Curr. Treat. Options in Oncol. (2019) 20: 9
DOI 10.1007/s11864-019-0605-x

Leukemia (PH Wiernik, Section Editor)

Blastic Plasmacytoid Dendritic Cell Neoplasm

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Published online: 4 February 2019

Topical Collection on *Leukemia*

Keywords BPDCN · Leukemia · CD123 · Bone marrow transplant · SL-401 · Venetoclax

Opinion statement

While there is a high initial response rate with standard chemotherapeutic regimens for blastic plasmacytoid dendritic cell neoplasm (BPDCN), the responses are typically not durable and this remains a very aggressive disease with generally poor outcomes. For this reason, the standard approach for eligible patients has been high-dose induction chemotherapy preferably with acute lymphoblastic leukemia (ALL)-based regimens followed by consolidation with allogeneic hematopoietic stem cell transplantation (alloHSCT). Unfortunately, many patients with this disease are elderly and/or frail and cannot tolerate this therapy, and the low-dose regimens being used in this population are generally not as effective. However, this paradigm may be changing with the advent of newer targeted therapies, particularly the exploitation of CD123. SL-401 has shown very promising results with manageable toxicities and durable responses and appears to be a viable option for elderly or frail patients who are not eligible for transplant. The other CD123-directed therapies, especially chimeric antigen receptor-therapy (CAR-T), may also give promising results in trials that are currently underway. CAR-T has shown promise in a number of other hematologic malignancies, and toxicities have become more manageable as its use is becoming more widespread. While SL-401 has shown potential to provide durable responses even without transplant, we do not yet know whether it will be effective as a means to avoid transplant in patients who are otherwise eligible. All transplant-eligible patients should undergo alloHSCT consolidation given the current available data indicating this is the optimal approach to achieve a long-term remission. Once the CD123-directed therapies are established as standard regimens, future studies may be designed to investigate whether these therapies can be utilized without the use of transplant. Furthermore, combination therapy using anti-CD123 agents with high-dose induction chemotherapy or other low-dose regimens for elderly/frail patients should be

investigated. Given the promising results in early clinical trials, it appears CD123 is the most viable target for BPDCN, and future studies should continue to exploit its expression on BPDCN cells.

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare malignancy (< 1% of acute leukemias) derived from precursor plasmacytoid dendritic cells that has been recently reclassified as its own entity in the 2016 WHO revision [1–4]. It is an aggressive disease with a poor prognosis that usually presents in elderly patients, with a median age at diagnosis of 67 years [5, 6]. While a common initial presentation is cutaneous lesions, most patients are found to have multisystem involvement at diagnosis (e.g., blood, bone marrow, lymph nodes [6, 7] and approximately 10% of patients will present with acute leukemia [8]. Skin lesions usually present as bruise-like infiltrates (Fig. 1); however, they can be non-specific (i.e., nodules or plaques) [3, 4]. Diagnosis is usually established via skin biopsy with immunophenotyping (i.e., immunohistochemistry or flow cytometry). Immunophenotype, rather than morphology alone, is required for diagnosis, with expression of five of the following markers considered sufficient: CD4, CD56, CD123, TCL1, and CD303 [3–5]. Figure 1 shows histology from a skin biopsy revealing a typical BPDCN pattern (Fig. 1b–c) as well as IHC for CD4, CD56, and CD123 (Fig. 1d–f). The initial work-up for BPDCN should include full imaging, either computed tomography (CT) or positron emission tomography/computed tomography (PET/CT) as well as analyses of the bone marrow (e.g., Fig. 1 g–g), CSF, and peripheral blood via flow cytometry. If there is evidence of circulating malignant cells and the patient has no symptoms to suggest CNS disease, CSF analysis should be delayed until clearance of circulating BPDCN cells to avoid iatrogenic contamination. BPDCN has a high rate of central nervous system (CNS) involvement [6], and incorporation of intrathecal prophylaxis has been shown to reduce the incidence of CNS disease and improve overall survival [9]. Multiple therapy algorithms have been previously published with similar general principles [3, 4]. Given the promising results from the studies with newer targeted agents discussed below, all newly diagnosed patients should be referred for clinical trial, if eligible [3, 4, 10]. For patients who have rapidly progressive disease with significant symptoms or clinical deterioration, intensive induction therapy with CNS prophylaxis should be offered, if feasible. If a response is achieved after induction (preferably CR), consolidation with either allogeneic (preferred) or autologous hematopoietic stem cell transplantation is indicated for transplant-eligible patients. Given the advanced age and comorbidities seen in many BPDCN patients, intensive therapy with induction ± transplant may not be an option. If these patients are also not eligible for a clinical trial, there are a few options for lower-intensity therapies as described below.

Induction chemotherapy

There are no large prospective studies for induction regimens in BPDCN given this is a rare disease. The treatments used for induction are based primarily on retrospective studies incorporating regimens based on acute leukemia or non-Hodgkin lymphoma (NHL) therapy. The efficacy of acute leukemia-based regimens has been generally superior to that of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens [11, 12]. One of the larger retrospective studies comparing NHL and leukemia-based regimens included 97 patients in four treatment groups: less intensive than CHOP, CHOP or CHOP-like, leukemia-based induction, and bone marrow transplant [12]. The best outcomes were seen with the leukemia-based induction with allogeneic transplant consolidation (~ 40% OS at 10 years) [12].

Regarding the choice of leukemia-based induction regimen, ALL regimens such as hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (hyperCVAD) have shown more success than acute myeloid leukemia (AML)-based regimens; however, without consolidative HSCT, prognosis is still poor, with median OS typically less than 2 years [6, 9, 13, 14]. Two characteristics of ALL-based regimens that may be factors related to better outcomes are their use in a

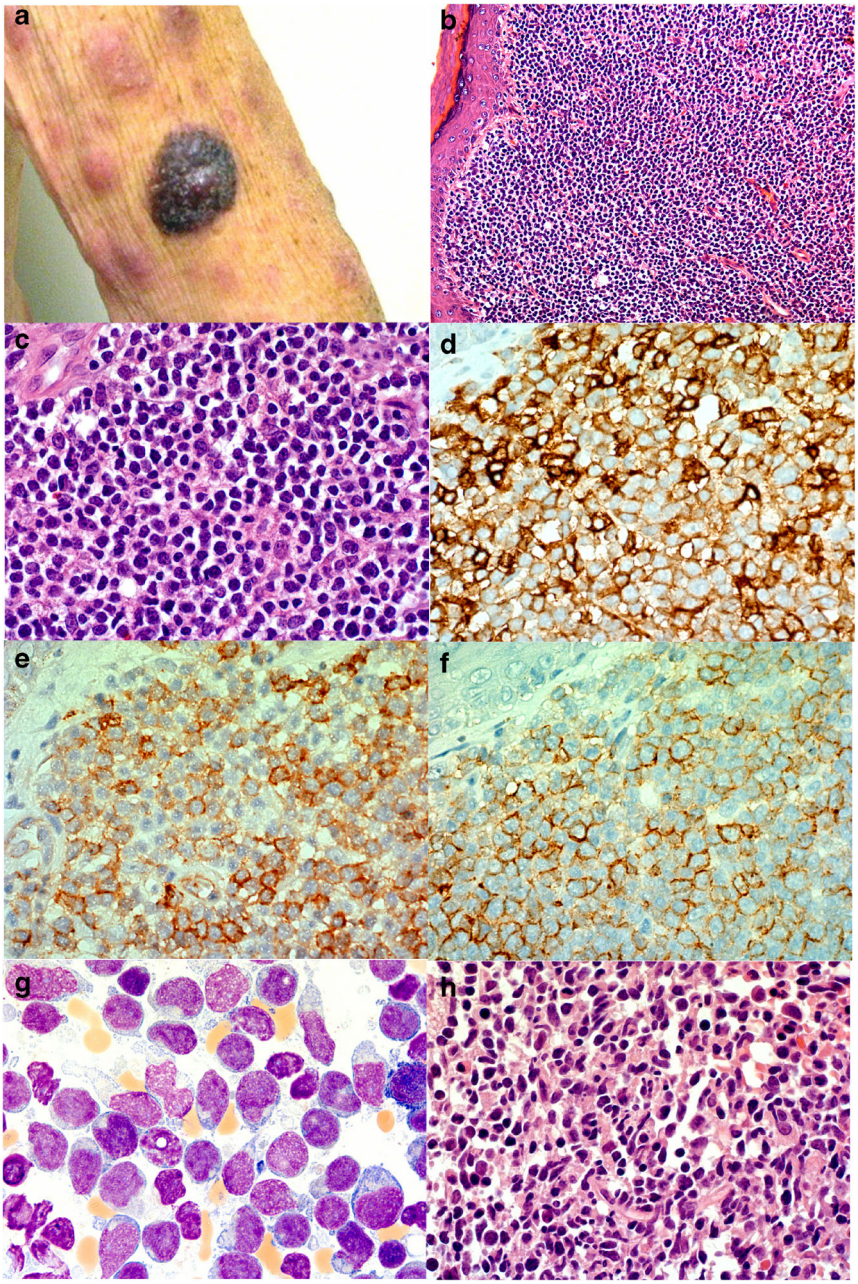

Fig. 1. **a** Cutaneous involvement by blastic plasmacytoid dendritic cell neoplasm (BPDCN) manifested with numerous pink-tan to dark-purple nodules in the background of rash and bruise-like areas. **b**, **c**. A punch biopsy of the skin lesion showed confluent subcutaneous cellular infiltrate composed of blastic cells with high N:C ratio, round to elongated nuclei, inconspicuous nucleoli, and a small amount of amphophilic cytoplasm. Some appear plasmacytoid by morphology (H&E, × 200 and × 600, respectively). **d**–**f**. A panel of immunohistochemical staining was performed which highlights the blastic cells to be positive for CD4 (× 600), CD56 (× 600), and CD123 (× 600) (immunoperoxidase). **g**–**h**. Disseminated disease (stage 4) was evident with a diffuse bone marrow infiltrate by BPDCN. The bone marrow aspirate (Wright-Giemsa) showed sheets of small to medium-sized immature precursors/BPDCN, oval to spindly in shape with delicate chromatin, round to oval or elongated nuclei with scant to abundant light bluish cytoplasm. Many of them exhibited characteristic cytoplasmic micro-vacuoles and pseudopodia (G, × 1000). The bone marrow core biopsy demonstrated an extensive replacement by BPDCN cells with focally spindly or lineal arrangements (H, H&E, × 600).

typically younger population and the incorporation of L-asparaginase. Since younger patients are more likely to tolerate these regimens and be candidates for alloHSCT, this may be a confounding factor related to the improved outcomes [9, 12]. L-asparaginase is often incorporated into pediatric ALL-based regimens [15, 16] and appears to have significant activity in BPDCN. For example, it has also shown efficacy even without being incorporated into a full ALL regimen e.g., when combined with high-dose methotrexate [17, 18]. There is currently a single-arm trial (not yet recruiting) for newly diagnosed BPDCN patients using a combination of L-asparaginase, methotrexate, idarubicin, and dexamethasone (NCT03599960). Patients who achieve a CR after 3 cycles will proceed to transplant, if eligible. For those not eligible, treatment will continue without idarubicin.

In general, eligible patients undergoing induction should receive an ALL-based regimen followed by alloHSCT consolidation. Other induction regimens (e.g., AML or NHL-based) may also be effective if alloHSCT is still incorporated. Pediatric patients may be an exception to this general rule; however, given retrospective data suggesting improved outcomes in these patients even without upfront transplant if they achieve CR1 after an ALL-based regimen.

Hematopoietic stem cell transplant

Given how aggressive BPDCN can be and the high relapse rate even after achieving a CR, HSCT is recommended for consolidation for most eligible patients, because outcomes are generally better compared to the use of induction therapy alone [6, 9, 12, 14]. While allogeneic HSCT is more aggressive with more significant toxicities than autologous HSCT, it has been shown to provide more durable remissions with lower rates of relapse (e.g., [12, 19, 20]. Kharfan-Dabaja et al. reviewed 45 cases treated with HSCT (37 allo, 8 auto) and reported improved outcomes with alloHSCT when compared to autoHSCT [19]. The 3-year OS was 58% in the alloHSCT group compared to a 1-year OS of 11% in the auto-HSCT group. The best outcomes were seen in alloHSCT patients who were in CR1 at the time of transplant, with a 3-year OS of 74%. When comparing conditioning regimens for the alloHSCT group, there was no difference in outcomes between the myeloablative (MAC, $n = 20$) and reduced-intensity (RIC, $n = 17$) regimens. Most of the deaths were related to complications from transplant (e.g., infection, GVHD) with only two deaths secondary to disease relapse or progression. These outcomes illustrate an important point regarding alloHSCT. This treatment provides better disease control; however, this is a very toxic therapy with many potentially fatal complications. Patients must be carefully selected, and many BPDCN patients are not eligible for alloHSCT due to age or comorbidities.

While a number of studies have shown better outcomes with alloHSCT compared to autoHSCT, an autologous transplant still may be a reasonable option for patients who are not eligible for allogeneic transplant. A retrospective study by Aoki et al. compared alloHSCT and autoHSCT for 25 patients (14 allo, 11 auto) with most patients in CR1 at the time of transplant [21]. For patients in CR1, the 4-year OS was comparable for both alloHSCT and autoHSCT (82% vs 69%, $p = 0.44$); however, the outcomes were very poor for patients not in CR1 [21].

Any eligible patient should be considered for alloHSCT after induction therapy given BPDCN is a very aggressive disease with poor prognosis in the relapsed setting. However, if a patient in CR1 is deemed unlikely to tolerate an allogeneic transplant or does not have a suitable donor, referral for an autologous transplant should certainly be considered.

Management of relapsed/refractory disease

In general, relapsed/refractory BPDCN is associated with an extremely poor prognosis with limited therapeutic options. There are no approved therapies in this disease and management is based on the patient's performance status. For patients who relapse after induction, a different regimen is recommended unless they happened to achieve a long-term remission after induction, which is very rare without HSCT. Given that many patients may not be able to tolerate re-induction, some of the lower-intensity regimens described below may be used. Clinical trials are underway with novel agents; however, trial eligibility is usually limited to fit patients. There are also reports showing a second response using donor lymphocyte infusion in patient who had previously received an ALL-type regimen with consolidative alloHSCT [22, 23].

Alternatives to induction chemotherapy: lower intensity regimens and novel agents lower-intensity regimens

Unfortunately, for many BPDCN patients who cannot tolerate aggressive therapy, there is limited data for lower-intensity chemotherapeutic regimens which is primarily from small case series (Table 1). 5-azacitidine is a hypomethylating agent (HMA) that is approved for myelodysplastic syndromes and has been shown to

Table 1. Alternatives to induction chemotherapy: lower-intensity regimens and novel agents for BPDCN treatment

Therapy	Mechanism	Outcomes	Ref
5-azacitidine	Hypomethylating agent	5 patients with PR, 3 with eventual progression, 2 died of sepsis	[24–26]
Pralatrexate	Anti-folate	2 patients with PR, 1 with leukemic relapse	[27–29]
Bendamustine	Alkylating agent/antimetabolite	4 patients: 2 PD, 1 died of TLS, 1 CR × 7 months	[30]
Gemcitabine/docetaxel	Pyrimidine analog/microtubule inhibitor	3 patients with cutaneous CR, 2 with marrow CR, median OS 13.3 months	[31]
SL-401	CD123-mediated internalization, inhibition of protein synthesis via DT	Short course therapy: 55% CR, median response 5 months continuous therapy phase 1/2 underway	[32–36, 37•, 38•]
CD123 CAR-T cells	T cell-mediated cytotoxicity	Phase 1 underway	[40–42]
IMGN632	Anti-CD123 Ab-drug conjugate with DNA-alkylating agent	Phase 1 underway	[39]
XmAb14045	BispecificCD123/CD3 antibody facilitating cell-mediated cytotoxicity	Phase 1 underway	
Venetoclax	Apoptosis via BCL2 inhibition	5 patients: 4 with PR (2 combined with HMA), 1 with CR × 10 months, phase 1 underway	[43, 44•, 45•, 46]

decrease progression to AML [24]. There are two case series (5 patients total) reporting use of 5-azacitidine as a single agent for BPDCN [25, 26]. All of the patients achieved initial responses; however, these responses were not durable. Laribi et al. reported two cases with rapid regression of cutaneous disease after only 1 cycle of 5-azacitidine in the first-line setting; however, both patients died from sepsis at 8 and 9 months with one patient developing severe neutropenia after 5 cycles of treatment [26]. The three patients reported by Khwaja et al. also received 5-azacitidine as first-line therapy and all achieved initial response with regression of skin lesions; however, all patients had eventual progression at 6, 7, and 14 cycles [25]. The median survival was longer in this series (17 months) with one patient alive at 25 months.

Another low-intensity, single-agent option is pralatrexate, which is an anti-folate that may be an alternative to methotrexate with potentially stronger anti-neoplastic effects [27]. There are two case reports using this agent as both first-line and after previous CHOP therapy [28, 29] both achieving PR; however, one patient had leukemic relapse after 5 cycles [28].

Bendamustine, a bifunctional alkylating agent and antimetabolite, was evaluated in five cases of relapsed BPDCN [30]. Four of these patients were evaluable for response, two of whom had disease progression and one achieved a CR until the end of follow-up (7 months). One patient died from tumor lysis syndrome (TLS) secondary to rapid peripheral blast clearance after initiation of therapy. Since one patient achieved a CR for at least 7 months in the relapse/refractory setting, this treatment should be investigated further with close monitoring for TLS especially in patients with high disease burden and/or circulating blasts.

The most significant responses observed using lower-intensity chemotherapy have been with the combination of gemcitabine and docetaxel [31]. In this report, all three patients evaluated were heavily pretreated, two of whom had relapsed after alloHSCT. Cutaneous CR was achieved in all patients with two patients also achieving CR in the bone marrow. The median OS was 13.3 months with one patient still in remission at 17 months [31]. While the follow-up was relatively short, these results are significant given all of these patients had relapsed/refractory disease.

Overall, most of these lower-intensity regimens, while tolerable, do not provide durable responses. Based on the limited data available, it appears gemcitabine/docetaxel may be the most efficacious, especially in the relapsed/refractory setting.

Clinical and pre-clinical development of novel agents

Given the significant toxicities associated with induction chemotherapy/transplant and the limited responses seen in the lower-intensity regimens, there is a need for development of novel agents that may provide durable responses with reduced toxicities. As shown in Table 1, there are a number of targeted and immunomodulatory therapies that are being investigated. Currently, the most promising data is with SL-401, which is a recombinant fusion protein including components of diphtheria toxin (DT) fused to interleukin-3 (IL3) [32]. As described above, CD123, otherwise known as IL3-receptor α, is expressed on the surface of BPDCN cells, and is part of the diagnostic criteria [3–5]. In preclinical studies, this unique fusion protein entered malignant leukemia cells via its interaction with CD123 caused inhibition of protein synthesis via the DT component and evaded certain drug efflux pumps associated with multi-drug resistance [33–35]. Follow-up studies showed significant sensitivity specifically in BPDCN models, both in vitro and in vivo [36].

In a phase 1/2 study, SL-401 used in 11 BPDCN patients, seven with relapsed/refractory disease [37•]. These patients received one course (up to five doses within 10 days) of SL-401. Adverse events (AE) were primarily low grade and resolved, with the most common being fever, chills, edema, transaminitis, thrombocytopenia, and hypoalbuminemia. Most patients (7/11) were able to complete therapy. In the evaluable patients, the overall response rate (ORR) was 77% (55% CR) with a median response of 5 months (1–20+ months). Six patients were alive at the end of follow-up. There were three patients who received a second cycle of therapy for relapsed disease, two of whom achieved a CR for 3 and 5 months; however, they both died of their disease. One patient remained alive but with disease progression at the end of follow-up. Overall, this treatment was very tolerable with a very high response rate including durable responses after one course of therapy. Continuous therapy may have proven more beneficial, especially given the initial responses seen in the relapsed patients. A current phase 1/2 study currently evaluating continuous SL-401 treatment (days 1–5 every 21 days) in both BPDCN and AML patients (NCT02113982). Treatment is being continued until progression or unacceptable toxicity. Early results from the phase 2 portion were presented at ASH 2017, showing very promising outcomes in both the first-line setting (ORR 95%, CR 79%) and in relapsed/refractory disease (ORR 69%, CR 31%). The median OS was not reached for first-line patients [38•].

The CD123 receptor is being exploited by several other methods as well in a number of phase 1 studies. A novel antibody-drug conjugate, IMGN632, incorporates an anti-CD123 antibody with a DNA-alkylating agent and has shown significant preclinical activity [39]. This is currently being evaluated in a phase 1 study for relapsed/refractory hematologic malignancies, including BPDCN (NCT03386513). A bispecific antibody, XmAb14045, targeting CD123 and CD3 has been developed that crosslinks CD123-positive cancer cells to cytotoxic T lymphocytes, and is also being evaluated in a phase 1 trial that includes BPDCN patients. Chimeric antigen receptor T cell (CAR-T) therapy has shown promise for a number of hematologic malignancies, and CAR-T cells against CD123 have shown preclinical activity in AML models [40–42]. There are phase 1 trials underway to evaluate anti-CD123 CAR-T cell therapy in patients with BPDCN and AML (NCT03203369 and NCT02159495).

Venetoclax, a BCL-2 inhibitor, has been showing promise AML in BPDCN and other myeloid malignancies, especially when combined with hypomethylating agents or other low-dose therapy [43, 44•]. In a xenograft mouse model for BPDCN, venetoclax treatment increased tumor cell apoptosis and prolonged survival, which was depending on BCL-2 expression [45•]. The authors also reported off-label use of venetoclax in two patients with relapsed/refractory BPDCN who had progressed after previous CD123-directed therapy. These patients had dynamic BH3 profiling performed on their biopsies to determine venetoclax sensitivity. Both patients achieved a PR at 4 weeks; one patient died from intracranial hemorrhage secondary to thrombocytopenia (predating venetoclax) and one patient had disease progression at 12 weeks [45•]. DiNardo et al. reported use of venetoclax in combination with other agents in 43 patients with various relapsed/refractory myeloid-related malignancies, including 2 patients with BPDCN [44•]. The two BPDCN patients, who had received two and four prior lines of therapy, were treated with venetoclax combined with a hypomethylating agent. Both patients achieved a cutaneous response with one patient achieving PET/CT response and > 50% blast reduction in the marrow [44•]. Another report described a BPDCN patient without extracutaneous disease who had relapsed disease after CHOP followed by auto-HSCT and subsequently received venetoclax [46]. His skin biopsy at relapse was BCL-2 positive. He achieved a CR after 5 months of therapy and remained in CR at 10 months

with no significantly therapy-related AE's. These results indicate venetoclax could be useful in selected BPDCN patients with increased BCL-2 expression. Furthermore, venetoclax use in combination with hypomethylating agents is showing promise in a number of myeloid-related malignancies as well as BPDCN. A phase 1 study at Dana Farber is currently recruiting to evaluate venetoclax in BPDCN patients (NCT03485547).

There are preclinical studies showing potential efficacy of other agents in BPDCN. For example, using a mouse xenograft model of primary bone marrow cells from a BPDCN patient, lenalidomide treatment both decreased tumor growth and increased tumor cell apoptosis [47]. The authors were also able to demonstrate decreased tumor cell engraftment and tumor vascularization. Using the proteasome inhibitor, bortezomib, Philippe et al. showed significant reduction in BPDCN cell growth both in vitro and in vivo, as well as decreased phosphorylation of the NF-kappa B subunit, RelA [48]. Furthermore, they were able to show a synergistic effect in vitro when combining bortezomib with several other drugs, including 5-azacitidine and a histone deacetylase inhibitor. While these are interesting results, clinical data is not yet available for lenalidomide or bortezomib in BPDCN.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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Papers of particular interest, published recently, have been highlighted as:
- Of importance

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