Treatment of blastic plasmacytoid dendritic cell neoplasm

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare myeloid malignancy with no defined standard of care. BPDCN presents most commonly with skin lesions with or without extramedullary organ involvement before leukemic dissemination. As a result of its clinical ambiguity, differentiating BPDCN from benign skin lesions or those of acute myeloid leukemia with leukemia cutis is challenging. BPDCN is most easily defined by the phenotype $CD4^+CD56^+CD123^+lineage^-MPO^-$, although many patients will present with variable expression of CD4, CD56, or alternate plasmacytoid markers, which compounds the difficulty in differentiating BPDCN from other myeloid or lymphoid malignancies. Chromosomal aberrations are frequent, and the mutational landscape of BPDCN is being rapidly characterized although no obvious molecular target for chemoimmunotherapy has been identified. Chemotherapy regimens developed for acute myeloid leukemia, acute lymphoid leukemia, and myelodysplastic syndrome have all been used to treat BPDCN. Relapse is frequent, and overall survival is quite poor. Allogeneic transplantation offers a chance at prolonged remission and possible cure for those who are eligible; unfortunately, relapse remains high ranging from 30% to 40%. Novel therapies such as SL-401, a diphtheria toxin conjugated to interleukin-3 (IL-3) is commonly overexpressed in BPDCN and other aggressive myeloid malignancies and has shown considerable promise in ongoing clinical trials. Future work with SL-401 will define its place in treating relapsed or refractory disease as well as its role as a first-line therapy or bridge to transplantation.

Learning Objectives

- To understand the clinical and laboratory approach for differentiating BPDCN from acute myeloid leukemia with cutaneous manifestations
- To consider appropriate first-line and salvage treatments for BPDCN, including the utility of hematopoietic allogeneic stem cell transplantation and novel agents in various patient populations

Introduction

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon hematopoietic malignancy which was renamed in the 2008 4th edition of the World Health Organization classification to reflect the accuracy of cytologic description and the evolving cytogenetic understanding of its plasmacytoid dendritic cell (pDC) origin[1]; BPDCN is now placed in the myeloid category of diseases. pDCs constitute a subset of DCs known as professional type 1 interferon-producing cells, which function in the innate immune response but are not typically found in healthy skin.[2-4] Over the years, pDCs have been viewed as lymphoid neoplasms, myeloid neoplasms, or hematopoietic cells of unclear origin. Thus, treatments have been varied and have met with limited success. Owing to its rarity and poor overall outcomes, there is no standard of care for BPDCN. Here, we discuss therapy selection based on the individual patient, comorbidity, and eligibility for stem cell transplantation (SCT).

Clinical presentation

Estimates suggest that BPDCN constitutes 0.44% of hematologic neoplasms annually, which equates to roughly 700 cases in the United States and 1000 cases in Europe.[5,6] Clinically, BPDCN most commonly affects patients who are middle-age or older, but it has also been described in children; it is threefold more common in men than in women, and the median age at diagnosis in generally in the 60s. Two manifestations of BPDCN or patterns of disease are prominent: in roughly 10% of patients, systemic involvement characteristic of an acute leukemia is present from the first recognition of disease, often concurrent with multiple skin nodules. However, in nearly 90% of patients, BPDCN presents with morphologically diverse cutaneous manifestations (Figure 1A) with or without additional extracutaneous sites of disease (bone marrow, lymph nodes, spleen, or other organs) before systemic leukemic dissemination. The cutaneous manifestations are nebulous and easy to confuse with many benign types of lesions. This is especially true in inflammatory disorders of the skin, which demonstrate cutaneous recruitment of nonmalignant pDCs. Despite originating as nondescript cutaneous lesions devoid of a predilection in site, number, or color, BPDCN is an aggressive and progressive malignancy with a median survival from diagnosis of only 12 to 14 months.[7-10] Moreover, coexistence with myelodysplastic syndrome (MDS) or transformation to acute myeloid leukemia (AML) has been observed in 15% to 20% of patients.[11-14]

Diagnosis

Differentiating BPDCN from other rash-producing entities, both nonneoplastic and neoplastic, is paramount in planning appropriate

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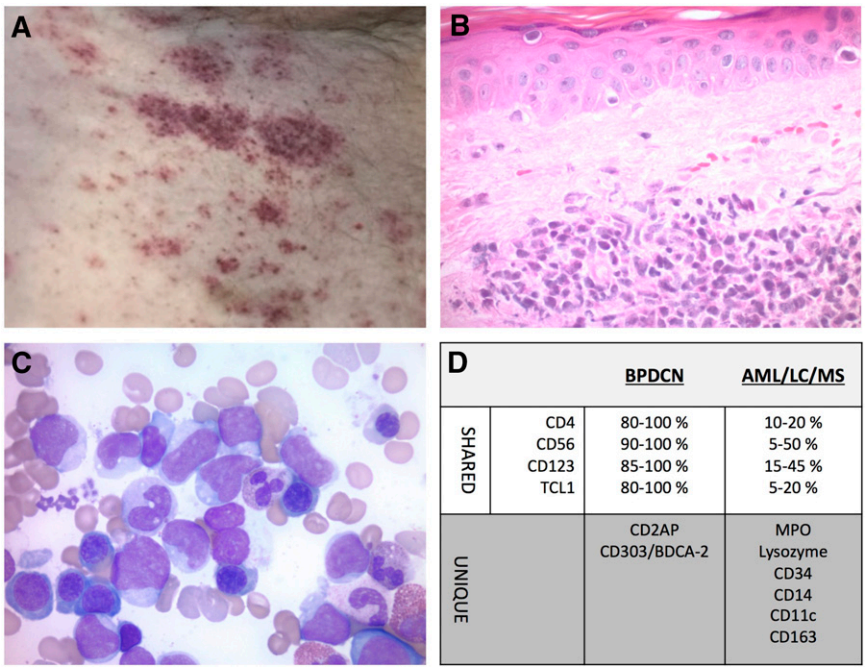

Figure 1. Morphologic evaluation and immunohistochemical markers that aid in the diagnosis of BPDCN. (A) Skin lesions of BPDCN can vary in shape, size, color, and distribution. Hyperpigmented red-brown macules, shown here, may be confused with neoplastic and nonneoplastic etiologies. (B) Skin biopsy (×500) of dermal infiltrate of immature mononuclear cells, which spares the epidermis (separated by a Grenz zone) typical of BPDCN, LC, and myeloid sarcoma (MS) and helps distinguish those diseases from mycosis fungoides which is usually epidermotropic. (C) Bone marrow aspirate (×1000) demonstrates medium to large cells with scant cytoplasm, immature chromatin, irregular nuclear contours, and prominent nucleoli. (D) Shared immunohistochemical markers are shown with a range of positive cases observed for BPDCN and AML/LC/MS. Ranges are rounded to the nearest 5% based on multiple series.[2,17,18,26] Clearly the overlap of shared markers and exception of atypical cases that lack a particular marker highlight the need for review of unique markers to differentiate BPDCN from AML/LC/MS.

therapy. Because of early uncertainty regarding its histogenesis, this entity, first described by Adachi et al[15] in 1994, has been known by myriad names highlighted by agranular $CD4^+$ natural killer (NK) –cell leukemia and agranular $CD4^+CD56^+$ hematodermic neoplasm, owing to the difficulty in defining its true heritage among hematologic neoplasms. As will be described, overlap in morphology, immunophenotype, and the genetic mutation profile of BPDCN compared with a multitude of acute myeloid, NK-cell, and even T-cell malignancies suggests that when suspicion of BPDCN arises, referral for pathology review by someone specially trained in hematopathology is encouraged.

Morphology

Similarities in both clinical presentation and basic histologic appearance between BPDCN and leukemia cutis (LC) preclude our ability to accurately differentiate these entities on the basis of gross pathology alone. The histology of cutaneous lesions of both BPDCN and LC have been described in the literature with pleomorphic cell size (small-medium or medium-large in different case studies) and infiltrates prominent in the dermis, sparing the epidermis, and occasionally extending to the sub-cutis (Figure 1B).[16] Infiltrates have been described as having perivascular or periadnexal distribution; however, they typically cluster in the superficial to mid dermis. As pictured in Figure 1C, chromatin is typically dispersed, and nuclear membranes are irregular with prominent nucleoli and increased mitotic activity.[17-19]

The clinical and histologic presentation are most similar to myelomonocytic (M4) or monoblastic/monocytic (M5) leukemia with skin involvement, typically referred to as LC, aleukemic myeloperoxidase LC (MPO-LC),[17,20] or more rarely $CD4^+CD123^+CD56^-$ pDC accumulations associated with myeloid disorders.[21,22] Thus, multiple recent case reports have further defined both immunophenotypic and cytogenetic profiles by which to differentiate BPDCN from other similar appearing myeloid-derived malignancies.[10,17,20,23]

Immunophenotype

Figure 1D shows the shared and unique immunohistochemical markers that allow BPDCN to be accurately differentiated from AML or AML-associated LC or myeloid sarcoma. For BPDCN originating as isolated cutaneous lesions without organ involvement, immunohistochemistry is of particular importance, because biopsy specimens may not yield sufficient cells for differentiation via flow cytometric analysis. As put forth by the 2008 World Health Organization classification, BPDCN typically express CD4 and CD56 in addition to at least 1 of the pDC-associated antigens—CD123, TCL-1, CD2AP, or CD303/BDCA2—in the absence of lineage-specific markers.[24] MPO is negative in BPDCN, and although it is expected in myeloid LC, the cutaneous lesions of LC seem to inconsistently express this marker.[17] Rarely, CD4, CD56, or both are negative in BPDCN.[10,18,25] In contrast, Cronin et al[17] observed expression of CD56 in ~50% and CD4 in 9% of myeloid LC. In instances of myeloid LC in which dual expression of CD4 and CD56 is present, the DC antigens, including CD123 and TCL-1, are absent. Cronin et al concluded that the use of immunohistochemical stains for CD4, CD56, CD123, TCL-1, and MPO could accurately differentiate BPDCN from myeloid LC in 100% of their patients. Similarly, Sangle et al[26] were able to accurately differentiate BPDCN from

myeloid sarcoma, another extramedullary manifestation of AML similar to LC, with a 7-stain score using the immunohistochemical stains for CD4, CD56, CD123, TCL-1, and human myxovirus resistance protein 1 (MxA-1) with negative staining for lysosome and MPO to indicate BPCDN. Further work demonstrated that a 2-stain score constituting positive CD56 and TCL-1 alone could replicate this differentiation with almost equal accuracy.

Conversely, leukemic presentation of BPDCN or prominent bone marrow infiltration provides an excess of cells readily characterized by flow cytometry. The immunophenotype established by flow cytometry in the early 2000s has been reported as $CD4^{+}CD56^{+}$ $lineage^{-}CD45RA^{+}CD116^{+low}$ $CD123^{+high}CD36^{+}HLA\text{-}DR^{+}$ $CD45RO^{-}CD11c^{-}CD34^{-}$.[12,23] However, recent studies highlight that BPDCN will frequently express antigens expressed by other cell lineages (CD2, CD33, CD79a, TdT) or is lacking major immunophenotypic markers that lead to diagnostic dilemmas.[9,18,25,27] Deotare et al[27] recently used a 10-color 4-tube AML panel to accurately describe the BPDCN phenotype and differentiate it from a host of other differentials, including AML, especially monocytic M4/M5 with which it is easily confused, T-cell lymphoblastic lymphoma, and NK-cell lymphoma/leukemia. BPDCN cells expressed CD4(bright), CD33(dim), CD56(heterogeneous), CD123(bright), CD36, CD38, HLA-DR, and CD71 and lacked a considerable number of lineage markers, most importantly MPO, CD34, and CD14. Flow cytometric diagnostic scoring criteria established by Garnache-Ottou et al[28] called attention to the stringency of the immunophenotype set by some of these analyses and provided accuracy for diagnosing both typical (pDC) and atypical (apDC) presentations of BPDCN. They used a 5-point layered score by first evaluating the cell population on the criteria of a $CD4^{+}CD56^{+/-}$ $MPO^{neg}cCD3^{neg}cCD79a^{neg}CD11c^{neg}$ profile; if present, this population received 1 point. Subsequently, $CD123^{high}$, BDCA-2 (highly specific), and BDCA-4 expression were given point values of 1, 2, and 1, respectively. By this rationale, all cases of BPDCN (typical and atypical) are identified when the total score is greater than 2, the initial profile criteria are not as stringent, and specificity for plasmacytoid malignancies is maintained.

Genetics

Chromosomal abnormalities occur in roughly 50% to 60% of patients with BPDCN; in a large proportion (70%), the karyotypes are complex with at least 3 aberrations present. On the basis of 2 larger series, recurrent mutations are found in 6 chromosomes: 5q, 12p, 13q, 6q, 15q, and 9; they have been demonstrated to have mild variation in frequency and none has been shown to be diagnostic for BPDCN.[29,30] Numeric abnormalities are frequently found for chromosomes 13, 9, and 15, whereas structural mutations were more common in chromosomes 6, 5, and 12. Structural abnormalities in 12p are among the most common, corresponding to a loss of the CDKN1B locus reported in more than 60% of patients with BPDCN.[10,31,32] Dysregulation of CDKN1B and its gene product p27 have been implicated in the pathogenesis of multiple malignancies. In a series of 21 patients with BPDCN, biallelic loss of 9p21.3 and the CDKN2A/CDKN2B genes encoding p16 and cyclin-dependent kinase inhibitors results in a poorer overall survival (OS) compared with wild-type patients.[10] Loss of chromosome 13, specifically 13q, the RB1 gene loci, and the RB tumor suppressor activated by p16 is a pathogenic mutation found in solid and hematologic malignancies. Although not typically the sole driver mutation, loss of RB tumor suppressor function may allow acceleration of alternate oncogenic pathways yet unexplored in BPDCN. By using multiple techniques, including fluorescent in situ hybridization, array-based hybridization, and next-generation or whole exome sequencing, mutations in TET2, TP53, NPM1, NRAS, FLT3, and IKZF1 genes have been described. These mutations are demonstrated repeatedly throughout the literature in myeloid and lymphoid malignancies as well as MDS. Their gene products are integral to myelopoiesis, including DNA methylation, chromatin remodeling, and cell-cycle regulation, suggesting an important role in oncogenesis (likely chemoresistance) and may be further evaluated in the future to described subgroups of BPDCN with different pathogenic behavior.[33,34] Not surprisingly, poor OS correlates with the presence of multiple mutations.[35] An extensive characterization of the mutation profile of BPDCN can be found elsewhere, although no specific mutation has yet been identified that targeted therapies can be directed toward.[16,36]

Treatment

At this time, no therapy for BPDCN is considered the standard of care, given the low incidence of this disease and poor durability of responses for most strategies used to date. Unfortunately, prospective series of chemotherapy in BPDCN are lacking. We direct the reader to a series of comprehensive retrospective chemotherapy reviews (more than 4 patients per series) in Pagano et al,[31] Kharfan-Dabaja et al,[37] and most recently Laribi et al.[36] We have not re-created the information contained in these articles, but we have proon thr basis of comorbidity and transplant eligibility, as shown in Figure 2. When deciding which therapy is most appropriate, it is important to remember that, although those with early-stage and isolated cutaneous lesions often have very good performance status, the majority of patients have advanced disease (stage III to IV) as defined by Ann Arbor staging and a median age older than 60 years at diagnosis. Early and aggressive therapy should be considered for all patients with an appropriate Eastern Cooperative Oncology Group performance score and a low score on the Cumulative Illness Rating Scale (CIRS) or Charlson Comorbidity Index, given the predominance of relapse in bone marrow, skin, and the central nervous system (CNS). Special consideration and early referral should be made for transplantation and participation in clinical trials, where available.

First-line therapy

BPDCN is highly responsive to chemotherapy used for acute leukemia and aggressive lymphoma-based protocols, with complete response (CR) rates ranging from 40% to 90%.[31,38] Unfortunately, early relapse with chemotherapy alone is imminent (50% to 90%). Acute lymphoid leukemia (ALL) and non-Hodgkin lymphoma (NHL) regimens have predominated in the literature with reasonable success for inducing early CRs. However, with reclassification of this disease as having myeloid lineage and with the lack of curative effect using lymphoid therapies, AML-based regimens are becoming more widely reported. That said, few studies have included 10 or more patients in their series. Thus, although ALL, AML, and lymphoma regimens are described, the regimens used vary to such a degree by institutional preference and region that drawing conclusions regarding outcome are grossly underpowered.

Feuillard et al[12] reviewed a series of 23 patients from 12 centers over 8 years. The majority of patients had both skin (83%) and bone marrow (87%) involvement at diagnosis, median age was 69 years, and 3 children were included. Twenty-one of 23 patients were treated with CHOP-like chemotherapy consisting of an anthracycline/anthracenedione or cyclophosphamide/ifosfamide base with vincristine and etoposide or cytarabine and prednisone (n = 11) (note that CHOP is defined as cyclophosphamide, doxorubicin, vincristine,

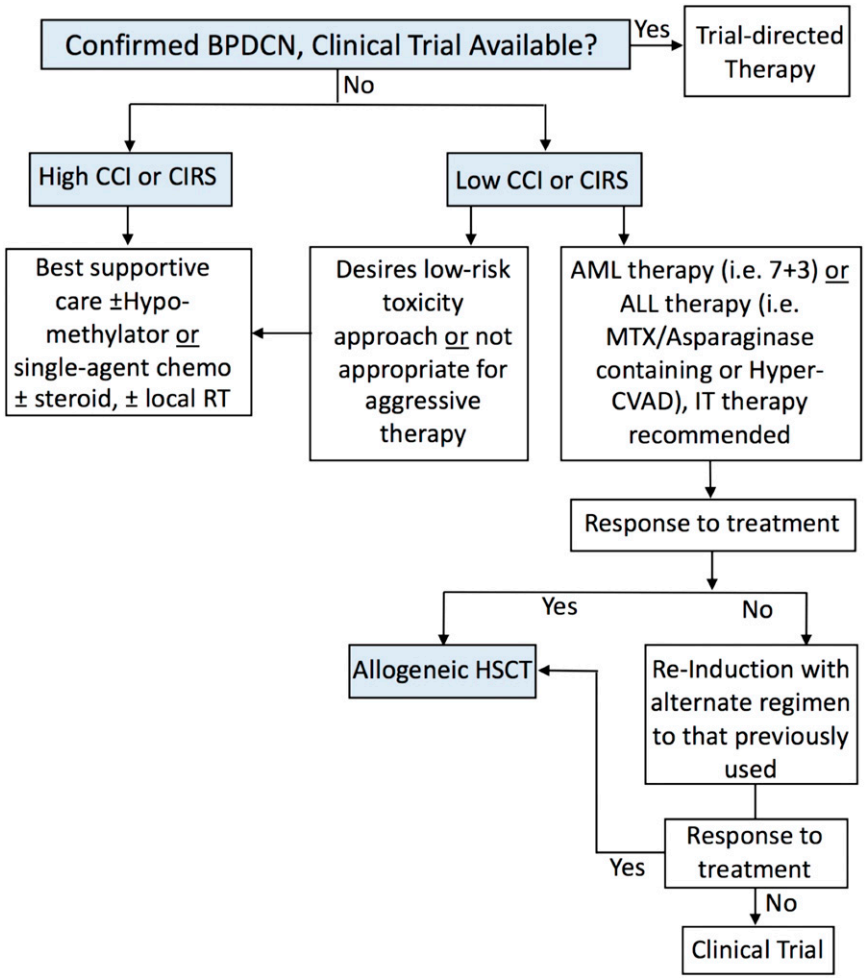

Figure 2. BPDCN treatment algorithm. Aggressive therapy, including allogeneic SCT, should be considered for all patients who have the performance status and comorbidity scores to support this rigorous process. Early referral for clinical trial is warranted and encouraged. We prefer to lead with an AML regimen; given the high rate of CNS relapse, intrathecal therapy (IT) is strongly recommended. CCI, Charlson Comorbidity Index; MTX, methotrexate.

and prednisone). CR was observed in 86% of patients; however, the rate of relapse was high in those achieving a CR with a median time to relapse of 9 months and OS of ~50% at 1 year and 25% at 2 years. Rates of skin, CNS, and bone marrow relapse were high, and only those patients who went on to receive allogeneic SCT (allo-SCT) after their first CR (CR1) had a durable remission.

In 2003 Reimer et al[39] presented the response rate and OS data for 93 evaluable patients amassed from publications dating from the description of BPDCN in 1994 through 2002. Reimer and colleagues separated patients into 4 groups of clinical treatment ranging in aggressiveness from dose-reduced CHOP through myeloablative protocols. Their age-adjusted evaluation clearly demonstrated the superiority of myeloablative chemotherapy followed by SCT consolidation in CR1 and highlighted (despite likely age bias in nonadjusted data) that more aggressive therapy, including acute leukemia protocols (CR, 94%) and ultimately myeloablative therapy, resulted in significant increase in the percentage and duration of CR and subsequently OS when compared with standard NHL CHOP (CR, 55%) or less than CHOP (CR, 68%). Interestingly, this group included patients treated with alternate cycles of cyclophosphamide, vincristine, doxorubicin, and dexamethasone followed by cycles of methotrexate and cytarabine (hyper-CVAD; n = 4; CR, 75%; median survival, more than 14 months), which we would regard as treatment reserved for aggressive NHL, along with their CHOP-like regimens. In a separate retrospective abstract by Pemmaraju et al,[40] 10 patients treated with hyper-CVAD demonstrated a CR rate of 90%, with a mean OS ranging from 23 months in patients with skin-only involvement to 29 months in patients with bone marrow involvement at diagnosis, suggesting a vast difference in response to CHOP and CHOP-like therapy.

What these data demonstrate is that more aggressive therapy with acute leukemia and aggressive NHL regimens results in higher CR rates, which translates to prolonged survival. What they do not define is which acute leukemia regimen, myeloid vs lymphoid, is superior. Pagano et al[31] focused on a minority of patients with BPDCN who presented with leukemic dissemination with high blast count and bone marrow involvement. They published a comparison of 41 patients, 26 treated with AML-like regimens and 15 with ALL-/lymphoma-like regimens. AML protocols included mitoxantrone, idarubicin, cytarabine, and etoposide (MICE); idarubicin, cytarabine, and etoposide (ICE); cytarabine and an anthracycline (standard 7+3); fludarabine, cytarabine, filgrastim, and idarubicin (FLAG); and FLAG-IDA (addition of Idarubicin). ALL and lymphoma regimens included hyper-CVAD; doxorubicin, vincristine, prednisone, and

sparaginase (GIMEMA AALL trial therapy); CHOP; or CHOP plus etoposide (CHOEP). Interestingly, CR in this series was low at 36%, with partial response (PR) in 19%. A higher percentage of patients treated with ALL or lymphoma regimens obtained CR (67%); however, relapse after ALL or lymphoma treatment was higher (60%) when compared with relapse in those patients treated with AML protocols (CR, 27%; relapse, 0). A statistically significant difference in OS was also observed, with median OS of 7.1 months in those treated with AML regimens vs 12.3 months in those treated with an ALL or lymphoma regimen. To complement these findings Martín-Martín et al[41] recently presented a study of 46 patients (9% children) treated with ALL, AML, or lymphoma regimens. CRs were obtained in the majority of patients (92%), despite the induction regimen, with a poor OS of 11 months; however, subanalysis demonstrated that patients treated with ALL-like regimens had better OS, confounded by the inclusion of children in this cohort, who can have prolonged survival to ALL regimens alone.

At this point, because there is no prospective trial to compare a standardized ALL with an AML regimen, data that suggest which type of regimen is superior in BPDCN should be viewed with caution. In the last 5 years in our institution, an equal number of patients have been treated using ALL, AML, aggressive NHL regimens, or best supportive care. All 3 of the initially mentioned regimens resulted in CRs, and many patients went on to receive either autologous SCT (auto-SCT) or allo-SCT. Now that BPDCN has been classified as having myeloid lineage, the coexistence of BPDCN with MDS or conversion to AML in 20% of patients and new genetic profiling demonstrating a number of AML/MDS mutations (NPM1, FLT3, TET2), our group has begun to favor the use of conventional AML regimens over other regimens.

Hematopoietic SCT

High-dose chemotherapy followed by allogeneic hematopoietic SCT (allo-SCT) offers the possibility of long-term remission and is potentially curative. Unfortunately, transplantation beyond CR1 may have an adverse impact on both OS and progression-free survival (PFS)[42-44]; thus, timing and patient selection remain important concerns. In their summary of the literature from 1994 to 2002, Reimer et al[39] reported on 10 patients: 6 patients treated with allo-SCT and 4 patients treated with autologous SCT (auto-SCT). Conditioning regimens included, at a minimum, cyclophosphamide and total body irradiation; however, median age at transplantation was 28.5 years, very different from the median age for the majority of patients affected by BPDCN. As noted above, myeloablative conditioning (MAC) followed by SCT consolidation significantly improved OS (31.5 months) compared with aggressive chemotherapy alone (OS, 13 months). Increased rate of relapse after auto-SCT was noted, but the study lacked power to truly elucidate inferiority compared with allo-SCT.

A larger retrospective series by Roos-Weil et al,[45] from the European Group for Blood and Marrow Transplantation hoped to address this question; unfortunately, despite having 139 patients who fulfilled initial inclusion criteria, only 39 patient had records that were sufficient for review. The majority (n = 34) had allo-SCTs. This study brought to light questions regarding the appropriate conditioning regimen: MAC (total body irradiation or busulfan plus cyclophosphamide [n = 17]) vs reduced-intensity conditioning (RIC: busulfan plus fludarabine-based regimen [n = 6]) and the source of allogeneic donor stem cells (related or unrelated) as it pertains to the ability to treat older adults with potentially curative therapy. Despite having used allo-SCT, 32% of their patient population experienced relapse at a median of 8 months posttransplant. Long-term survival was not observed in the RIC cohort because of complication by high rates of nonrelapse mortality. Three-year disease-free survival and OS for patients allografted in CR1 with MAC were 45% and 60%, respectively. Age (range, 10 to 64 years), donor stem cell source, and occurrence of graft-versus-host disease affected outcomes. In a study of the elderly with a median age of 67 years (range, 55 to 80 years), Dietrich et al[38] demonstrated successful RIC (submyeloablative busulfan, fludarabine, and cyclophosphamide) allo-SCT after induction with acute leukemia protocols in 2 of 4 patients with sustained CR at 19 and 57 months after allo-SCT. Interestingly, the latter patient was transplanted in second CR (CR2) from a mismatched unrelated donor; he was the oldest of the study participants but was affected by skin disease only. The authors suggest that the existence of a graft-versus-leukemia (GVL) effect was a component of the success observed in this patient. This topic, however, has yet to be fully explored.

More recently, a retrospective analysis of 25 patients from the Japan Society for Hematopoietic Cell Transplantation (15 auto-SCT and 11 allo-SCT) demonstrated a 4-year 82% OS rate and a 73% PFS after auto-SCT in CR1 compared with allo-SCT (69% OS and 60% PFS, respectively) with a median follow-up of 53.5 months.[42] Nearly 50% of patients undergoing allo-SCT in that study were older than 60 years of age, and they were also more likely to have a leukemic presentation. Allo-SCT patients conditioned with either MAC (n = 8) or RIC (n = 6) regimens had no significant difference in OS at 4 years (45% vs 60%, respectively).

Relapsed or refractory disease

Despite aggressive measures, relapse of BPDCN occurs in the majority of patients treated with chemotherapy alone (median, 3 to 9 months), and relapse after SCT occurs in roughly 30% of patients. Fortunately, in the transition to more aggressive chemotherapy and away from basic lymphoma regimens (eg, CHOP therapy), less resistance or fewer PRs are observed. In addition to relapse within bone marrow, which occurs in ~75% of patients, skin involvement (if present initially) will be uniformly involved at relapse.[12] Recent literature brought attention to the high percentage of primary CNS involvement (10%) at diagnosis or during relapse of disease (30%) observed in BPDCN, suggesting that the CNS is a sanctuary for cells in patients with primary leukemic presentation and perhaps all BPDCN, given the high incidence encountered in relapse.[31,46] In support of this concept, patients treated with ALL-type regimens, which include aggressive CNS prophylaxis followed by allo-SCT, seem to do better. Upon validation with an additional retrospective cohort of 23 patients, Martín-Martín et al[46] demonstrated that patients receiving prophylactic intrathecal therapy (5 of 23) had both prolonged CNS recurrence-free disease and OS. These results suggest that we should consider prophylactic intrathecal therapy with induction or select regimens in which high-dose CNS-penetrating chemotherapy is used in all cases of BPDCN.

In patients with relapse after allo-SCT, we have used a regimen of clofarabine alone followed by donor lymphocyte infusion (DLI), as has been described in other limited case series. Kaloyannidis et al[47] described the case of a 57-year-old male diagnosed with BPDCN who was initially treated with hyper-CVAD therapy resulting in CR, followed by RIC and related allo-SCT. At relapse, 26 months after transplant, interleukin-2 (IL-2) and interferon-α were used to evoke a GVL effect but no response was seen. The patient received 2 donor lymphocyte infusions (1×10^7/kg and 4×10^7/kg $CD3^+$ cells) 1 month apart with concurrent radiation to recurrent skin lesions and

obtained CR lasting 7 months at the time the study was published. Repetitive donor lymphocyte infusions have been documented by Steinberg et al[48] and Unteregger et al[49] with similar success. The first patient, a 41-year-old female, received 4 infusions of 0.1 to 1.12×10^8 $CD3^+$ cells per kilogram after either Linker's cycle 1A (similar to hyper-CVAD) alternating with high-dose cytarabine and mitoxantrone (HAM) or cyclophosphamide, etoposide, and clofarabine (CEC) therapy over the course of 1 year with CRs noted at each administration and with disease-free and symptom-free periods. The latter patient described by Unteregger received allo-SCT after MAC but relapsed 8 months after transplantation. In that patient, DLI was given 4 times in dose escalation starting with $CD3^+$ cells at 3×10^6/kg and then increasing to 1×10^7/kg, 3×10^7/kg, and 1×10^8/kg. This treatment regimen exerted a potent GVL effect; however, CR2 was complicated by severe chronic graft-versus-host disease; ultimately, the patient relapsed within 1 year. It would seem that although the GVL effect was potent, this load of $CD3^+$ cells was overwhelming and resulted in adverse effects. Given the GVL effect seen with DLI, and as suggested in these patients, one could more strongly consider RIC vs MAC regimens before allo-SCT with reasonable salvage using DLI.

Treatment of elderly, infirm, or transplant-ineligible patients

Few studies address the care of patients who are more infirm with a high CIRS or who are otherwise unfit for rigorous therapy such as transplantation. In that patient population, best supportive care should be stressed and palliative or hospice care enlisted early. As discussed by Reimer et al,[39] 28 elderly patients (median age, 79 years) were treated with less-than-CHOP therapy. Cyclophosphamide, vincristine, and prednisone (COP) was used most frequently in patients presenting with extracutaneous disease, followed by radiation therapy in limited cutaneous disease, and a smattering of other therapies, including hydroxyurea, 6-mercaptopurine-methotrexate-prednisone, etoposide-prednisone, or prednisone alone. CR was seen in 68% of the patients with a median OS of 9 months (range, 3 to 20 months). Sugimoto et al[50] presented a patient with limited-stage cutaneous BPDCN treated with dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC) chemotherapy, which was devised as a salvage chemotherapy for aggressive lymphoma, and local radiation therapy (RT) produced a durable response of more than 1 year, suggesting that this is a reasonable alternative to either chemotherapy alone or RT alone in elderly patients who are not candidates for SCT. Cutaneous BPDCN is responsive to RT, although responses are transient (range, 2 to 22 months), and the radiation dose is not standardized[39,51]; thus, RT alone should be reserved for those patients who are ineligible for concurrent chemotherapy or in whom quality of life is compromised primarily by skin involvement.

A single report of relapsed cutaneous BPDCN treated with pralatrexate, a promising agent in cutaneous T-cell lymphomas, resulted in regression of skin tumors and a sustained response of more than 6 months.[52] Most recently, 2 studies have shown utility of the hypomethylating agent azacitidine in BPDCN. Overlap with MDS, conversion to AML in a percentage of BPDCN patients, and recognition of novel mutations in DNA methylation genes (eg, TET2), all lend credibility to the use of epigenetic modification in BPDCN patients. Laribi et al[53] discussed 2 elderly patients (78 and 81 years of age) treated with first-line 5-azacitidine with excellent response after a single cycle; OS was complicated by infection. Khwaja et al[54] reported an additional series of 3 patients, age 75, 76, or 80 years, treated with azacitidine with or without local radiation resulting in PFS of 6, 7, and 24 months, respectively, and a median OS of 17 months. Limited toxicity was noted, which suggests that azacitidine is an appropriate therapy for patients unfit for more aggressive chemotherapy and, as often happens in our institution, serves as a bridge from relapsed disease to experimental therapy.

Novel therapy

Thus, it is clear that new approaches to therapy are needed. CD123, the α subunit of IL-3R (IL-3Rα) and marker of pDCs, is widely expressed in BPDCN.[28] The IL-3Rα chain has long been recognized as a unique marker in AML stem cells, which establishes it as a novel target for the myeloid lineage.[55] Increased expression of CD123/IL-3Rα has subsequently been demonstrated in related malignancies, including MDS, chronic myeloid leukemia, and aggressive NHLs, among others.[56-58] The α subunit of IL-3R is a type I transmembrane glycoprotein (cytokine receptor superfamily) that co-dimers with CD131 (common β chain). Leukemic blasts seem to differentially express IL-3Rα compared with normal stem cells,[55] and this may relate to differential sensitivity to therapy. Testa et al[59] demonstrated CR rates attained after intensive AML induction chemotherapy in 70% of patients (median duration of CR, >24 months) whose AML blasts expressed low IL-3Rα, whereas only 36% of those with high IL-3Rα achieved CR (median duration, 6 months). In an analogous situation, primary BPDCN blasts expressed this receptor and, in vitro, requireed IL-3 supplementation for survival and growth, which demonstrates the necessity of this pathway in BPDCN survival.[60] These data validate IL-3Rα (CD123) as a novel target in multiple hematologic malignancies, including BPDCN, and support development of strategies to augment signaling through this receptor.

SL-401 (formerly known as DT388-IL3) is a recombinant protein that consists of human IL-3 fused by acid-labile amino acids to diphtheria toxin truncated at its receptor-binding domain (AA 1-388). SL-401 internalization results from receptor-mediated binding to IL-3R and endocytosis. Cytotoxicity is mediated by the catalytic domain after processing through the endosome, which inactivates protein synthesis by adenosine 5′-diphosphate-ribosylating a diphthamide residue in elongation factor 2, resulting in cell lysis or apoptosis. Angelot-Delettra et al[61] demonstrated that SL-401 decreased viability in 75% of BPDCN primary cells compared with a 13% decrease in ALL and a 26% decrease in AML cells. The degree of cell killing was inversely proportional to the expression of the IL-3Rα chain (CD123) but not the IL-3Rβ chain (CD131). Finally, a significant OS of 58 ± 2 days was observed in an irradiated NSG xenograft model inoculated with BPDCN cells and treated with 5 days of intraperitoneal SL-401 2 μg/day vs controls treated with phosphate-buffered saline that survived only 17 ± 1 days.

The safety and efficacy of SL-401 has been demonstrated in phase 1 trials in relapsed or refractory AML and MDS first conducted at our center.[62] Frankel et al[62] treated 45 patients (5 de novo AML, 15 first-relapse AML, 8 second-relapse AML, 5 MDS) for a total of 46 courses; 2 patients had previous allogeneic bone marrow transplants. After the initial dose-escalation human study, the trial followed a standard 3+3 design assessing dose-limiting toxicity, including transaminitis (mild to moderate), vascular leak syndrome (hypoalbuminemia, edema, dyspnea, hypotension), and fever. The expanded phase 2 study treated 11 patients who had BPDCN with 1 course of therapy (1 course comprised 5 daily treatments of SL-401 12.5 μg/kg intravenously given over 15 minutes). Seven (78%) of 9 evaluable patients with BPDCN had objective responses, including 5 CRs and 2 PRs with a median response duration of 5 months (range, 1 to more than 20 months),[63] clearly, an encouraging response in this high-risk population. Importantly, the mechanism by which SL-401 kills is

unique in that it is not cell-cycle dependent, and thus can kill both proliferating and dormant malignant cells but spares normal marrow progenitors and is not subject to multidrug resistance mechanisms.[64] These data have led to a larger ongoing confirmatory registration study (NCT02113982).

Conclusion

Clinical presentation of BPDCN can be ambiguous and easily confused with neoplastic and nonneoplastic etiologies. This highlights the importance of having a reliable panel of markers that will not exclude BPDCN in the case of atypical immunophenotypic presentation yet will be specific enough to prevent rendering a diagnosis of acute leukemia of ambiguous lineage. Review of pathology, at the very least, should be undertaken by an experienced hematopathologist who can perform extensive immunophenotyping. If BPDCN is confirmed, referral to a center specializing in clinical trials with novel agents for this entity should be considered.

Our current treatment schema has been to provide a swift, dose-intense induction using an AML-based regimen to attain remission. Patients eligible for transplantation should be offered allo-SCT. Participation in a clinical trial upfront or at relapse is strongly recommended. In disease immediately refractory to primary AML-directed chemotherapy, an alternate aggressive regimen should be attempted; in such circumstances, we prefer to switch to an ALL-type regimen containing asparaginase, but other options may include clofarabine or methotrexate as the primary agents. In those with a high CIRS who are more infirmed, hypomethylating agents demonstrate promise and can be administered with supportive care in such patients. Local RT should be reserved for lesions affecting patient quality of life or with concurrent chemotherapy.

Although evaluation of complex chromosomal changes and gene modifications continues, neither a specific set of driver mutations nor a specific molecular focus with an existing targeted therapy have been identified in the current mutational landscape of BPDCN. Recent interest has been placed in a novel immunotherapy directed at the cancerous cells by targeting IL-3R, notably overexpressed in BPDCN as well as in other myeloid malignancies. This led to the development of SL-401 an IL-3–diphtheria toxin conjugate that has demonstrated promise for BPCDN in early-phase trials.[61-63,65] Thus, a variety of prospective phase trials are greatly needed to unravel the many questions that persist in the treatment of this aggressive and elusive neoplasm.

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