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Short Communication

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BPDCN: Review of Literature with recent updates on diagnosis and treatment modalities

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Short Communication

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare aggressive hematological malignancy arising from the precursors of plasmacytoid dendritic cells (professional type 1 interferon producing cells). Mature plasmacytoid dendritic cells share the common ancestor with Langerhans dendritic cells and interdigitating dendritic cells and are all arising from a CD34 positive myeloid stem cell. In vitro studies show that the precursor cells can be differentiated to plasmacytoid dendritic cells (PDC) upon IL-3 and CD40-L exposure. Not surprisingly, IL-3 receptor α (CD123) is a characteristic surface marker that distinguishes PDC from other macrophages and dendritic cell subtypes. Of note, follicular dendritic cells arise from mesenchymal stem cells (CD21 positive, CD35 positive) [1-2].

BPDCN is distinct from the aggregates of mature PCDs (CD56 negative) that are frequently present in association with chronic myeloid neoplasms and most commonly are identified in bone marrow biopsies in a patient with chronic myelomonocytic leukemia (CMML) [1,3]. No convincing data is suggesting that mature aggregates of PDCs progress to BPDCN. However, studies have shown that plasmacytoid dendritic cell proliferation associated with myeloid neoplasms like acute myeloid leukemia carry similar mutations as the myeloid blasts [4].

BPDCN is more common in men in their 60s and can arise de novo or in association with other hematological malignancies. A case of BPDCN has been reported as a progression of myelodysplastic syndrome [1,5]. The most common sites of involvement are skin, bone marrow, peripheral blood, and lymph nodes [1].

Morphologically, BPDCN is characterized by diffuse monomorphic proliferation of medium size blast-looking cells infiltrating the tissue. The cutaneous infiltrates usually involve the dermis and spares the epidermis and adnexal structures. Immunophenotypically, the neoplastic cells predominantly express surface markers: CD4, CD56, CD123, CD303, CD45RA, and nuclear/cytoplasmic markers: TDT, TCL-1, and TCF-4 among others (image 1A-1B). The tumor cells are negative for MPO, CD19, cCD3. It is important to note that many of the antigens including the

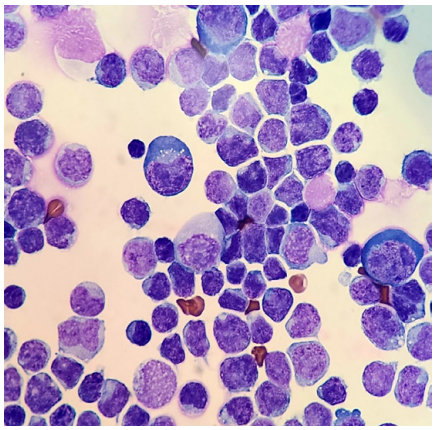

Figure 1A: Blastic plasmacytoid dendritic cell tumors presented as a neck mass. The tumor cells are medium to large blast cells with fine chromatin and cytoplasmic microvacuoles.

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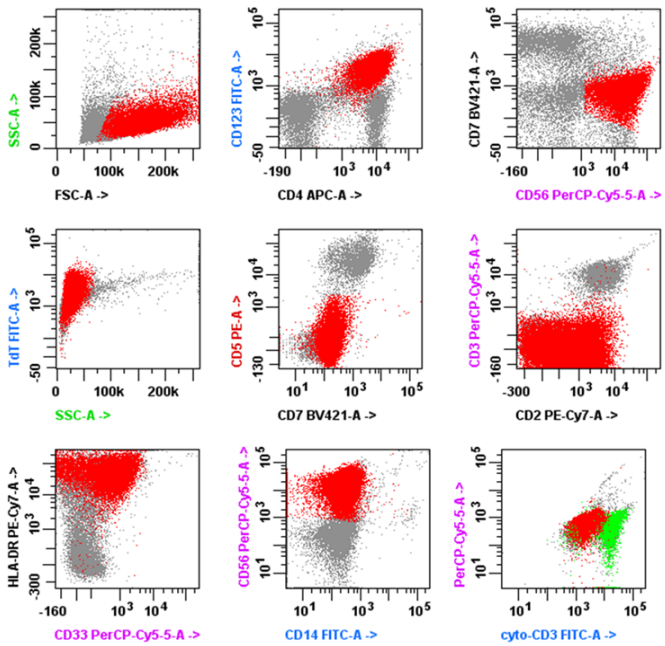

Figure 1B: By flowcytometry, the BPDCN (red population) cells are positive for CD123, Cd4, CD56, HLA-DR and TDT and are negative for CD14, CD7, CD5, CD33 and cytoplasmic CD3. The green population is the normal T cells (positive for cCD3).

characteristic TCL-1 in BPDCNs are also present on the mature counterpart cells. CD56 is the exception to the rule and is identified only on the neoplastic cells, e.g. BPDCN [2]. The Combination of flow cytometry and immunohistochemical stains on tissue biopsy can reliably identify and differentiate many cases of the BPDCNs from other myeloid and lymphoid neoplasms. Designed cocktails of CD123 (red) and TCF-4(brown) dual immunostain are shown to be highly sensitive and specific for blastic plasmacytoid dendritic cell neoplasm [6].

Genetic profile studies show some similarities between BPDCN and other acute and chronic myeloid neoplasms. The most common chromosomal abnormalities include complex karyotype and abnormalities involving 5q21 or 5q34 in 72% and 12p13 and 13q13-21 in 64% of the cases [1,7]. Multiple studies also show that TET-2 is the most common mutated gene identified in BPDCN cases. A recent study compared genetic landscapes of 7 cases of TET2 mutated AML with 6 BPDCN cases and concluded that none of the most highly enriched pathways (top 400 of 4762 interrogated) in both diseases were shared [8].

In one study, single-cell RNA sequencing data of 4 BPDCN cases were compared along with various types of dendritic cells and monocytes. The study shows that although malignant cells express some key B cell genetic marker (FCRLA, IGLL1, TCL1A, and IGLL5) they are most closely related to plasmacytoid dendritic cells [9]. Expression of some key B cell genetic markers by BPDCNs may partially explain the fact that traditionally lymphoblastic leukemia-oriented induction treatments were more effective than AML oriented therapies in both children and adults with BPDCN.

Two other very important studies on BPDCNs shed more light on unique pathophysiologic aspects of the disease. Cerbelli et al. studied the RNA interference screening data of the BPDCN cell lines and show that unlike other myeloid and lymphoid neoplasms, the E-box transcription factor TCF4 serves as a faithful diagnostic marker of BPDCN, and its downregulation caused the loss of the BPDCN-specific gene expression program and apoptosis [10]. Another beautiful RNA-sequencing study of 12 BPDCN samples and 4 plasmacytoid dendritic cells from healthy donors confirmed BCL2 overexpression in tumor cells [11].

BPDCN carries a poor prognosis with a median survival of 10-19.8 months irrespective of the initial pattern of the disease [1]. This data is extracted from the 2017 WHO classification of tumors of hematopoietic and lymphoid tissue. A more recent international multi-institutional study that was published in Oct. 2020, surveyed 398 adult BPDCN patients and compared different treatment strategies and the survival data. The data show after a median follow-up of 12 months, the median overall survival (OS) was 18 months [7].

The various treatment regimens in the above study include non-Hodgkin lymphomas (NHL)–like regimens in (32.8%) of patients and acute leukemia (AL)–like regimens in (23.5%) of patients. In (15.5%) and (4.1%) patients, chemotherapy was followed by allogeneic and autologous hematopoietic stem cell transplantation (HSCT), respectively. 6.9% of patients received radiotherapy and 1.5% received new agents (see below), while 15.7% received palliative care. The data show patients who received NHL/AL-like regimens, followed by allogeneic HSCT, had the best outcome; median OS was not reached. OS was 65 months for patients who underwent autologous HSCT; 18 months and 14 months, respectively, for those treated with AL-like and NHL-like regimens without consolidation; and 4 months for those receiving palliative care ($P < .001$) [7].

In the past few years, there has been a rise in new therapeutic modalities in the treatment of BPDCNs. The most important categories include Anti-CD123 therapies and Anti-BCL-2 therapies. These methods are still in various stages of clinical trials, but the data are promising.

Tagraxofusp, (SL-401) Tagraxofusp -erzs (Elzonris®) is a Recombinant Diphtheria Toxin and Interleukin-3 and is the first FDA approved

CD123-targeted therapy of BPDCN in patients aged 2 years and older. The base of the drug is a truncated diphtheria payload in which one part of the diphtheria toxin is replaced with a human recombinant IL-3–fused protein. The phase 1 study of 9 BPDCN cases with SL-401 shows 78% of BPDCN patients had major responses after a single course of SL-401. The median duration of responses was 5 months (range, 1-20+ months) and the phase 2 study reported 79% Complete remission rate in the first line and 31% complete remission rate in relapsed/refractory patients. Results from stage 3 and 4 have not yet been published [12-15].

It is important to know that SL-401 in combination with other therapeutic agents is being investigated as a treatment modality for other hematologic malignancies including multiple myeloma, myelodysplastic syndrome, acute myelogenous leukemia (AML), CMML, and myelofibrosis [15].

Multiple other anti CD123 targeted therapies including a humanized anti CD123 monoclonal antibodies are in clinical trials. IMGN632 is a humanized antibody-drug conjugate that consists of a humanized anti-CD123 (Ig)G1 monoclonal antibody conjugated to a cytotoxic, DNA-alkylating cytotoxic payload of the recently developed IGN (indolinobenzodiazepine pseudodimer) class, with potential antineoplastic activity. Phase 1/2 clinical trial data on the efficacy of the drug on relapsed/refractory BPDCN cases show 3 of 9 (33%) of patients achieved a response after 1-2 doses of the drug [16-19].

XmAb14045 is a tumor-targeted antibody that contains both a CD123 binding domain and a cytotoxic T-cell binding domain (CD3). Phase 1 clinical trial for the treatment of CD123-expressing hematologic malignancies has started however, this drug is on partial hold on due to safety concerns [16,20].

In another effort to target CD123, chimeric antigen receptor (CAR) T cells were used. With the help of Retrovirus or lentivirus viral vectors, CD123 CAR T cells were designed by the fusion of parts of the anti CD123 antibody to T-cell signaling domains. The investigators show that CD123R CAR T cells (using retrovirus vector) demonstrated effective cytotoxicity against BPDCN cell lines. *In vivo* humanized mice models also revealed lower tumor burden upon administration of CD123L CAR T cells (using lentivirus) [21]. A phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT02159495) is recruiting cases to study the side effects and best dose of CD123 CAR T cells for PBDCN and AML patients. Patients are first subjected to lymphodepletion via chemotherapy regimens followed by a dose of CD123 CAR T cells. Patients with evidence of disease at > 28 days and CD123 antigen expression may receive a second dose. The results of this study are not published yet [22].

A recent single-institution retrospective study of 49 BPDCN cases shows no significant overall survival (OS) difference among the patients treated SL-401 (12 cases) versus other chemotherapies as a first-line treatment (37 cases). The same study shows that patients who received allogeneic stem cell transplant (allo-SCT) had significantly longer OS. The study supports using SL-401 or hyper-CVAD as the first-line treatments followed by consolidation with allo-SCT in the eligible responders to induction therapy to further improve survival outcomes in BPDCN patients [23].

In a different approach, after it was shown that BPDCN tumor cells overexpress BCL-2 and are dependent on BCL-2, anti-BCL-2 (venetoclax) therapies are investigated. Animal models with transplanted human BPDCN tumors were treated with BCL-2 inhibitor, venetoclax and show decreased disease burden in the bone marrow and blood, and cases of refractory/relapsed BPDCN show a significant response to the addition of venetoclax therapy (venetoclax and azacytidine). Published case reports reveal that patients with refractory/relapsed BPDCN show significant response upon the addition of venetoclax therapy [11,24-26].

Phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT03485547) started in April 2018 in recruiting cases to test the safety and standard dose for the treatment of BPDCN. Data from the clinical trial is not published yet and Venetoclax is not yet FDA approved as a treatment of BPDCN [27].

Conclusion

In conclusion, BPDCN is an aggressive hematologic malignancy with a unique immunophenotypical and genetic profile. It appears that ALL-based induction chemotherapy regimens followed by allogeneic bone marrow transplant offers better survival to patients. Recently, hypomethylating agents (azacytidine), anti CD123 directed immunotherapies including the FDA approved anti CD123 drug, Elzonris®, and the BCL-2 inhibitor venetoclax showed promising clinical activity.

Conflict of Interest

None Declared.

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