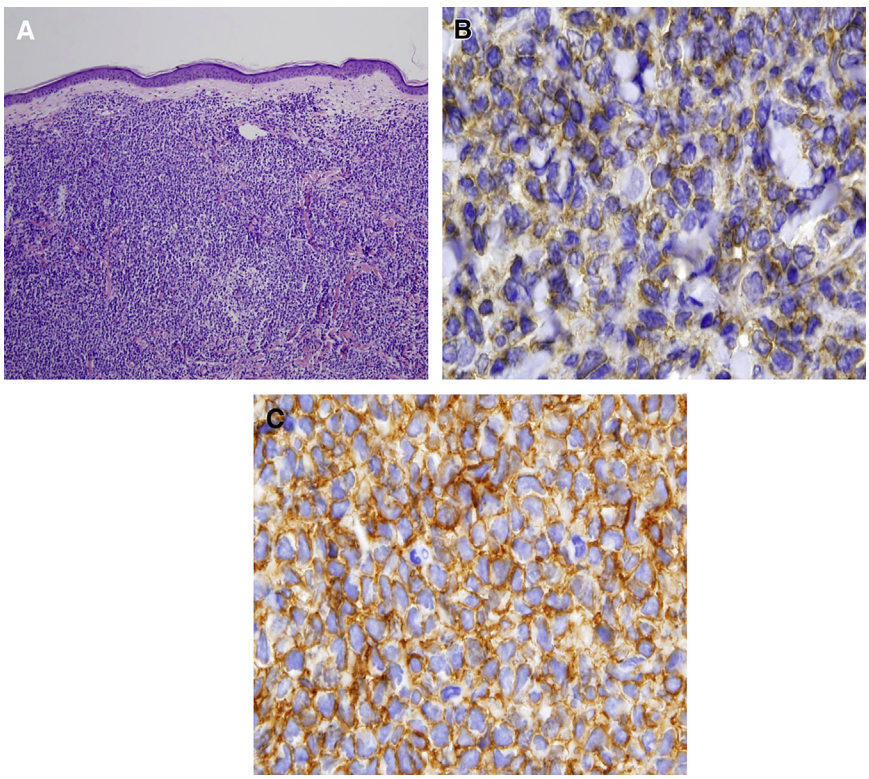

Figure 1. (A) Punch biopsy of a skin lesion in a patient with BPDCN showing a striking diffuse infiltrate of atypical mononuclear cells with round to oval nuclei and scant cytoplasm throughout the papillary and superficial reticular dermis (H&E staining). Immunohistochemical staining showing expression of CD4 (B) and CD56 (C) on malignant cells. (Parts A and B reproduced from Hamadani M, Magro CM, Porcu P. $CD4^+$ $CD56^+$ hematodermic tumor [plasmacytoid dendritic cell neoplasm]. Br J Haematol 2008;140:122, with permission from ©John Wiley and Sons [license number: 3034330839698]. All rights reserved.)

Table 1
Selected Published Data Evaluating Conventional Chemotherapy for BPDCN (with at Least 4 Cases)

Author	Publication Year	n (Gender)	Median Age (Range) yr	Chemotherapy Regimen	Responses	Outcomes
Reimer et al. [13]	2003	83*	—	(1) Acute leukemia–like (n = 17), (2) NHL-like (n = 38), (3) less than CHOP-regimen (n = 28)	CR rates: (1) 94%, (2) 55%, (3) 68%	Median OS: (1) 13 mo, (2) 13 mo, (3) 9 mo CR at last follow-up 35% in (1)
Bueno et al. [7]	2004	5 (M = 4)	63 (52-80)	Various (CHOP; IDA+cytarabine; cytarabine+ thioguanine; daunorubicin+cytarabine; vincristine+daunorubicin+prednisone	CR1 = 4 PR1 = 1	Two relapsed, median DFS 6 mo (range, 0 to 54), 4 died, median OS 10 mo (range, 2 to 54)
Dalle et al. [18]	2010	39 (M = 26)	70 (8-94)	NHL-like (n = 23), AML-like (n = 6), ALL-like (n = 3), others regimens (n = 7)†	CR1 = 19 PR1 = 9 PD = 11	Median RFS 6 mo (range, 2 to 42), 18 received salvage therapy, 1 received auto-HCT, 9 received allo-HCT
Tsagarakis et al. [11]	2010	19 (M = 13)	73 (17-83)	ALL-like (n = 9), AML-like (n = 6), NHL-like regimen (n = 4)	CR1 = 15 (78.9%)	Six (40%) relapsed, 5 (26.3%) received allo-HCT
Dietrich et al. [20]	2011	6 (M = 4)	68 (55-80)	ALL-like (n = 3), AML-like (n = 2), CHOP14	CR1 = 5 PR1 = 1	Median TTR 7 mo (range, 3 to 11) Received allo-HCT in CR1 (n = 1), in PD (n = 2), and after salvage therapy with high-dose methotrexate (8 g/m^2)-based regimen (n = 2)
Lucioni et al. [17]	2011	15 (M = 10)	64 (9-84)	ALL-like (n = 9), NHL-like (n = 4), others regimens (n = 2)	CR1 = 9 PR1 = 6	Ten relapsed, median TTR 9 mo (range, 4 to 36), 9 died, 5 alive and disease free, 2 alive with disease, median survival 13 mo (range, 8 to 72), 2 received HCT after relapse
Borchiellini et al. [42]	2012	4 (M = 1)	69 (50-79)	NHL-like (n = 2), AML-like (n = 1), other regimens (n = 1)	CR1 = 2 SD = 2	All 4 relapsed, one received allo-HCT
An et al. [43]	2012	6 (M = 3)	34 (18-62)	CHOP (n = 2), VPDL (n = 2), daunorubicin+ cytarabine (n = 1), VAD (n = 1)	CR1 = 3 PD = 3	Alive in CR (n = 3), PFS ranges from 2.6 to 28.9 mo, OS ranges 4.4 to 31.2 mo One received auto-HCT
Pagano et al. [36]	2012	41	—	AML-like (n = 26), ALL/lymphoma-like regimen (n = 15)	CR1 = 17 (41%) PR1 = 6 Resistant = 11	Six of 17 CR relapsed, 7 died during induction, median OS 8.7 mo (range, 0.2 to 32.9), 6 received allo-HCT
Summary of listed studies	2003-2012	218	Median age 6th decade of life	AML- or ALL-like (n = 98), NHL-like (n = 104), miscellaneous or unknown (n = 16)	CR with AML/ALL-like regimens around 80%-90%, with NHL-like regimens ~40%-50%	Median OS generally 12 to 18 mo in most listed studies

— indicates not reported/not specified; M, male; ALL, acute lymphoblastic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR1, first complete remission; IDA, idarubicin; NHL, non-Hodgkin lymphoma; PD, progressive disease; PR1, first partial response; SD, stable disease; VAD, vincristine, doxorubicin, dexamethasone; VPDL, vincristine, methylprednisolone, daunorubicin, L-asparaginase; TTR, time to relapse.

* Represents compiled case reports from various publications (summarized by Reimer et al. [13]).

† Chemotherapy regimens are summarized in the table by Dalle et al. [18].

lymphoblastic leukemia–like induction regimen containing dexamethasone, methotrexate, vincristine, cyclophosphamide/ifosfamide, and idarubicin/daunorubicin (n = 3) [20]. Unfortunately, the median time-to-disease relapse was only 7 months (range, 3 to 11) from start of induction therapy; four cases were able to proceed with allogeneic HCT (allo-HCT).

These findings suggest that conventional chemotherapy does not appear to be sufficient by itself to ensure durable long-term remissions. The potential role of maintenance therapy warrants investigation in BPDCN. Table 1 summarizes outcomes using various conventional chemotherapy regimens that include at least 4 patients [21-34].

Hematopoietic Cell Transplantation

There are no published randomized controlled trials evaluating the role of autologous HCT (auto-HCT) or allo-HCT in patients with BPDCN. Most data are limited to small case series or single case reports.

Autologous HCT

Several investigators used high-dose therapy and auto-HCT consolidation in BPDCN, with the goal of maximizing depth and duration of responses (Table 2) [13,18,21,35]. Suzuki et al. reported outcomes of high-dose therapy followed by auto-HCT in 6 patients; 3 died from progression, and the remaining 3 were alive and disease-free at 11, 22, and 37 months after auto-HCT, respectively [35]. On the other hand, Reimer et al. reported relapses after auto-HCT in 3 of 4 cases at a median of 13 months [13]. Several limitations are inherent to these retrospective reports, including lack of centralized review to confirm this rare histology, heterogeneity in number and types of prior chemotherapies used, varying remission status at the time of transplantation, and a possible publication bias toward reporting favorable outcomes. There are no available data to suggest an optimal conditioning regimen for auto-HCT in BPDCN (eg, total body irradiation–based versus non–total body irradiation-containing regimens). The total body irradiation–based conditioning regimen used in the report by Reimer et al. was associated with disease relapse in 3 of 4 patients [13]. In the case series by Suzuki et al., 3 of 6 autografted cases were disease-free; however, the conditioning regimens were not specified [35].

The paucity of published literature precludes identification of a particular subset of BPDCN likely to benefit from high-dose therapy and auto-HCT. It appears, however, that patients with chemorefractory disease and those with active central nervous system or bone marrow involvement at time of autografting are not likely to achieve durable remissions after auto-HCT [13]. These cases should ideally be considered for enrollment in clinical trials. However, in the absence of such trials, acknowledging the limitations and quality of available data, high-dose therapy and auto-HCT could be offered to patients with chemosensitive disease, preferably early in the disease course.

Allogeneic HCT

Allo-HCT appears to have the most favorable data in patients with BPDCN but is anecdotal as well [13,18,20]. Not surprisingly, most reported BPDCN cases undergoing allo-HCT are males (Table 3) [11,13,18,20,22,28,31,36,37]. Available data suggest that patients with BPDCN achieve long-term remissions, mostly if allografted in CR [13,18]. The European Group for Blood and Marrow Transplantation, recently in the largest registry study to date (n = 34), reported 3-year cumulative incidence of relapse, disease-free survival (DFS), and OS rates of 32%, 33%, and 41% respectively, after allo-HCT [37]. Patients included in this study had a careful central review of their diagnosis to confirm this rare histology. Patients allografted in first CR showed a statistically nonsignificant trend toward better 3-year DFS (36%) and OS (52%) compared with patients who underwent transplantation during more advanced disease (DFS, 26%; OS, 29%). No relapses were seen in any patients after 27 months, suggesting a possibility of cure with allo-HCT. It is, however, important to recognize that no robust evidence of a potent and clinically relevant graft-versus-BPDCN effect is available. None of the reports has examined the rates of relapse in patients developing graft-versus-host disease compared with those without graft-versus-host disease, and no data are available to determine if post allo-HCT relapses are responsive to donor lymphocyte infusions.

Reduced-intensity conditioning (RIC) regimens could in theory expand the applicability of allo-HCT to BPDCN patients with advanced age and at a higher risk of associated comorbidities, which would preclude them from receiving myeloablative regimens. For instance, Dietrich et al. described outcomes in 4 patients, with a median age of 66 years (range, 56 to 70), who received unmanipulated peripheral blood stem cells from unrelated donors after a combination of fludarabine, cyclophosphamide, sub-ablative doses of busulfan with or without antithymocyte globulin, or fludarabine plus treosulfan [20]. None of these patients died from transplantation-related toxicities, and 2 were alive in CR at 16+ and 57+ months after allografting (Table 3) [20]. These findings demonstrate feasibility of RIC regimens in elderly patients. It is important to point out,

Table 2
Selected Published Data Evaluating High-Dose Chemotherapy and Auto-HCT for BPDCN

Author	Publication Year	n (Gender)	Median Age (Range) y	Status at Auto-HCT	Regimen	Outcomes
Reimer et al. [13]	2003	4* (M = 4)	28.5 (23-51)	CR1 = 3 CR2 = 1	CY-TBI±VP-16	Alive in CR = 1 Dead = 3 (all from relapsed disease)
Yamaguchi et al. [21]	2005	1 (male)	57	CR1 = 1	CY-TBI-VP-16	Alive in CR at 20 mo
Suzuki et al. [35]	2006	6 (M = 5)	35.5 (14-61)	CR1 = 2 CR2 = 1 PR1 = 1 PD = 2	—	Median survival 13.5 mo (range, 6-37)
Dalle et al. [18]	2010	1 (female)	25	CR2 = 1	—	Alive in CR at 38 mo
An et al. [43]	2012	1 (male)	18	CR1	BuEAM	Alive in CR at 31.2 mo

— indicates not reported/not specified; M, male, BuEAM, busulfan, etoposide, cytarabine, melphalan; CY, cyclophosphamide; CR1, first complete remission; CR2, second complete remission; PD, progressive disease; PR, first partial response; TBI, total body irradiation; VP-16, etoposide.

* Represents compiled case reports from various publications (summarized by Reimer et al. [13]).

Table 3
Selected Published Data Evaluating High-Dose Chemotherapy and Allo-HCT for BPCDN

Author	Publication Year	n (Gender)	Median Age (Range) y	Disease Status at Allo-HCT	Donor Source	Cell Source	Regimen	Outcomes
Reimer et al. [13]	2003	7* (M = 5)	28 (6-35)	CR1 = 4 CR2 = 2 CR3 = 1	—	BM = 6 PBSC = 1	Various	Alive in CR = 3 (at 76+, 98+, and 115+ mo) Rel/PD = 2 (1 died from sepsis, 1 alive at 12 mo) Dead in CR = 2 (1 from ARDS and 1 therapy-related)
Male et al. [22]	2010	1 (male)	50	CR = 1	MRD	PBSC	—	Alive in CR (at 18 mo)
Tsagarakis et al. [11]	2010	5 (gender NS)	—	CR1 = 5	—	—	—	OS = 60% Median follow-up 15 mo (6.6-23.4)
Dalle et al. [18]	2010	9 (M = 8)	38 (25-67)	—	—	—	—	Median OS 21 mo (12-77)
Mitteldorf et al. [24]	2010	1 (male)	36	PD	—	BM	FLU-BU-CY	Achieved CR but died from PD at 7 mo
Dietrich et al. [20]	2011	4 (M = 3)	66 (56-70)	CR1 = 1 CR2 = 1 PR4 = 1 Untreated relapse = 1	WMUD = 2 PMUD = 1 MMUD = 1	PBSC	FLU-CY-BU-ATG† = 3	Alive in CR = 2 (at 16+ and 57+ mo) Alive with relapsed disease = 1 (at 20+ mo) Dead = 1 (in PD)
Lucioni et al. [17]	2011	4 (M = 4)	49 (19-64)	PD = 2 Two as initial therapy	—	—	—	Two achieved CR, 3 died, 1 alive with disease at 72 mo
Dohm et al. [27]	2011	1 (male)	32	CR2	MUD	—	FLU-BU-CY	Relapsed at 7 mo, died at 66 mo
Ham et al. [28]	2012	1 (male)	26	CR = 1	MUD = 1	PBSC	CY-TBI-ATG‡	Alive in CR (at 2 y)
Pagano et al. [36]	2012	6 (gender NS)	—	CR = 3 PR = 1 PD = 1	—	—	—	Median OS = 22.7 mo (range, 12 to 32.9) Alive in CR = 2 (at 16 and 19 mo) Dead = 4 (1 from bleeding, 1 from GVHD, 2 from PD)
Borchiellini et al. [42]	2012	1 (female)	60	—	—	BM	—	Alive in CR at 40 mo
Gambichler [33]	2012	1 (male)	15	CR1	MRD	—	—	
Piccin et al. [31]	2012	1 (female)	33	—	MUD = 1	—	CY-TBI-ATG§	Died at day +120 post-allograft from organ failure
Roos-Weil et al. [37]	2012	34 (M = 21)	41 (10-70)	CR1 = 19 >CR1 = 15	MRD = 11 MUD = 23	BM = 19 PBSC = 9 Cord blood = 6	MA = 25 RIC = 9	Three-year DFS and OS 33% and 41%, respectively

— indicates not reported; M, male; BM, bone marrow cells; ARDS, adult respiratory distress syndrome; BU, busulfan; CY, cyclophosphamide; FLU, fludarabine; GVHD, graft-versus-host disease; MA, myeloablative; MMUD, mismatched-unrelated donor; MRD, matched-related donor; MUD, matched unrelated donor; NS, not specified; PBSC, peripheral blood stem cells; PD, progressive disease; PMUD, partially matched unrelated donor; Rel, relapse; TBI, total body irradiation; WMUD, well-matched unrelated donor.

* Represents compiled case reports from various publications (summarized by Reimer et al. [13]).

† Fludarabine 125 mg/m^2, cyclophosphamide 120 mg/kg, busulfan 12 mg/kg orally, ATG 30 mg/kg.

‡ Dosage and frequency not reported.

§ TBI 12 Gy, cyclophosphamide 120 mg/kg, ATG dose not specified.

however, that only 1 of 9 patients undergoing an RIC allo-HCT in the European Group for Blood and Marrow Transplantation study survived disease-free posttransplantation, whereas the DFS of patients undergoing myeloablative allo-HCT reached a plateau at 40% [37].

The absence of data regarding the presence (or lack thereof) of a clinically relevant graft-versus-BPDCN effect limits our ability to recommend RIC regimens for all allo-HCT candidates. RIC regimens should probably be considered for patients who are not fit to undergo myeloablative allo-HCT due to advanced age or medical comorbidities as previously noted. Collaborative prospective clinical trials are certainly needed to better define the role of allo-HCT in BPDCN.

DISCUSSION

This review highlights the remarkable paucity of data on the biology of BPDCN and its optimal therapy. It is possible that this disease is under diagnosed and under reported. In cases where skin manifestations predominate the clinical presentation, a focused dermatological evaluation may inadvertently miss the hematological findings associated with BPDCN. Accordingly, BPDCN should be considered in the differential diagnosis of atypical skin rashes that are refractory to conventional therapies. These include entities such as lichen planus, systemic lupus erythematosus, psoriasis, and others, especially when present in elder men [23,38]. Conversely, in leukemic cases, BPDCN is likely to be misdiagnosed as leukemia cutis [15,39]. As a matter of fact, differentiating BPDCN from leukemia cutis could pose a serious diagnostic challenge. Marafioti et al. showed that these could be distinguished apart by differential expression (more abundant in BPDCN) of signaling molecules, namely CD2AP or transcription factors such as ICSBP/IRF8 [15]. BPDCN's clinical presentation may also mimic some lymphoproliferative disorders, suggesting it should be incorporated in the differential diagnosis of patients presenting with lymphadenopathy and organomegaly, especially if associated with dermatological findings [15].

Prospective clinical trials aimed at maximizing clinical responses to frontline therapy are needed. In the interim, it

appears logical to offer these patients intensive induction programs using acute lymphoblastic leukemia–like regimens such as hyper-CVAD [19] or AML-like therapies based on limited published evidence [13,20].

BPDCN patients should be referred for an allo-HCT evaluation as soon as possible to determine their candidacy for the procedure and to initiate donor identification in eligible cases. If a suitable human leukocyte antigen–compatible donor is identified, allo-HCT should be considered in patients in first CR, which appears to be a prerequisite for long-term durable remissions. Auto-HCT could be offered in the setting of chemosensitive disease, preferably early in the disease course if a suitable donor is not available. In our opinion, this represents an important treatment algorithm to consider due to relatively short-lived remissions after frontline therapies and because effective second-line therapies remain elusive.

It is important to recognize the possibility of inherent selection bias while interpreting the beneficial role of allo-HCT in BPDCN. For instance, it is probable that only younger patients (age bias) attaining a CR eventually received an allo-HCT. By definition, this younger patient group with chemosensitive disease is already a better population from a biological standpoint. Hence, allo-HCT may appear superior just by virtue of patient selection. Moreover, most available information on management of BPDCN is derived from retrospective case reports and single-institution experiences and as such, suffers from several limitations. First, no prognostic models are available to tailor therapy to individual cases. Second, no prospective data exist to define optimal frontline combination chemotherapy regimen(s). Third, it is not known which subgroup of patients (if any) is more likely to do well (or not) with aggressive chemotherapy programs. Fourth, optimal consolidation modality of patients in first remission (maintenance chemotherapy versus auto-HCT versus allo-HCT) is not known. Fifth, timing and decision to offer either an autograft or allograft to any given patient (in first or subsequent remissions) remain largely factors of physician preference.

FUTURE DIRECTIONS

Moving forward, concerted efforts are required to improve our understanding of the biology of this aggressive malignancy and to define an evidence-based treatment algorithm. Establishment of large, national and/or international tumor registries could prove invaluable in elucidating the natural history of BPDCN and to further identify prognostic markers. Cooperative group efforts are needed to develop prospective trials aimed at defining the most effective therapeutic strategy for this disease. Although only a randomized study can clarify the role and timing of auto-HCT versus allo-HCT for BPDCN, it is unlikely that a large, adequately powered prospective study in this rare disorder would ever be feasible.

Moreover, studies to define the gene expression profile in BPDCN might identify targeted therapeutic approaches. Recently, Pagano et al. described FLT3-internal tandem duplications in a small subset of BPDCN cases [36]; this observation, if confirmed by others, could provide the basis for further understanding the role of commercially available FLT3 inhibitors in BPDCN. Additionally, a xenograft mouse model of human BPDCN has shown that lenalidomide results in tumor reductions, along with significantly augmented levels of active caspase-3, consistent with potential in vivo proapoptotic and cytotoxic effects [40]. Lenalidomide could be potentially explored in the setting of relapsed disease or as a maintenance approach after first CR. Surface CD22 expression is not uncommon in dendritic cells and BPDCN [41]; accordingly, epratuzumab might play a role in this disease. Similarly, some cases of BPDCN express CD33 on the cell surface, identifying a possible role for gemtuzumab ozogamicin provided it becomes commercially available in the future. Future progress in the treatment of BPDCN hinges on better understanding the pathogenesis of this disease and developing novel therapeutic modalities.

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