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ACUTE MYELOID LEUKEMIAS (H ERBA, SECTION EDITOR)

Updates in Novel Therapies for Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

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Abstract

Purpose of Review Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematologic malignancy that has heterogeneous presentation and can involve the skin, lymph nodes, and bone marrow. Recent advancements in our patho-biologic understanding of the disease have led to the development of new targeted therapies for BPDCN. In this review, we aimed to describe some of the novel treatments that are being put forward for the management of BPDCN.

Recent Findings Tagraxofusp is the first CD123-targeted therapy approved as the first ever targeted treatment of BPDCN in patients aged 2 years and older. This agent was approved based on a pivotal clinical trial that showed that it was associated with high rates of clinical responses in both treatment-naïve and treatment-experienced patients. The most serious adverse event was occurrence of the capillary leak syndrome. Other targeted therapies are actively being investigated in clinical trials. These include other CD123-targeted approaches, as well as active investigation in targets beyond CD123, such as the BCL-2 inhibitor, venetoclax.

Summary BPDCN is a rare hematologic clonal disorder with historically poor outcomes. Newer targeted therapies have been recently introduced, with promising results and novel toxicities that are important to recognize and understand. Stem cell transplantation after achievement of complete remission remains the mainstay of therapy among younger/fit, eligible patients, regardless of treatment modality used.

Keywords BPDCN · Tagraxofusp · Stem cell transplantation · Leukemia

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a clinically aggressive hematologic malignancy that presents most commonly with characteristic cutaneous lesions and often bone marrow and lymph node involvement [1]. BPDCN is thought to be derived from precursors of plasmacytoid dendritic cells and characterized by the expression of CD4, CD56, and CD123 [2]. Although BPDCN malignant cells may express several B cell markers, they are most closely related to plasmacytoid dendritic cells [3]. Historically, BPDCN has been noted to transform to acute myeloid leukemia (AML) in many cases, and in general, has been associated with very poor prognosis [4]. The nomenclature used to describe BPDCN has changed several times over the past four decades. It appears to be more recently described in 1994, as agranular CD4 natural killer cell leukemia due to its agranular morphology [5]. Over time, the name of this entity changed multiple times adding to the difficulty of identifying the exact incidence of the disease [5]. Following the discovery that BPDCN is derived from type 2 dendritic cells (plasmacytoid), it is now classified under its own entity among myeloid malignancies per WHO 2016 [1].

Until recently, no treatment guidelines were established for the management of BPDCN. The most commonly used approaches have involved implementation of acute myeloid leukemia (AML)/acute lymphocytic leukemia (ALL)–type

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regimens followed by stem cell transplantation (SCT) upon first remission. The use of central nervous system (CNS) prophylaxis has not been clearly established although there is evidence that BPDCN can present with CNS involvement [6]. The finding that CD123 is overexpressed in BPDCN [7] has been of great interest for many years in the field of AML and BPDCN [8]. Importantly, tagraxofusp is a recombinant fusion protein that contains domains of diphtheria toxin and was the first targeted therapy directed to CD123 [9]. It was recently approved by the US Food and Drug Administration (FDA) for the treatment of adults and children aged 2 years or older with BPDCN [10]. Novel agents and other CD123 targeted therapies have shown potential benefit and are currently being explored.

In this review, we will analyze the current targeted treatment for BPDCN and focus on emerging therapies that may have a role in the future.

Established Therapy for BPDCN

BPDCN is an aggressive hematologic malignancy, with historically, a very poor prognosis [1]. Given the rarity and under-diagnosis of this disease, no standard of care existed until most recently the FDA-approved tagraxofusp in appropriate patients. Current treatment includes the use of tagraxofusp if available and if feasible for the patient in consideration. If not an option, patients with good performance status will undergo evaluation for induction chemotherapy (typically with an ALL-type regimen) with intrathecal CNS prophylaxis followed by SCT at first remission. Older patients who are not fit for intense chemotherapy can be considered for lower intensity treatment typically in the form of a hypomethylating combination regimen. Surgical and radiation options have been tried in patients with limited skin disease with variable results [11]. In our modern understanding, we think of BPDCN as a systemic disease that affects multiple organ systems. Even in the sole presence of skin findings, systemic involvement is common at some point of the disease and outcomes have been shown to be poor in "skin-only" BPDCN patients compared with other patients with BPDCN with more overt systemic presentations, further underlying this important point [12–15]. As a result, even though surgical excision and radiation therapy were used in the past [12, 16, 17], the need for systemic treatment is now clearly established; surgery and radiation options are used now mostly in the palliative setting. Finally, newer treatment options are currently investigated in clinical trials. These include CD123–targeted therapies and other immunomodulatory agents used either alone or in combination with conventional chemotherapy.

Conventional Chemotherapy

High-intensity induction chemotherapy followed by SCT has been used for many years, and has been the treatment of choice for younger/fit patients with BPDCN. Treatment usually consists of AML or ALL-type regimen that had initially good overall response rate; however, the durability of the response has been short [18–20]. In our experience, ALL-based regimens (including both those containing asparaginase and those that do not [e.g., hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone-HCVAD]) appear to be more effective than AML-based regimens in the upfront management of BPDCN [6, 21]. Patients who receive conventional chemotherapy should always receive CNS prophylaxis, as BPDCN has a predilection for CNS involvement [22] and intrathecal chemotherapy has been associated with improved overall survival (OS) [21].

In patients who are not candidates for aggressive induction regimens, low intensity treatment is a reasonable alternative approach. Similar to other myeloid malignancies, one of the more common practices in this setting has been the use of hypomethylating agent-based therapy. Most of the data that exist come from small retrospective studies and involve the use of azacitidine and decitabine [23–25]. Treatment with these agents was well tolerated, however had only moderate efficacy as single agent approach. Gemcitabine in combination with docetaxel has also been used and showed activity in one study of previously treated BPDCN [26]. However, again this data comes from a small case series. Robust prospective studies are lacking. Finally, the combination of hypomethylating agents with venetoclax a B cell lymphoma 2 (Bcl-2) inhibitor was an effective salvage option in two patients with BPDCN after a median of two treatment cycles [27•].

Need for CNS-Directed Therapy?

CNS involvement may occur in up to 30% of patients with BPDCN. A case of isolated CNS BPDCN has also been reported [22]. As a result, in planning treatment for a patient with a new diagnosis of BPDCN with conventional cytotoxic chemotherapy-based regimens, one should include flow cytometry evaluation of cerebrospinal fluid if possible [6, 21]. In addition, whenever conventional chemotherapy is used (regardless of the choice of induction regimen), prophylactic administration of intrathecal chemotherapy appears to be of importance [28–30]. CNS relapse is frequent and is as high as 50% in patients not receiving intrathecal prophylaxis [6]. In addition, Martin-Martin et al. showed that in patients who did not receive ALL-based regimens (and thus not receiving routine intrathecal chemotherapy), higher relapse rates as high as 30% were observed [21]. It is important to note that trials with tagraxofusp have not reported CNS relapse with short follow-

up [31••]. However, trials involving tagraxofusp usually excluded patients with active CNS disease at the time of enrollment. The hypothesis that tagraxofusp may have CNS penetration and thus lower relapse rates needs to be investigated further in patients with active CNS disease.

Stem Cell Transplant in BPDCN

Allogeneic SCT

Chemotherapy followed by SCT is associated with improved OS when compared with chemotherapy alone in patients with BPDCN [6, 17, 21]. Most eligible patients will receive allogeneic SCT after first CR (CR1). In a recent meta-analysis of four studies evaluating the role of allogeneic SCT in BPDCN, a pooled OS of 50% (95% confidence intervals [CI], 41–59%) was reported [32]. Better OS was reported if patients received SCT while in CR1 vs beyond CR1 (67% vs 7%). In addition, lower relapse rate was reported if patients underwent myeloablative conditioning regimens vs reduced intensity conditioning (18% vs 40%). One of the major clinical problems with BPDCN is that median age of diagnosis in adults is around 70 years old, an age that often precludes the use of intensive myeloablative preparative regimens. In a contemporary analysis of 59 patients from three major cancer institutes in the USA, 25 (42%) underwent SCT with 20 of them (80%) receiving allogeneic SCT [14]. Median OS from time of transplant was 6.6 years, while median OS for the entire cohort was 2 years (95% CI, 1.4–3.5). In another multicenter retrospective analysis of 45 patients receiving SCT, 37 (82%) received allogeneic SCT [33]. Allogeneic SCT in CR1 yielded improved 3 year OS when compared with SCT not in CR1 (74% (95% CI 48–89%) vs 0, $p < 0.0001$). Allogeneic SCT recipients were younger and had 3-year OS of 58% (95% CI 38–75%). Allogeneic SCT outcomes were not impacted by preparative regimen intensity in this analysis. Qazilbash et al. [34] found that in 14 patients with BPDCN receiving allogeneic SCT, 100-day and 1-year non-relapse mortality was 7% and 32% respectively. Finally, in the European bone marrow transplantation registry, 34 patients with allogeneic SCT were reported, and the 3-year OS was 41% [35•].

Autologous SCT

Autologous SCT has also been investigated in BPDCN with encouraging results in selected cohorts of patients. The largest study was a retrospective case series showing that in 11 patients undergoing autologous SCT in CR1, 4-year OS was 82% regardless of induction type regimen used [36•]. .In a recent study from our group, 24 consecutive patients with BPDCN who received SCT were studied and 10 of them (42%) received autologous SCT [34]. One year non-relapse mortality in autologous SCT was 35%. The high number observed may be attributed to patients being older in this series and accounting for other comorbidities and incidence of infections in this older sub-cohort. Two-year OS was 26% (95% CI: 4%–57%), compared with 56% in allogeneic SCT patients (95% CI 24–80%; $p = 0.33$). The ongoing question with auto-SCT will be to further investigate in clinical trials which patients with BPDCN will be ideal (e.g., older/unfit, skin-only) vs allogeneic SCT; this will be an important question in the field moving forward. Another future area will be the concept of post-SCT maintenance therapy as is being considered in AML patient populations.

Targeted Therapy

CD123, also known as interleukin-3 receptor alpha-chain, is normally expressed in multiple cells including plasmacytoid dendritic cells [8, 37, 38]. CD123 is overexpressed in several hematologic malignancies including AML, ALL, hairy cell leukemia, myelodysplastic syndrome, myeloproliferative neoplasms, CMML, and BPDCN [8, 39, 40]. Given its overexpression in these conditions, the concept of and development of directed therapy against this receptor has been an active research concept in the field since at least 2000 [9]. Newer agents used commonly for other hematologic malignancies including the Bcl-2 inhibitor venetoclax have gained attention recently.

CD123 Targeted

Tagraxofusp

Tagraxofusp (formerly known as SL-401) is a CD123-targeted cytotoxin composed of interleukin-3 fused to truncated diphtheria toxin (a potent inhibitor of protein synthesis) [41••, 42, 43]. Initially, tagraxofusp was studied in preclinical studies in in vitro models showing exquisite cytotoxicity in low concentrations against cell lines derived from patients with BPDCN [41••].

Based on the encouraging preclinical data, tagraxofusp was evaluated in a pilot study by Frankel et al., which included 11 patients with BPDCN [43]. In this study, 7 patients (78%) attained major clinical response (CR in 5 patients; partial response [PR] in 2 patients) after a single course with tagraxofusp. Median response duration was 5 months (range 1–20 months) and the most frequent side effects included hypotension, edema, fevers, and chills. No treatment-related death was reported and most of the adverse events were easily manageable.

A subsequent recent phase I/II, open label, multicenter clinical trial was conducted in order to investigate the efficacy and safety of tagraxofusp in patients with treatment-naïve or

relapsed/refractory BPDCN [31]. In 29 of the patients that were treatment-naïve, tagraxofusp led to a combined CR and clinical CR rate of 72% ($n = 21$). The 2-year OS in these patients was 52%. Notably, 45% of the patients ($n = 13$) were successfully bridged to SCT after CR1. Among the 15 patients with relapsed/refractory disease, tagraxofusp led to a response rate of 65% with median OS of 8.5 months. The most serious adverse event was capillary leak syndrome which led to two deaths in this initial dataset. Other common side effects included elevation of alanine and aspartate aminotransferase levels and hypoalbuminemia. This study led to US FDA approval of tagraxofusp on December 21, 2018, for the treatment of both treatment-naïve and previously treated BPDCN in adults and pediatric patients aged 2 years and older and "black-box warning" for occurrence of capillary leak syndrome [10]. The recommended dose of tagraxofusp is 12 mcg/kg once daily intravenously on days 1 to 5 of a 21-day cycle. Treatment is continued until disease progression or unacceptable toxicity.

IMGN632

IMGN632 is a CD123-targeted antibody-drug conjugate that consists of humanized anti-CD123 antibody covalently linked to a novel highly potent DNA alkylating agent. IMGN632 couples the targeting features of the antibody with the cancer-killing impact of the payload and it has been shown to be active in AML xenograft models [44]. IMGN632 is currently being studied in a phase I study (NCT03386513) for relapsed/refractory hematologic malignancies (including BPDCN). Preliminary results were presented at ASH 2018 and showed that of the 3 patients with BPDCN that were treated, one had partial response, one had stable disease, and one had unconfirmed complete remission with incomplete hematologic recovery [45]. All 3 patients received tagraxofusp previously and had improvement of their skin lesions with IMGN632.

Chimeric Antigen Receptor T Cell Therapy

Chimeric Antigen Receptor (CAR) T cell therapy has shown great promise in several hematologic malignancies and is now FDA approved for the treatment of patients up to 25 years of age with B cell ALL that is refractory or in second or later relapse based on the results of studies in these patients which showed sustained remission rates [46, 47]. The field of targeting CD123 with CAR-T is in its initial investigation stages. UCART123 cells are genetically modified allogeneic T cells that contain CD123 CAR in addition to a ligand that confers susceptibility to rituximab. UCART123 has been reported to have BPDCN-specific killing secondary to T cell degranulation and robust production of interferon-gamma [48]. Challenges with these new agents include the possibility of increased rate of host-mediated rejection and management of CAR-T cell–related toxicities [49]. Budde L et al. [50] treated a 74-year- old male patient with BPDCN who presented with a bulky subcutaneous mass, with CD123+ CAR-T cells. This patient maintained CR at 60 days post-infusion with complete resolution of his clinical symptoms and no evidence of cytokine release syndrome. Most frequent side effects included febrile neutropenia and infusion-related reactions including chills, tachycardia, nausea, and vomiting.

Beyond CD123

Bcl-2

Bcl-2 dependence of BPDCN has been reported by Montero et al. [51] Clinically, venetoclax was administered in 2 patients with relapsed/refractory BPDCN who had progressed after treatment with CD123-targeted therapy led to partial response at 4 weeks [51]. Venetoclax has also been studied in combination with HCVAD. In relapsed/refractory cases with BPDCN, the combination of HCVAD plus venetoclax has shown encouraging results so far with 3 of the first 3 patients treated with this combination achieving CR with no major adverse events [52]. In addition, 2 patients were successfully bridged to SCT. Based on these promising results, a trial evaluating the use of venetoclax monotherapy in relapsed/refractory BPDCN is currently ongoing (NCT03485547). Finally, venetoclax was studied in combination with hypomethylating agents in a retrospective review of patients with relapsed/refractory myeloid malignancies including BPDCN [27•]. In the 2 patients with BPDCN, 1 achieved cutaneous response and 1 achieved more than 50% blast reduction in the bone marrow.

Bromodomain Protein Inhibitors

Bromodomain and extra-terminal domain (BET) protein inhibition is gaining interest in BPDCN. Sensitivity of BPDCN to BET inhibitors has been demonstrated in vitro [53]. BET inhibition was also associated with induction of BPDCN apoptosis secondary to disruption of BPDCN-specific transcription proteins including TCF4 [54]. Future directions may include clinical studies including BET inhibitors in treatment of BPDCN.

Multiple Myeloma-Based Therapy in BPDCN

Daratumumab

Daratumumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that targets CD38 and promotes cell death

with interaction with complement and activation of cytotoxic T lymphocytes [55, 56]. Daratumumab has important immunomodulatory effects in multiple myeloma and this is hypothesized to also play a role in BPDCN [56]. In a recent case report of daratumumab use in a 70-year-old patient with BPDCN who was not fit for intensive regimen, great clinical response was achieved after one cycle of daratumumab [57]. The proportion of neoplastic plasmacytoid dendritic cells in the bone marrow decreased from 4 to 0.1% after one cycle of monotherapy. No significant toxicity was observed and patient proceeded to receive low-intensity chemotherapy regimen after 4 cycles of treatment with daratumumab. Further studies are needed.

Lenalidomide

Lenalidomide is a frequently used therapeutic option in multiple myeloma and in certain myeloid malignancies including 5q- MDS [58]. Its mechanism of action includes immunomodulatory, anti-inflammatory, and anti-angiogenic properties [59]. Lenalidomide has shown preclinical activity in mouse models with BPDCN cell lines [60].

Proteasome Inhibitors

Activation of the nuclear factor-kappa B (NF-kB) pathway has been demonstrated in BPDCN [61]. In the same study, the proteasome inhibitor bortezomib was able to inhibit cell cycle progression in BPDCN cell line. This hypothesis was further studied in 2017 when Philippe et al. reported that in 7 patients with BPDCN, bortezomib led to a decrease in NF-kB subunit expression and increased xenograft mouse survival [62]. One patient is still in CR, 10 months after treatment; the 2nd patient died from heart disease; and the 3rd one died from infectious complications following allogeneic SCT.

Combination Treatment

In a recent case series of 3 patients with treatment-refractory BPDCN, combination of lenalidomide, bortezomib, and dexamethasone led to CR in all 3 patients after 2 or 3 cycles of treatment [63•]. In another case report of a 43-year-old male with treatment-refractory BPDCN, combination treatment with lenalidomide and bortezomib led to CR [64]. These studies represent a possible new approach to treatment of BPDCN that needs to be validated in prospective series.

Future Directions

BPDCN is a rare disease with historically poor outcomes and historically a lack of standard available therapies. Recently, increased understanding of the patho-biological genesis of the disease in addition to the development of new targeted therapies in the field of leukemia has increased the strategies in our therapeutic approach to BPDCN. Specifically, tagraxofusp, the first-in-class CD123-targeted therapy that was recently approved by the US FDA, leads to high CR rates with successful SCT after CR1.

We believe that newly diagnosed patients with BPDCN should be considered for tagraxofusp treatment in the first-line setting unless a contraindication exists. A thorough evaluation of baseline cardiac, renal, hepatic, pulmonary, and other clinical factors as assessed in the clinical trials and as represented on the package insert is mandatory when considering a new patient for administration of tagraxofusp. Furthermore, rigorous evaluation both at baseline and regularly during administration of doses is necessary for several laboratory values including albumin, creatinine, liver tests, and other factors as performed in the clinical trials and available in package insert. It is important to understand and recognize the capillary leak syndrome in clinical practice as this can be a rapidly fatal process, particularly in older patients and those with lower albumin levels or suboptimal cardio-pulmonary status. Management strategies include delaying or withholding additional tagraxofusp doses as appropriate/as per package insert cut-offs, administration of albumin infusions along with corticosteroids, and close management of volume status. If a patient is not eligible for tagraxofusp, they should be offered clinical trial options with one of the newer directed therapies discussed above, especially consideration of venetoclax-based therapies if available. If clinical trial is not an option, patients that are fit for intense chemotherapy should undergo an ALL-based regimen; otherwise, less intense chemotherapy in the form of hypomethylating agent-based strategy should be pursued. Stem cell transplantation should be pursued after CR1 no matter what treatment is chosen.

The need for CNS prophylaxis with tagraxofusp is a question that needs to be evaluated in the future. Whether tagraxofusp has CNS penetration, or CNS relapse was not observed due to the exclusion of patients with CNS disease at baseline, remains unknown. Combinations of targeted therapies will also be tested and of particular interest will be the potential combination of tagraxofusp with the Bcl-2 inhibitor venetoclax (both of these agents have shown promising results as monotherapy).

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Compliance with Ethical Standards

Conflict of Interest Minas P. Economides declares no conflict of interest.

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- • Of importance
- •• Of major importance

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