

# The beneficial role of allogeneic hematopoietic cell transplantation in blastic plasmacytoid dendritic cell neoplasm

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**Abstract**

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare aggressive hematopoietic malignancy. The median survival is approximately 12 months, and for patients >65 years the survival rate is 7 months, when only chemotherapy is administered. Clinically, it is characterized by skin involvement and most often bone marrow lesions accompanied by lymphadenopathy and in some cases hepato- and/or splenomegaly. The diagnosis is based on histopathological examination of the skin or bone marrow lesions and tumor cell immunophenotyping. The etiopathogenesis of the disease is not fully understood. Therapeutic decisions are based only on the results of a few retrospective analyses and case reports. This article presents the important role of allogeneic hematopoietic cell transplantation in the treatment of BPDCN.

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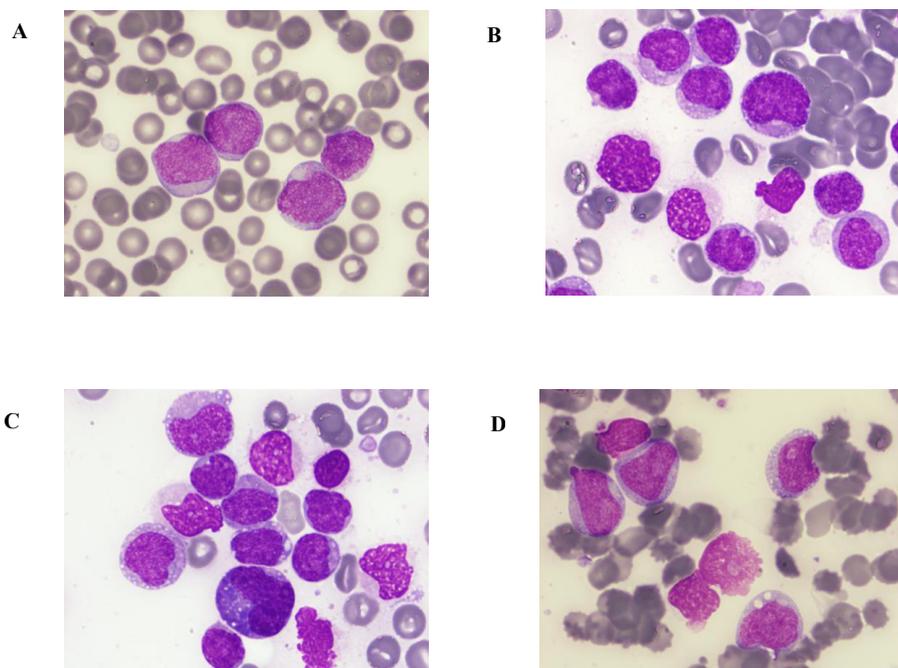
blastic plasmacytoid dendritic cell neoplasm, allogeneic hematopoietic stem cell transplantation, treatment, prognosis

**Introduction**

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a very rare hematopoietic malignancy, characterized by an aggressive course and poor prognosis [1]. The disease was described in 1994, and in 2008 it was included in the World Health Organization (WHO) classification for the first time, in a group of acute myeloid leukemia (AML) and related neoplasms [2, 3]. In the latest WHO classification, a separate nosological unit in myeloid neoplasms and acute leukemia subgroup was defined, and therefore BPDCN is no longer classified as AML [4]. BPDCN is very rare, accounting for about 0.44% of all hematological cancers and 0.7% of acute leukemias, with an incidence of 2 per 10,000,000 people [5]. The disease mainly affects older people in the sixth–seventh decades of life with a higher incidence in males (M:F = 3:1), although cases in children and infants have also been reported [1, 6, 7]. The clinical picture of BPDCN is quite characteristic. Most patients have skin lesions in the form of single or multiple nodules or bruise-like plaques, brownish or red, between a few millimeters and a few centimeters in size. They are located in different parts of the body, often affecting the face, upper limbs, and torso, involving the dermis and subcutaneous tissue, without epidermal involvement, necrotic lesions, and vascular or inflammatory infiltrations. Due to the variable skin presentation, BPDCN is divided into three groups, namely, nodular (the most common), bruise-like, and disseminated with the presence of both nodular and bruise-like lesions. Mucosal presentation is rare [8, 9]. Skin biopsy is often the first test to diagnose the disease [10]. There are a few reports of local, limited skin

involvement, including a series of cases as described by Ishibashi et al. [11]. In addition to the skin manifestations, bone marrow or, more rarely, extramedullary organs involvement are often observed, including the central nervous system, lungs, testicles, mediastinum, conjunctiva, stomach, nasopharynx, paranasal sinuses, and gums [12–16]. In the case of bone marrow infiltration, medium-sized blasts with irregular nucleus, large amounts of cytoplasm, devoid of azurophilic granules, and lack or blurred nucleoli are usually present (Fig. 1) [17]. Another rare variant is the infiltration of medium to large blasts with eccentric nuclei, regular round or oval in shape, with a fine, diffuse chromatin and one or more pronounced nucleoli, abundant, basophilic cytoplasm, fine vacuoles, and pseudopodia cytoplasmic protrusions, and clear Golgi zone located distantly from the nucleus (plasmablastic features) [18]. Immunophenotyping plays an extremely important role in the diagnostic process. The most important clusters of differentiation (CDs) expressed by the cells are CD4+, CD56+, CD123+, and TCL1+. The presence of CD38 antigen may be of therapeutic significance due to the potential to administer anti-CD38 antibodies. Cytogenetic and molecular studies play an auxiliary role. The most common lesions in the karyotype include 5q, 12p, 13q, 6q, 15p, and 9q deletions. In addition, reduced expression of tumor suppressors, RB1 and LATS2, as well as *CDKN1B*, *CDKN2A*, *TP53*, *TET2*, and *PTE* mutations are observed [19, 20]. Different predilection of cancer cells that are home to specific locations seems to be related to their maturity. The least mature group of CD34-expressing cells almost exclusively infiltrates the bone marrow, does not infiltrate the skin and extramedullary organs,

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**Fig. 1. Microscopic image of BPDCN cells in the bone marrow (own collection)**

The images show atypical, polymorphic BPDCN cells. Some of them have a blast-like morphology (A, D), while others resemble aggressive malignant lymphoma cells (B, C)

and has the tendency to disseminate via peripheral blood. Due to accompanying cytopenias, the course of the disease is similar to that of leukemia [21]. On the contrary, immunophenotypically mature cells infiltrate the extramedullary organs and the disease may resemble aggressive lymphomas. Because of this, in the past the disease was classified in the group of both lymphomas and acute leukemia under various previously functioning names, including CD4+CD56+ cutaneous neoplasm/lymphoma, blastic NK-cell lymphoma/leukemia, agranular CD4+CD56+ hematodermic neoplasm, hematodermic neoplasm CD4+/CD56+, and blastic plasmacytoid dendritic cell neoplasm. Most BPDCN studies published to date are retrospective. The first prospective study was focused on the use of SL401 protein as targeted treatment [22]. By 2019, 356 BPDCN cases have been reported [23]. Only 14 patients have been described in the Polish literature so far [24–27]. Therefore in this article we present four new cases of BPDCN and discuss the optimal treatment in Poland, with particular emphasis on the role of allogeneic hematopoietic cell transplantation (allo-HCT).

### Case study

All patients were men >40 years of age (Tab. I). Except in one case, skin presentation was predominant in the clinical picture. The extramedullary involvement included lymph nodes, spleen, and liver. In complete blood count (CBC), normal or moderately elevated white blood cell counts associated with cytopenias in other lines, i.e., thrombocytopenia in all, and anemia in three out of four patients have been observed. In peripheral blood smear, the presence of abnormal cells (blasts or lymphoid cells) has been described. All patients

had significant bone marrow infiltration, ranging from 70% to 92%. Interestingly, all four typical antigens (CD4, CD56, CD123, TCL1) were expressed only in a single patient. In one case, CD4 antigen was absent, and CD56 expression was dim. However, in two patients plasmacytoid dendritic cell antigens were detected (CD123 and TCL1 or CD123 only); in the other two, these antigens were not determined, and the diagnosis was based on typical cell morphology. The expression of HLA-DR, TdT, and CD38 was observed in three out of four patients. In two patients, in whom cytogenetic and molecular tests were performed, the karyotype was normal and mutations in FMS-like receptor tyrosine kinase-3 (*FLT3*), nucleophosmin 1 (*NPM1*), and CCAAT/enhancer binding protein alpha (*CEBPA*) genes were not detected. Three patients were qualified for induction treatment with the hyperCVAD/MA regimen (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytosine arabinoside). All achieved complete remission (CR) in cytological and cytometric examination, and two of them continued the treatment with either two or one cycle (Cases 1 and 3, respectively), followed by allo-HCT after myeloablative conditioning (MAC) from an unrelated, fully compatible donor with total body irradiation (TBI) at a dose of 12 Gy + cyclophosphamide + antithyocytic globulin (Case 1) or from an unrelated donor with a single mismatch at the B locus (TBI 12 Gy + cyclophosphamide + anti-thymocyte globulin) (Case 3). In Case 4, the treatment was de-escalated due to infectious complications and was continued with five cycles of CHOP (cyclophosphamide, daunorubicin, and vincristine prednisone). The patient had a relapse while waiting for the transplantation procedure. The last patient (Case 2) was not eligible for intensive treatment and received three cycles of CHOP. Despite the initial partial response (PR), disease progression was

Table I. Clinical characteristics of the described cases

	Case 1	Case 2	Case 3	Case 4
Age	67	74	46	55
Sex	M	M	M	M
Skin lesions	Brown, flat, or slightly raised, "bruise-like", on the torso 0.5–1.5 cm; under the shoulder blade 8 x 5 cm	Brown, flat, or slightly raised, ("bruise like") on the torso and in the lumbosacral region	None	Nodular on the face and chest
Lymphadenopathy in diagnostic imaging	+	+	+	+
Splenomegaly in diagnostic imaging	+	+	+	+
Hepatomegaly in diagnostic imaging	+	+	–	+
WBC (G/L) at diagnosis	11	24	5.8	5.29
Hb (g/dL)	10.6	13	7.3	7.5
PLT (G/L)	43	70	70	87
Peripheral blood film	27% blasts	15% blasts	22% blasts	14.5% lymphoid cells
Blast infiltrates in the bone marrow (%)	70	85	81	92
Immunophenotype (major antigens)	CD4+, CD56+, CD123+, TdT+, CD 45+, HLA-DR+, CD71+, NG2+, CD33+, CD38+, TCL1+	CD123+, CD 56±, CD45RA+, CD7+, CD33+, CD45+, CD38+, CD4-, HLA DR+, CD36+, CD99+	CD4+, CD56+, TdT+, CD43+, CD68+, CD99+, CD33+	CD56+, CD4+, TdT +, CD7±, CD43+, CD33+, CD38+, HLA-DR+, CD36+
Cytogenetics	Not performed	Normal karyotype	Normal karyotype	Not performed
Molecular assays	Not performed	<i>FLT3 ITD</i> (-), <i>NPM1</i> (-)	<i>FLT3 ITD</i> (-), <i>NPM1</i> (-), <i>CEBPA</i> (-)	Not performed
Treatment	3 x hyperCVAD/MA + allo-HCT-MUD	3 x CHOP	2 x hyperCVAD/MA + allo-HCT- MMUD	1 x hyperCVAD/MA + 5 x CHOP
Response to the treatment	CR	PR	CR	NR
Survival (months)	36+	3	25+	9+

M – male; WBC – white blood cells; Hb – hemoglobin; PLT – platelets; hyperCVAD/MA – cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytosine arabinoside; CHOP – cyclophosphamide, doxorubicin, vincristine, prednisone; allo-HCT-MUD – allogeneic hematopoietic stem cell transplantation-match unrelated donor; allo-HCT-MMUD – allogeneic hematopoietic stem cell transplantation-mismatch unrelated donor; *FLT3-ITD* – FMS-like receptor tyrosine kinase-3 internal tandem duplication; *NPM1* – nucleophosmin 1; *CEBPA* – CCAAT/enhancer binding protein  $\alpha$ ; CR – complete remission; PR – partial remission; NR – no response

observed, including recurrence of skin lesions and development of neurological symptoms. The patient died shortly after the progression onset.

## Discussion

The presented cases can serve as a good illustration of a typical course of the disease. The dominant clinical symptom was skin lesions (mainly "nodular" and "bruise like"). One patient had a very rare form of leukemia without skin involvement – by 2018, only 39 such cases were reported [16]. Skin lesions may imitate other diseases. In one of these patients, diagnostic process was delayed for 6 months from the onset of the first skin lesions, which highlights the need to rapidly perform biopsies of atypical, persistent skin lesions. According to the literature, BPDCN skin lesions have been erroneously described as leprosy, melanoma, diffuse large B-cell lymphoma (DLBCL), and systemic lupus erythematosus [18, 28, 29]. Differential diagnostics of the skin lesions should include dermatological diseases, such as psoriasis, eczema, and lichen planus [30]. A patient with local infiltration of the paranasal sinuses

(without skin and bone marrow involvement) has also been described [16, 31]. Cases of BPDCN development have also been observed in patients with previously diagnosed myelodysplastic syndrome [1, 15, 32]. Table II shows differential diagnosis of BPDCN. Computed tomography (CT) provides some help due to the typical image of the skin and subcutaneous tissue – these changes are round or oval ("ovate") with uniform density of soft tissues [33]. In the faciocranial CT scan performed in one of the patients with skin lesions located on the left half of the face, an oval, well-delimited hyperdense structure in subcutaneous fat measuring 24 x 12 mm was observed on the same side of the face. Positron emission tomography (PET) combined with CT may be needed to identify patients with disease limited to a single location. The SUVmax value is not high, but is usually in the range of 2.4–3.5 [11, 34].

## Diagnostics

The most useful diagnostic tool is bone marrow immunophenotyping using flow cytometry. The diversity of expression of antigens, including those typical for BPDCN, is significant and often not all antigens listed

**Table II. Differential diagnosis involving diseases that may resemble BPDCN**

Disease	Age at onset (median)	Skin	Organ involvement	The most common antigens	Treatment	5-year survival
BPDCN	60–70 years, mainly males	Tumors, nodules, brown “bruise like” lesions	Lymph nodes, bone marrow, spleen, liver, CNS	CD4+, CD56+, CD123+, TCL1+, CD43+, CD45RA+, CLA+, CD2AP+, BDCA2+, BDCA4+	No standards (in the US, treatment with SL401 protein)	No data; OS 12 months
PCLBCL	70 years, mainly females	Red or purple-red nodules on one or both lower limbs	Lymph nodes, bone marrow, CNS	CD19+, CD20+, CD10+, CD79a+, Bcl2+, MUM1+, FOXP1+	R-CHOP + Rtx	From 36% 45% to 100%, depending on the number of skin lesions
AML (M5)	67 years slightly more often in females	Flat skin lesions or nodules	Bone marrow, lymph nodes, liver, spleen, gums	CCD4+, CD56+, TdT±, CD33+, CD34+ MPO±, CD117+, CD13+, CD15+	DAC	In patients >60 years of age <10%
ENKTCL	50–60 years, mostly males	Multiple infiltrates or tumors on the skin of the trunk and extremities or a single tumor in the nasopharynx with a tendency to ulceration	Lymph nodes, nasal cavity, digestive tract, kidneys, testicles, orbits	CD56+, CD2+, CD5±, CD7±, CD4+, CD8+	Rtx 50 Gy and prevention of changes in CNS; possibly rtx and chtx	42%
C-ALCL	60 years, mostly males	Tumors, nodules, reddish, single or multiple, often with ulceration	Lymph nodes – secondary	CD30+, CD4+, CLA+; no EMA and ALK	Surgical or Rtx	90%
MS	38 years, mostly males	2–20 cm tumor, erythematous rash, maculopapular eruptions	Lymph nodes, gums, soft tissues, paranasal sinuses	CD4+, CD14+, CD133+, CD43+, CD68+, CD163+	Systemic chtx as in AML	As in AML
PTCL NOS	55–60 years, mostly males	Nodules and patches	Lymph nodes, bone marrow, liver, spleen	CD2+, CD3+, CD5+, CD7+, CD4+, CD8+	CHOP	32%
Lichen planus	30–60 years, M = F	Pink to bluish red papules 1–3 mm, Wickham mesh	Mucosa of the mouth	Inflammatory infiltrate	Glucocorticosteroids, retinoids, cyclosporine, sulfones, phototherapy; spontaneous healing	As in general population
Psoriasis	At any age, without sex predisposition	Red-brown papules with adherent scales in typical areas (knee and elbow joints, scalp)	Does not occupy internal organs	None	Local or systemic treatment (retinoids, methotrexate, cyclosporine) or phototherapy	As in the general population

BPDCN – blastic plasmacytoid dendritic cell neoplasm; PCLBCL – primary cutaneous large B-cell lymphoma; AML – acute myeloid leukemia; ENKTCL – extranodal NK/T-cell lymphoma, nasal type; C-ALCL – primary cutaneous anaplastic large cell lymphoma; MS – myeloid sarcoma; PTCL NOS – peripheral T-cell lymphoma, not otherwise specified; Rtx – radiotherapy; Chtx – chemotherapy.

as characteristic of this disease are detected. All major antigens were present in only one patient from our cohort. The second did not show CD4, and CD56 expression was low. In the next two patients, the cytometric analysis was carried out to an incomplete extent, and CD123 and TCL1 expression was not assessed. However, a few cases lacking CD4 and/or CD56 expression were described in the literature [10, 35, 36, 37]. In addition to the above two, at least one antigen typical for plasmacytoid dendritic cells should be present: CD123, BDCA2/CD303, TCL1, CLA, CD2AP in the absence of markers specific for B cells (CD19, CD79a), T cells (CD3), as well as myeloid (myeloperoxidase) and monocytic cells (CD11c, CD163, lysozyme). Other commonly observed antigens include CD68 (in 50% of cases), CD43 (95% of cases), TdT (20%–60% of cases), CD45, CD45RA, as well as CD5, CD7, CD33, and sporadically also CD117 [38]. These antigens were found in the studied patients in various configurations; however, CD4 or CD56 were always present.

In unclear cases, histopathological examination should be the standard practice. All of these patients underwent trepanobiopsy and in two cases lymph nodes were collected for histopathological examination. Skin biopsy was performed in one case. Interestingly, CD38 expression was commonly observed in the studied group. This antigen was positive in three out of four patients. To date, there are no data on the expression of this marker in BPDCN, even though CD38 expression suggests the possibility of daratumumab treatment – the first experience with this therapy is promising [39]. One of the CD38-positive patients, who relapsed during the preparation for allo-HCT, was considered for daratumumab therapy; however, the patient progressed while waiting for approval to use daratumumab. CD123 expression, typical for plasmacytoid dendritic cells, was confirmed only in two patients with BPDCN. CD34, maturation antigen, was negative in all the studied patients. Some researchers suggest that CD34 expression excludes the diagnosis of BPDCN, while others do

**Table III. Targeted therapies for BPDCN treatment**

Mechanism of action	Drug	Notes	References
BCL-2 inhibition	Venetoclax	Sensitivity of BPDCN cells to a drug at least as observed in AML; Ongoing recruitment – NCT03485547	Montero et al. [58] and Grushchack et al. [56]
BET inhibition	BET inhibitors (OTX015)	NR3C1 deletion (5q31) and lincRNA-3q fusion – resistant to GS (glucocorticoid receptor mutation) – poor prognosis	Emadali et al. [59]
Overexpression of the LXR gene – inhibition of the NF-κB pathway	LXR agonist	Cholesterol homeostasis abnormalities in BPDCN; agonists probably cross the blood–brain barrier	Ceroi et al. [60]
Inhibition of BRD4 and downregulation of TCF4		TCF4 is the main pleiotropic regulator of BPDCN cell survival (treatment may be more effective than classical targeted therapies)	Kleppe et al. [61] and Ceribelli et al. [62]
Binding to IL-3 receptor	SL-401	Single prospective study in BPDCN; intrathecal administration of SL401 is also considered	Frankel et al. [22]
Inhibition of the NFκB pathway	Bortezomib	The sensitivity of BPDCN cells to bortezomib was confirmed	Sapienza et al. [19]
Restoration of p27 suppressor function (CDKN1B)	Rapamycin		Wiesner et al. [63]
DNA hypomethylation	Decitabine Azacitidine	More effective than bortezomib	Sapienza et al. [64]
CART T cells (anti-CD123)	UCART 123	NCT03190278 – Phase I study in the United States	
Binding to IL3 receptor	XmAb14045 Bispecific anti-CD123/anti-CD3 antibody	NCT02730312	
Binding to IL3 receptor	IMGN632 Antibody drug conjugate	NCT03386513	
CD38	Daratumumab		
PD1/PDL1 inhibition	Pembrolizumab, nivolumab	Potential role – requires further research	Aung et al. [65]

not agree with this criterion [40, 41]. Considering the high antigenic diversity, Salva et al. [42] highlighted the need to search for other markers characteristic of BPDCN, suggesting frequent expression of CD31/PECAM (positive in 8/10 of cases studied). The aforementioned antigen was not assessed in our cohort.

Cytogenetic and molecular tests play an important role in the diagnosis. In two examined patients, no changes in chromosome structure were found, although BPDCN is often associated with a complex karyotype (74%) and suppressor gene abnormalities [10]. The literature describes the case of a patient with BPDCN diagnosed in nodular skin lesion biopsy, who despite the lack of morphological, immunohistochemical, and immunophenotypic changes in the bone marrow, had abnormalities in chromosomes 12 and 22 [10]. TET2 is one of the most commonly mutated genes (54%) [43]. Krause et al. [44] described a patient with protoporphyria with TET2 mutation, who developed BPDCN after 3 years of primary diagnosis. Table III summarizes the frequency of other common molecular abnormalities, including mutations, epigenetic and molecular changes, and signaling pathways, and their potential significance in targeted therapy.

### Treatment

There is no standard protocol for BPDCN treatment. Treatment decisions are often complicated by the advanced age of the patients (median incidence of 60–70 years) and comorbidities. Therefore, in each of the described cases, treatment decisions were made

individually. Three patients were treated with intensive hyperCVAD/MA (in two patients, Cases 3 and 4, with intrathecal prophylaxis of central nervous system involvement) and subsequent allo-HCT. Prophylaxis of CNS involvement seems to be an important element of the treatment due to frequent latent CNS involvement, as confirmed by Martin-Martin in 6/10 of patients studied [12]. All three patients treated with hyperCVAD/MA achieved CR after the first cycle. Due to high frequency of life-threatening infections, in a single patient the treatment was de-escalated and continued with CHOP; however, it led to rapid relapse. The remaining patients were treated with hyperCVAD/MA, followed by allo-HCT with MAC.

The choice of the treatment in the studied patients was based on the experience of other treatment centers. The results of French retrospective studies show that a combination of drugs active against lymphoid (methotrexate, L-asparaginase, and dexamethasone) and myeloid lineage (anthracycline) is the most beneficial [45]. Several large retrospective studies compared responses after induction protocol used in the treatment of acute lymphoblastic leukemia (ALL) – hyperCVAD vs. GIMEMA ALL and acute myeloid leukemia protocol. The efficacy of ALL protocol (hyperCVAD/MA) was higher with CR of about 90% [1, 46]. According to Pagano, overall survival (OS) in patients treated with the AML protocol was 7.1 months vs. 12.3 months in patients treated with the ALL protocol [1]. Longer survival (19 vs. 11 months) was shown in another study comparing ALL protocols: hyperCVAD vs. VPDL (vincristine, methylprednisolone, daunorubicin, and L-asparaginase) [47]. Based on these data, hyperCVAD/MA

treatment was initiated in all of our patients who were eligible for therapy. However, none of the above studies confirmed long-term remissions (OS, 29 months) and the authors emphasize the need to intensify the treatment [48].

### **Allo-HSCT**

Allogeneic hematopoietic cell transplantation appears to be main curative treatment, which, in a retrospective study of a group of 34 patients from the European Group for Blood and Bone Marrow Transplantation (EBMT) register, allowed to achieve long-term OS in 41% and disease-free survival (DFS) in 33% of patients [49]. Better results were reported by American centers: in the group of 37 patients, 3-year progression-free survival (PFS) was 69%, and 3-year OS 61% and 62%, for MAC and reduced intensity conditioning (RIC) conditioning, respectively [50]. Conditioning is not specific to BPDCN, the choice of the protocol is based on age and comorbidities of the patient. The studies published so far suggest using MAC conditioning before allo-HCT whenever possible. Although the results of retrospective analysis from eight centers from the United States and Canada showed a similar 3-year PFS (55%) in both MAC (n = 20) and RIC (n = 17) groups, and a fairly good 3-year OS of 61% and 55%, respectively, the EBMT study showed long-term survival only after MAC conditioning. The procedure should be carried out in the first remission (CR1), as no long-term survival in subsequent remissions was observed. High-dose chemotherapy combined with autologous hematopoietic stem cell transplantation (auto-HCT) is a potential alternative to allo-HCT. However, the data on the effectiveness of auto-HCT are contradictory. In one Japanese study (n = 11), auto-HCT was superior to allo-HCT in CR1, namely: 4-year OS was achieved in 82% patients treated with auto-HCT vs. 69% patients treated with allo-HCT and 4-year PFS in 72% vs. 60%, respectively [51]. However, these results were contradicted by Reimer et al. [52], who showed that three out of four studied patients died due to relapse after auto-HCT. Similarly, in the analysis of US registers (n = 8), 1-year PFS and OS were 11%. The explanation for this may be different eligibility criteria – some patients were not in CR1 and the median age of the studied population was higher. In light of the above discrepancies, only allo-HCT remains a recommended therapeutic option (Leukemia and Lymphoma Society). Such treatment was used in two patients from our cohort. Hematopoietic cell transplantation in both patients was preceded by MAC based on cyclophosphamide and TBI. Antithymocyte globulin, cyclosporin, and methotrexate were used in immunosuppressive therapy. Hematopoietic stem cells were derived from peripheral blood (in the first patient –  $7.13 \times 10^6/\text{kg}$  bw CD34+ cells, and  $5.52 \times 10^6/\text{kg}$  bw in the second). Apart from infectious and cutaneous GvHD, in both cases no other serious complications were observed. These patients remain in CR from 2016 and 2018 to date. In the other two patients, who did not undergo allo-HCT, treatment failure was observed.

Patients diagnosed with BPDCN subjected to retrospective analysis in Polish centers had a typical presentation: the median incidence was 67 years, male sex predominated (M:F 9:5), all patients had skin involvement, and lymph nodes were the most common extramedullary organs involved. In the vast majority the expression of CD4 and

CD56 was observed, and in several cases CD123 was positive. Unfortunately, most of the patients were treated with non-intensive protocols, i.e., CHOP, CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone), or CVP (cyclophosphamide, vincristine, prednisone). Some received more intensive treatment, i.e., IVAC (etoposide, ifosfamide, and cytarabine), AraC + Mtx (cytarabine and methotrexate). Only a single patient, who was treated according to the G-MALL T-LBL 2004 protocol, underwent allogeneic bone marrow transplantation and was the only one to achieve long-term survival of at least 80 months. In another patient treated according to the protocol for AML, allo-HCT was planned but not performed. Eight patients died and no data are available on the survival of the remaining patients. The results of patients from other Polish centers are consistent with our experience – allo-HCT gives a chance for cure in BPDCN [24–27].

### **New therapies**

Due to poor outcomes of the standard treatment there is a need to develop new, more promising treatment strategies. The drugs and their mechanism of action shown to be effective in prospective studies are listed in table III. Among them, only tagraxofusp-erzs (Elzonris) has been approved for BPDCN treatment in children and adults in the United States so far. In Europe, the approval is still pending. Tagraxofusp-erzs is a fusion protein (called SL401) consisting of interleukin IL3A conjugated with tetanus toxin. The drug targets IL3 receptor on cancer cells and in Phase I and II studies, response rate reached 78% with 55% of complete responses [22]. It can be used both in the first and second lines of treatment, and importantly, it can be used in several lines of treatment as the cancer cells retain sensitivity to SL401 protein at relapse [53]. Usually, after remission, allo-HCT is suggested. The limitations of the use of the drug are adverse effects, including the most significant – capillary leak syndrome, which affected 55% of the patients. In children, the outcome is worse, and the responses shorter [54]. The reason for this is not clear. One of the reasons is that the biology of the disease in children is slightly different. It is confirmed by the fact that, unlike in adults, longer survivals are observed in cases without skin involvement [55]. In salvage therapy, other drugs are tested. Strong expression of Bcl-2 in BPDCN compared to pDC cells encouraged the use of venetoclax and the expression of CD38 suggests a potential to use daratumumab. Grushchak et al. [56] described a patient with CR and survival of at least 10 months after 5-month venetoclax therapy, while Iversen et al. [39] showed remissions after using daratumumab in monotherapy. Another protocol that has recently proved effective in individual cases consisting of bortezomib, lenalidomide, and dexamethasone. This protocol, without success, was used in one of our patients in progression [57].

### **Conclusion**

BPDCN is a challenge for doctors of various specialties. The difficulty in diagnosing the disease is associated with a varied clinical picture and rare occurrence. The disease is characterized by rapid relapses despite initial sensitivity to treatment, and long-term remissions

are observed after intensive treatment protocols combined with allogeneic bone marrow transplantation. Increasing numbers of studies on the etiopathogenesis of BPDCN and the use of targeted drugs should translate into increase in the cure rate or prolonged survival, especially in patients who are not candidates for intensive treatment and allo-HCT.

### Authors' contributions

MB – gave the study idea. EU, JMZ – contributed to the study concept. EU – was responsible for collecting data and writing the manuscript. JMZ – carried out editing, evaluation, and acceptance of the manuscript. KL – was responsible for image processing, evaluation, and acceptance of the manuscript.

### Conflict of interest

None.

### Financial support

None.

### Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; uniform requirements for manuscripts submitted to biomedical journals.

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