

TO THE EDITOR:

Blastic plasmocitoid dendritic cell neoplasm with leukemic spread: a GIMEMA survey

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy arising from the precursors of plasmacytoid dendritic cells (pDCs) with a high frequency of primary cutaneous involvement and dissemination to bone marrow with disease progression.^{1,2} In 2016, in the World Health Organization classification update of acute myeloid leukemia (AML), the disease has been given a separate category under myeloid neoplasms.^{3,4}

Cutaneous involvement is often the first manifestation of BPDCN, with subsequent or simultaneous spread to bone marrow. Leukemia as the first presenting symptom is a sporadic finding and can masquerade as acute undifferentiated leukemia.^{1,2,5,6} The overall incidence of BPDCN is extremely low, accounting for 0.44% of all hematologic malignancies and 0.7% of cutaneous lymphomas.¹ BPDCN affects males predominantly (male:female ratio of 3:1), with 61 years as the median age of diagnosis.^{1,2,7-9} It is exceedingly rare to see BPDCN with a leukemic presentation (blastic plasmacytoid dendritic cell leukemia [BPDCL]) at the onset, and the leukemic form of the disease is reported in 1% of cases of acute leukemia.^{5,6}

With the improvement in the understanding of the disease biology, it has become crucial to extend the epidemiology of this life-threatening hematologic malignancy. To date, there have been no formal studies on the epidemiology of BPDCL to our knowledge.

In such a scenario, the Gruppo Italiano Malattie EMatologiche dell'Adulto (GIMEMA) group performed a cross-sectional survey to assess hematologists' practices regarding the management of BPDCN with a leukemic presentation in Italy. The participating centers were asked to provide aggregate information on clinical and laboratory data and therapeutic approaches for patients with BPDCN diagnosed from January 2018 to December 2019 (Table 1). The attention was focused on tools to make diagnosis and timely; also, information was collected about the incidence of new cases of AML. Survey data were collected and managed using the REDCap electronic data capture tools hosted at GIMEMA.¹⁰ Survey results were exported for analysis at the end of May 2020 and analyzed using the R Core Team (2020).

Among 124 centers referring to GIMEMA, 39 compiled the survey for BPDCN diagnosis. Overall, 68 cases of BPDCN were diagnosed during the study period. We confirmed the rarity of the leukemic form, with 24 new cases of BPDCL identified per year. BPDCL accounts for 1.8% of all new diagnoses of AML (Table 2). The clinical presentation was in agreement with the classical well-known features. Of note, 6 patients had neuromeningeal involvement (12.5%), 4 cases at diagnosis of disease and 2 at relapse, confirming the data published in major studies that reported central nervous system (CNS) involvement in 4% to 9% of patients at diagnosis and 17% to 33% at relapse.^{1,2,7,8}

Diagnosis of BPDCL can be difficult because of clinical, biological, and phenotypic heterogeneity, with overlapping features with other hematologic malignancies. By now, it is well known that

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Requests for data sharing may be submitted to Caterina Giovanna Valentini (c.giovannavalentini@gmail.com).

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Table 1. Cross-sectional survey

	Replies	Percentages
Do you have a BPDCN immunophenotypic panel (CD4-CD56-CD123-BDCA2/CD303) that you use on a regular basis?	✓ Yes ✓ No ✓ Only in selected cases	33 17 50
Your immunophenotypic panel includes markers that exclude BPDCN, such as: CD3, CD19, myeloperoxidase, CD11c, CD14, CD64?	✓ Yes ✓ No	0 100
Does your histochemical panel include CD4, CD56, CD123, BDCA2, TCL1, or excludes: MPO, CD3, CD20 or CD19, CD163, Lysozima?	✓ Yes ✓ No	57 43
Do you routinely perform CD123 in acute myeloid leukemia at diagnosis?	✓ Yes ✓ No	59 41
Do you routinely perform a cerebral fluid exam at diagnosis?	✓ Yes ✓ No	70 30
Do you use a different therapeutic approach between BPDCN patients with leukemic spread or without?	✓ Yes ✓ No	26 74
What type of chemotherapy do you use? AML-oriented, ALL-oriented or NHL-oriented?	✓ AML-like ✓ ALL-like ✓ NHL-like	39 44 17

NHL, non-Hodgkin lymphoma.

immunophenotyping is mandatory to confirm the diagnosis. It relies on strict immunophenotypic criteria by immunocytochemistry (IHC) and/or flow cytometry.¹⁻⁴ The minimum requirement for diagnosis is a CD4⁺, CD56⁺, and CD123⁺ phenotype associated with negativity

Table 2. Clinical, laboratory, and therapeutic features of 48 cases of BPDCN with leukemic spread (BPDCL) diagnosed in 39 Italian centers referring to the GIMEMA group for the period 2018 to 2019

	N (%)
New diagnosis of AML	2686
BPDCN	68
With leukemic spread (BPDCL)	48 (71)
Without leukemic spread	20 (29)
BPDCL	48/2686 (1.8)
FLT-ITD*	3 (6.3)
NPM1-ITD*	2 (4.2)
Males/females (ratio)	36/12 (3/1)
Age (y)	16 (33.3)
<60	32 (66.7)
>60	
Time at diagnosis (wk)	24 (50)
<4	24 (50)
>4	
CNS involvement	6 (12.5)
At onset	4
At relapse	2
Therapeutical approaches	44†
Conventional chemotherapy	39 (88.6)
BSC	5 (11.4)
CR after chemotherapy	21/39 (54)
alloHSCT	20/44 (45)
OS (mo)	10 (20.8)
<6	19 (39.6)
6-12	19 (39.6)
>12	

BSC, best supportive care.

*One patient presented both FLT3/NPM mutation.

†Four early deaths (only 44 of 48 cases evaluable).

for lineage-specific (Lin⁻) markers; the diagnosis is further supported by expression of BDCA2/CD303 and other pDC-associated antigens (eg, TCL1, CD2AP, and E2-2/TCF4).⁵ Diagnosis of BPDCN can be particularly challenging when tumor cells do not completely fit the typical CD4⁺, CD56⁺, HLA-DR, CD123⁺, and (Lin⁻) profile. Moreover, aberrant myeloid and lymphoid antigen expression is frequently observed.^{1,11,12} From the analysis of our data, it emerges that half of the Italian hematologists (50%) performed a flow cytometry panel including CD123, CD303, and TCL1 only in selected cases after the exclusion of other forms of acute leukemia. Regrettably, this often leads to a 1-month delay on diagnosis and subsequent treatment. Conversely, cerebral fluid evaluation has been performed in most patients, regardless of neurologic symptoms (Table 2).

Cytogenetics and molecular tests were performed routinely, revealing abnormalities classically reported in BPDCN, typically nonspecific.¹

BPDCL has a highly aggressive clinical course with a dismal prognosis, irrespective of the initial pattern of disease. Treatment commonly included intensive chemotherapy regimens, which are generally reserved for the management of acute leukemia. There is no standardized therapeutic approach. Some patients have shown better response with an acute lymphoblastic leukemia (ALL)-like regimen, whereas others have shown good response with an AML-like regimen.^{1,2} Whatever be the initial response, the disease has a very high propensity to relapse, especially with CNS involvement, because CNS appears to be a sanctuary site during the systemic therapies. This warrants prophylactic intrathecal therapy as well. Remissions are usually short term, with a median overall survival (OS) of 12 to 18 months.^{7,8} Recent data suggest that the median OS of patients who received allo-hematopoietic stem cell transplantation (HSCT; mostly in patients in first complete remission [CR]) were superior to those who received chemotherapy alone.¹³

Our data revealed heterogeneity in therapeutic options among the Italian centers, without a clear indication for the first-line chemotherapy. When we analyzed pretransplant treatment, the highest CR rates were observed after leukemia-like regimens, with no difference

observed between the AML-like or ALL-like regimen. Of note, 60% of our patients survived less than 12 months (Table 2). We confirmed that the achievement of CR after first-line treatment is required to obtain long survival and that prolonged survival is observed only in patients receiving allo-HSCT during the first CR. Patients refractory to or relapsing after this first treatment do not respond easily to further therapy, and the success of second-line therapy is very low, even when an allo-HSCT is performed in the subsequent response.

Our survey endorses that BPDCL with leukemic presentation is a rare disease, accounting for 1.8% of all new diagnoses of AML. We present a snapshot of Italian clinical management of BPDCL, highlighting criteria that should alert the physicians to the possibility of such a diagnosis and hurried investigation of pDC marker expression to confirm it. We stress that BPDCL presentation in the hematology laboratory is quite heterogeneous, and cytogenetics and mutation profiles are not specific. Nevertheless, confirmation of a new diagnosis can pose a significant challenge in many cases, because most hematologists will usually encounter it only once or twice a year or even less (our experience amounts of 0.8 cases/y per center). Therefore, the clinician must have a high degree of suspicion, particularly in patients presenting with cytopenias and skin lesions. The diagnosis of BPDCL can be accurately established by a specific flow cytometry panel.⁷⁻¹² In Italian centers, unfortunately, this diagnostic study is not performed routinely at the onset of disease, but only in selected cases. This results in a delay in diagnosis and following treatment in about half of the patients. Regarding this topic, we suggest that a central revision of cases may be helpful to confirm the diagnosis and prompt therapies.

After diagnosis, the question of the best treatment is still a major issue for physicians. Leukemia-like regimens have shown their efficacy, although toxicity in the population of elderly remains a challenge. Hypomethylating agents, anti-CD123-directed immunotherapies, and the BCL-2 inhibitor venetoclax showed promising single-agent clinical activity.^{1,14} In particular, the finding of overexpression of CD123, also known as interleukin-3 receptor α -chain, in several hematologic malignancies, including BPDCL and AML, has been of great interest.

Tagraxofusp is the first targeted therapy directed to CD123 that was approved by the U.S. Food and Drug Administration for the treatment of BPDCL.¹⁵ Since its approval in December 2018, tagraxofusp has changed the therapeutic landscape for this disease and has been an integral part of treatment of BPDCL patients ages 2 and older.^{16,17} It is presently under evaluation in several ongoing clinical trials as a single drug (NCT04317781) or in association with other agents (NCT04216524 and NCT03113643). Currently, newly diagnosed patients should be considered for upfront treatment with CD123-based therapy followed by HSCT in CR1, unless contraindicated. In 2020, a novel CD123-targeted antibody–drug conjugate achieved FDA breakthrough designation for relapsed and refractory cases of BDCN.¹⁸ Further early immunologic investigation in therapeutic options for recurrent BPDCL include anti-CD123 chimeric antigen receptor T-cell therapy (NCT02159495 and NCT03203369), which shall provide further data over the coming years.

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