Blastic plasmacytoid dendritic cell neoplasm with leukemic presentation: an Italian multicenter study

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ABSTRACT

The objective of this study was to evaluate the clinical features, prognostic factors, and efficacy of treatments in patients with blastic plasmacytoid dendritic cell neoplasm with a leukemic presentation at onset of the disease. In order to do this, a retrospective multicenter study was performed from 2005-2011 in 28 Italian hematology divisions in which 43 cases were collected. Forty-one patients received an induction therapy, consisting of an acute myeloid leukemia-type regimen in 26 patients (60%) and acute lymphoid leukemia/lymphoma-type regimen in 15 patients (35%). Six patients (14%) underwent allogeneic hematopoietic stem cell transplantation. Seventeen patients (41%) achieved a complete remission: seven after acute myeloid leukemia-type treatment and 10 after an acute lymphoid leukemia/lymphoma-type regimen, with a significant advantage for acute lymphoid leukemia/lymphoma-type chemotherapy (P=0.02). Relapse occurred in six of the 17 patients (35%) who achieved complete remission, more frequently after acute lymphoid leukemia/lymphoma-type chemotherapy. The median overall survival was 8.7 months (range, 0.2-32.9). The patients treated with an acute myeloid leukemia-type regimen had an overall survival of 7.1 months (range, 0.2-19.5), whereas that of the patients receiving acute lymphoid leukemia/lymphoma-type chemotherapy was 12.3 months (range, 1-32.9) (P=0.02). The median overall survival of the allogeneic hematopoietic stem cell transplant recipients was 22.7 months (range, 12-32.9), and these patients had a significant survival advantage compared to the non-transplanted patients (median 7.1 months, 0.2-21.3; P=0.03). In conclusion, blastic plasmacytoid dendritic cell neoplasm with bone-marrow involvement is an aggressive subtype of high-risk acute leukemia. The rarity of this disease does not enable prospective clinical trials to identify the better therapeutic strategy, which, at present, is based on clinicians' experience.

Introduction

Recently classified among "acute myeloid leukemia (AML) and related precursor neoplasms" in the 2008 World Health Organization (WHO) classification, blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare subtype of acute leukemia characterized by the clonal proliferation of precursors of plasmacytoid dendritic cells, also known as professional type I interferon-producing cells or plasmacytoid monocytes.[1-3]

There are no formal studies on the incidence of BPDCN in the general population. The few available data reported indicate that its overall incidence is extremely low, accounting for 0.44% of all hematologic malignancies[4] and 0.7% of cutaneous lymphomas.[5] Moreover, the leukemic form of disease is a rare phenomenon, representing <1% of cases of acute leukemia.[6] BPDCN predominantly affects males, with a sex ratio of 3:1, and generally occurs in the elderly, with the median age of affected patients being in the sixth decade of life.[7,8]

BPDCN is characterized by an aggressive behavior with rapid systemic dissemination, despite the often indolent clinical presentation, with apparently isolated cutaneous involvement in the form of solitary or multiple lesions. More rarely, patients show features of an acute leukemia with systemic

 doi:10.3324/haematol.2012.072645
Manuscript received on June 21, 2012. Manuscript accepted on September 26, 2012.
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involvement from the beginning without skin manifestations. Most of these patients present with cytopenia, particularly thrombocytopenia, associated with extremely variable rates of bone marrow infiltration.[9,10] Despite an initial response to systemic chemotherapy, the disease regularly relapses and the median overall survival is dismal (12-14 months).[9,12,13]

The few series published so far rarely exceed 20 cases, and most of them include cases with exclusive or predominant cutaneous involvement, making it difficult to define the biological, clinical and prognostic features of the disease and, in particular, of the leukemic form.

Given its rarity and only recent recognition as a distinct clinico-pathological entity, no standardized therapeutic approach has been established for BPDCN and the optimal therapy remains to be defined. The purpose of this multicenter study was to gather information on BPDCN cases with a leukemic presentation diagnosed and treated in Italy since 2005 in order to evaluate the diagnostic criteria, the clinical and prognostic features, and the outcome of different therapeutic approaches.

Design and Methods

A retrospective study was conducted among patients with BPDCN with a leukemic presentation at the onset observed in *Gruppo Italiano Malattie EMatologiche dell'Adulto* (GIMEMA) centers reporting to the Acute Leukemia Working Party. The participating centers enrolled consecutively diagnosed cases from January 2005 to December 2011 and were asked to provide information on clinical and laboratory data for each patient from the onset of disease to last follow-up or until death. More specifically, the information requested included date of diagnosis, age, race, gender, other clinical presentations of the disease (i.e. cutaneous manifestations, hepato-splenomegaly, extramedullary sites of disease), serum biochemistry, hematologic parameters, evaluation of the bone marrow blast infiltrate with immunophenotypic analysis by flow-cytometry and immunohistochemistry, conventional cytogenetic analysis and/or fluorescence *in situ* hybridization (FISH) examination, molecular analysis of *NPM/FLT3* mutations as well as data from additional instrumental examinations and biopsies performed to confirm the diagnosis and to detect extramedullary involvement. Finally, information was requested about the patients' treatment, particularly regarding the induction regimen applied and, when performed, hematopoietic stem cell transplantation (HSCT), treatment outcomes, relapses or deaths, and causes of death. Registered data were managed in accordance with the Italian Data Protection (Privacy) law. The study was approved by the ethics committee of each participating site (P/484/CE/2010).

The diagnosis of BPDCN was made by the pathologist of each participating center; subsequently, tissue specimens were centrally reviewed by two of the authors (FF and SP). Inclusion criteria for diagnosis of BPDCN were expression by blastic tumor cells of CD4 and/or CD56, coupled with at least one plasmacytoid dendritic cell-associated antigen among CD123, TCL1, CD2AP and BDCA2/CD303, in the absence of any of the lineage-specific markers for B cells (CD20, CD79a), T cells (CD3), myeloid cells (myeloperoxidase) and monocytes (CD11c, CD163, lysozyme). Furthermore, the diagnosis of BPDCN required the lack of CD34 expression (Table 1). All immunostains were performed on formalin-fixed, paraffin-embedded tissue sections, using the following reagents: CD4 (4B12, Novocastra Laboratories, Ltd., Newcastle upon Tyne, UK), CD56 (123C3.D5, Thermoscientific, Fremont, CA, USA), CD123 (7G3, BD Biosciences, San Josè, CA, USA), TCL1 (27D6/20, Medical & Biological Laboratories, Naka-ku Nagaya, Japan), CD2AP (B-4, Santa Cruz Biotechnology, Santa Cruz, CA, USA), CD303/BDCA2 (124B3.13, Dendritics, Lyon, France), CD79a (HM47/A9, Thermoscientific), CD20 (L26, Novocastra Laboratories), CD3 (SP7, Thermoscientific), myeloperoxidase (Rabbit polyclonal, Dako, Glostrup, Denmark), CD11c (5D11, Monosan, DBA-Italia, Milan, Italy), CD163 (10D6, Thermo scientific), Lysozyme (Rabbit polyclonal, Dako), and CD34 (QBEND/10, Thermoscientific) (Table 1).

Table 1. Markers useful for confirming or excluding a diagnosis of BPDCN on formalin-fixed, paraffin-embedded sections. Values between brackets refer to the percentages of antigen expression in a series of more than 300 published cases.[37]

Antigens that confirm the diagnosis of BPDCN	Antigens that exclude the diagnosis of BPDCN
CD4 (94.6%)	CD3
CD56 (96.5%)	CD11c
CD123 (95.3%)	CD20
TCL1 (89.3%)	CD34
CD2AP (80.5%)	CD79a
BDCA2/CD303 (75.0%)	CD163
	Lysozyme
	Myeloperoxidase

Clinical data were evaluated by the diagnostic committee (LP, CGV, and AP). Only patients diagnosed with BPDCN according to the WHO 2008 classification and who had bone marrow involvement consistent with leukemia were included in the study.[1]

The last follow up was assessed as of December 31st, 2011. According to previously standardized criteria,[14] complete remission was defined as the contemporary: (i) absence of blasts in the peripheral blood; (ii) <5% blasts in the bone marrow; and (iii) a hemoglobin level of ≥9 g/dL with no red blood cell transfusions for at least 2 weeks, an absolute neutrophil counts ≥1.5×10^9/L, and a platelet count ≥100×10^9/L without platelet transfusions for at least 1 week, without residual evidence of extramedullary leukemia. Patients with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone-marrow aspirate were considered in partial remission. All patients who did not achieve a complete or partial remission were considered non-responders with resistant disease. Relapse after complete remission was defined as a reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow and/or a reappearance of extramedullary disease.

Statistical methods

The overall survival was measured for all patients from the date of diagnosis to death or to last follow-up. The disease-free survival was measured only for patients who achieved a complete remission and was defined as the time from first documentation of complete remission to the time of relapse, censoring the data at the time of the last follow-up visit or death.

Differences in proportions were estimated by Fisher's exact test or the χ^2 test (P values <0.05 considered statistically significant). Relative risks with their 95% confidence intervals (CI) were calculated using 2x2 contingency tables.

All survival data were analyzed using the Kaplan–Meier method to estimate the probabilities of death (overall survival) and relapse (disease-free survival) as a function of time; univariate comparisons were carried out with the log-rank test (P values <0.05 considered statistically significant). Multivariate analysis was per-

formed to estimate the relative risk of death as a hazard ratio (HR) with the use of a Cox proportional hazards regression model.

Statistical analyses were performed using GraphPad PRISM 5.0 software for the univariate methods and Intercooled Stata program, version 11, for Windows for the multivariate methods.

Results

Sixty-eight cases of possible BPDCN were collected from 28 Italian hematology centers. Of these, 25 (37%) were excluded after a clinical evaluation or histopathological review, since they did not fulfill the criteria for study inclusion (3 cases of AML, 5 acute monoblastic leukemia, 2 leukemias of ambiguous lineage, 1 plasmacellular leukemia, 2 cases of unclassified leukemia, 1 T-NK leukemia, 2 cases of BPDCN with only skin localization, 1 pediatric case; in 4 cases the data available in the medical records were insufficient, and the other 4 were excluded because of lack of central review). The remaining 43 cases (63%) were classified as BPDCN; their main laboratory and clinical features are reported in Table 2.

Clinical characteristics

The majority of the patients were males (males/females 31/12); the median age of all the patients was 68 years (range, 20-80).

The median bone marrow infiltration was 73%, with a fair residual bone marrow function; 21 patients (49%) presented with a median percentage of blasts of 39% (range, 12-97) and a median white blood cell count of 13.9×10^9/L (range, 2.3-300). Skin lesions were observed at diagnosis in 33 cases (77%) and all were histologically confirmed as disease sites; the lesions varied in size and morphology (nodules, patch-plaque or bruise-like areas) and were distributed widely, with multifocal cutaneous involvement in most cases and solitary manifestations in only five patients.

Lymphadenopathy was identified in 24 cases (56%), splenomegaly in 19 (44%), and hepatomegaly in 18 (42%). Involvement of other extramedullary sites was found in nine patients (21%): central nervous system (CNS, n=4), pleural fluid (n=3), paranasal cavities (n=1), and paravertebral involvement (n=1).

Of note, in ten cases (23%) BPDCN was diagnosed as a secondary leukemia: in four patients as a post-myelodysplastic syndrome (MDS) and in six as a therapy-related leukemia after treatment for non-Hodgkin's lymphoma (2 patients), prostate cancer (2 patients), acute lymphoblastic leukemia (ALL) and breast cancer (1 patient each). In detail, in three cases the BPDCN was preceded by a low-risk MDS, such as refractory anemia, whereas only one patient had a prior high-risk MDS (refractory anemia with excess blasts-2). All four of these patients received only supportive therapy with blood transfusions and erythropoietin. The median time of latency between the myelodysplastic phase and the onset of BPDCN was 3.5 years (range, 1-4). As for the therapy-related forms of BPDCN, all six affected patients received chemotherapy for the first neoplasm; the two patients with prostate cancer also received radiotherapy; the patient with a previous non-Hodgkin's lymphoma 4 years ago underwent a double autologous HSCT. The median time of latency between the first exposure to cytotoxic treatment for the primary neoplasm and the diagnosis of BPDCN was 5 years (range, 1-15).

Table 2. Main laboratory and clinical characteristics of the study population (43 patients).

Demographic and laboratory features (all patients)	Median value (range) or N. (%)
Age (years)	68 (20-80)
Gender (male/female, ratio)	31/12 (2.6/1)
ECOG performance status	0-1 : 31 patients (72) 2-5: 12 patients (28)
Type	*De novo*: 33 patients (77) Therapy-related: 6 patients (14) Post myelodysplastic syndrome: 4 patients (9)
Hemoglobin (g/dL)	10 (6-14)
White blood cell count ($x10^9$/L)	5.8 (0.55-300)
Platelet count ($x10^9$/L)	68 (1-290)
Blast cells in peripheral blood	21 patients
Lactate dehydrogenase (IU/ L)	476 (177-2724)
Creatinine (mg/dL)	1.1 (0.6-6.8)
Uric acid (mg/dL)	6 (0.5-11.7)
Bone marrow blast infiltration (%)	73 (20-99)

Clinical features (all patients)	N. (%)
Skin lesions	33 (77)
Lymphadenopathies	24 (56)
Splenomegaly	19 (44)
Hepatomegaly	18 (42)
Extramedullary localizations (other than skin)*	9 (21)

Cytogenetic/molecular features	N. (%)
Cytogenetic risk (28 patients)**	28 (65%)
Normal karyotype	13
Abnormal [10 patients complex karyotype, 1 patient -7/-5, 1 patient del(5q)]	12
No metaphases	3
Molecular studies (14 patients)	14 (32%) All patients *NPM* wildtype 3 *FLT3*- ITD

*at diagnosis 4 CNS, 3 pleural fluid, 1 paranasal cavities, 1 paravertebral involvement; **evaluated by standard cytogenetic examination and/or FISH.

Conventional cytogenetic analysis of bone marrow samples was performed in 28 patients (65%), with the addition of FISH in four (Table 1), revealing clonal chromosomal aberrations in 12 cases. Molecular studies were carried out in only 14 cases (32%): all patients had germline *NPM1* genes; three patients with a normal karyotype had the *FLT3*-ITD mutation (Table 1).

Treatment

Two patients died early, allowing administration of only supportive therapy and hydroxyurea. Forty-one patients were evaluable for efficacy of induction therapy with an acute leukemia-like regimen, consisting of AML-type therapy in 26 cases (60%) and of ALL/lymphoma-type therapy in 15 (35%) (Table 2).

The AML-type therapeutic protocols were MICE

(mitoxantrone, cytarabine, etoposide; 9 patients), ICE (idarubicin, cytarabine, etoposide; 8 patients), anthracycline plus cytarabine in the standard 3+7 fashion (5 patients), FLAG and FLAG-IDA (fludarabine, cytarabine, filgrastim, idarubicin; 4 patients). The ALL/lymphoma-type therapeutic protocols were hyper-CVAD (alternate cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate and cytarabine; 5 patients), GIMEMA ALL trial therapy (association of doxorubicin, vincristine, prednisone, asparaginase; 4 patients), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; 4 patients) and CHOEP (CHOP plus etoposide; 2 patients).

Allogeneic HSCT was performed in six cases (14%) at some point in the management of the disease. In five patients (3 in complete remission, 1 in partial remission, and 1 with resistant disease) the transplant completed the first-line approach after induction and consolidation schedules; the other patient underwent allogeneic HSCT after re-induction in first relapse of disease.

Six patients with extramedullary sites of disease received additional treatment simultaneously with the induction therapy: intrathecal methotrexate and cytosine arabinoside for neuromeningeal localizations (4 cases) and radiotherapy for cutaneous lesions (2 cases).

Response to treatment and outcome

After induction, 15 patients (36%) achieved complete remissions, eight (19%) had partial remissions, 11 (27%) did not respond to treatment, and seven (17%) died during the aplasia following induction treatment. Notably, two of eight patients in partial remission in whom consolidation treatment was carried out achieved complete remission, increasing the overall complete response rate to 41% (17 of 41 patients) (Table 3). In detail, seven complete remissions were registered after AML-type regimens, and ten after ALL/lymphoma-type regimens, with a significant advantage for the ALL/lymphoma-type approach (P=0.02).

Among the six patients who underwent allogeneic HSCT, only two treated with AML-type induction maintained their complete remissions after transplantation and were still alive 16 and 19 months after HSCT, while the other four patients died, two of disease progression, one of hepatic graft-*versus*-host disease (GVHD) and one of cerebral bleeding during aplasia after conditioning. The mortality rate associated with HSCT was 66% among patients (4/6) and 33% considering the transplant procedures (2/6).

Of the 17 patients who achieved complete remission, six (35%) subsequently relapsed, more frequently after ALL/lymphoma-type chemotherapy, at a median time of 9.1 months (range, 5.8-19.8) after diagnosis. Of note, there were three CNS relapses, in two patients treated with AML-type therapy and in one treated with an ALL/lymphoma-type regimen, none of whom had previously received intrathecal prophylaxis.

Overall 34 patients died, for a mortality rate of 79%. Most of them (25 patients) died from disease progression; seven patients died of complications due to the induction or conditioning therapy, and one because of hepatic GVHD.

The median overall survival of the whole population was 8.7 months (range, 0.2-32.9), with an actuarial survival of 28% at 12 months and of 7% at 24 months (Figure 1A). The overall survival was 14 months (range, 2-32.9) in patients who reached complete remission after induction therapy and 4.5 months in those with resistant disease or who had a partial remission (range, 0.2-19.5; P<0.0001), with the risk of death associated with a lack of complete remission increased by 4.58 times (95% CI: 2.21-9.49)

Table 3. Induction therapy and outcome (41 assessable patients; two early deaths).

Response (outcome)	All patients (n=41)	AML-type (n=26)	ALL/ lymphoma-type (n=15)	*P* value
Complete remission	17 (41%)	7*	10	0.02
Partial remission*	6	5	1	0.63
Resistant	11	10	1	0.03
Death in induction	7	4	3	0.69
Relapse	6/17 (35%)	0/7	6/10	0.03

**Two patients, partial responders, achieved complete remission after consolidation.*

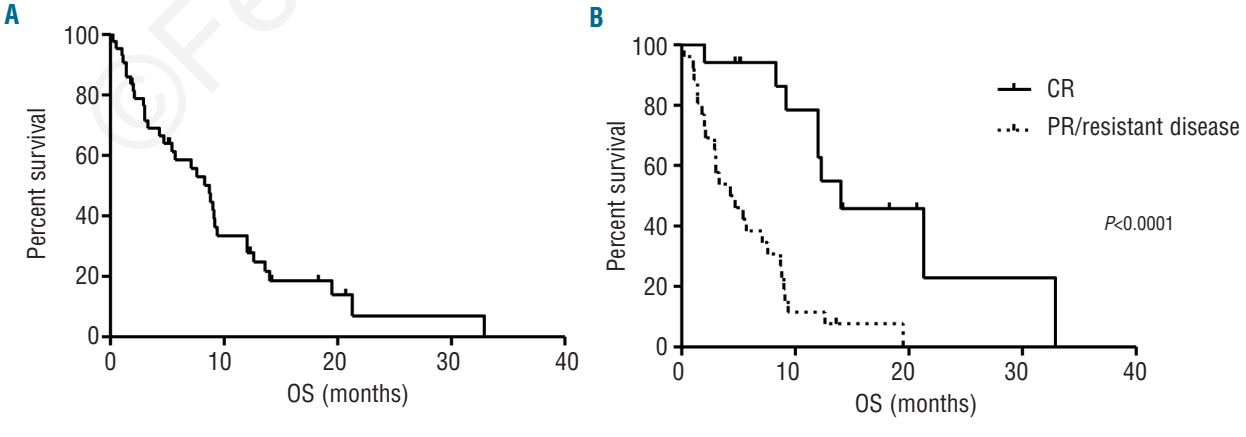

Figure 1. (A) Overall survival (OS) of the whole population (43 patients). The median survival was 8.7 months (range, 0.2-32.9). (B) OS in the 17 patients who reached complete remission (CR) after induction compared to patients in partial remission (PR) or with resistant disease. The median OS was 14 months (range, 2-32.9) and 4.5 months (range, 0.2-19.5), respectively (P<0.0001).

(Figure 1B). The median disease-free survival for all 17 patients achieving complete remission was 8.6 months (range, 1–16.5), with a disease-free survival rate of 37% at 12 months (Figure 2).

At univariate analysis age emerged as a significant prognostic factor: in fact the median overall survival was 12.6 months (range, 1.4-32.9) for patients <65 years old, compared to 7.1 months (range, 0.2-21.3) for patients >65 years old (P=0.04). The overall survival was also significantly influenced by the type of induction. In fact the median overall survival was 7.1 months (range, 0.2-19.5) in patients treated with an AML-type regimen and 12.3 months (range, 1-32.9) in those treated with an ALL/lymphoma-type regimen (P=0.02) (Figure 3). Finally, the median overall survival in allogeneic HSCT recipients was 22.7 months (range, 12-32.9), with a significant advantage with respect to non-transplanted patients (median 7.1 months; range, 0.2-21.3; P=0.03).

At multivariate analysis the following parameters were evaluated: age (<65 *versus* >65 years old), ECOG performance status (0-1 *versus* 2-5), sex, cutaneous localizations, induction with ALL/lymphoma-type regimen, allogeneic HSCT, achievement of complete remission. Only achievement of complete remission resulted significantly correlated with death (P=0.007; 95% CI: 0.00-0.34).

Discussion

BPDCN, previously called agranular CD4$^+$/CD56$^+$ hematodermic neoplasm or blastic natural-killer lymphoma, is a rare, clinically aggressive hematologic malignancy derived from the precursors of plasmacytoid dendritic cells and characterized by co-expression of CD4 and CD56 without other lineage-specific markers. In 2008 it was recognized by the WHO as a distinct entity and separately listed in the group of acute myeloid leukemias and related precursor neoplasms.[1,7]

BPDCN predominantly affects the elderly, although pediatric cases have been reported.[9] BPDCN in children is characterized by less frequent cutaneous involvement than in adults and shows a significant response to intensive ALL-type chemotherapy, allowing patients to reach complete remission, with a better prognosis including long-term survival; all these features suggest that childhood BPDCN might represent a separate subset of the disease.[15,16]

An accurate diagnosis of BPDCN is essential in order to provide treatment promptly, especially considering that the initial clinical presentation is often indolent. BPDCN may be suspected from a set of converging features from the clinical presentation and histological findings, but overlaps with other hematologic neoplasms are considerable and the final diagnosis relies on a compatible immunophenotype. The triple positive CD4$^+$CD56$^+$CD123$^+$ phenotype associated with negativity for lineage-specific markers is a minimum requirement for defining BPDCN. In addition, the highly specific marker BDCA2/CD303, as well as other plasmacytoid dendritic cell-associated antigens (e.g. TCL1 and CD2AP), might be of great support for definitely establishing the diagnosis and for excluding potential mimickers of BPDCN (acute myeloid and monocytic leukemias, precursor lymphoblastic T-cell leukemia/lymphomas and T- and NK/T cell lymphomas).[8,17-19] In our experience 37% of cases were not confirmed after review, so we underline that cases should be discussed in a multidisciplinary meeting including at least a hematologist and a pathologist, and we emphasize the importance of accurate immunohistochemical and cytofluorimetric analyses, with extended panels also including antibodies for dendritic cell lineage in cases of unclassifiable acute leukemia, monoblastic forms and doubtful cases.

In this study we analyzed the largest number of patients affected by BPDCN with leukemic presentation reported in the literature, providing a detailed description of the clinical presentations, therapeutic approaches, and outcomes. The clinical features of the patients in our series are compatible with those previously reported, as regards gender, age, performance status, and clinical presentation, except for lesser involvement of the skin. Isolated skin lesions are frequently the first symptom leading patients to seek medical advice, and without therapy, they disseminate rapidly. Conversely BPDCN without cutaneous

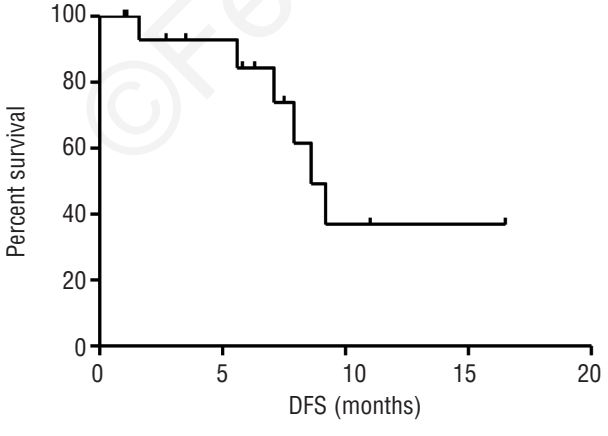

Figure 2. Disease-free survival (DFS) in the 17 patients achieving complete remission. The median DFS was 8.6 months (range, 1-16.5).

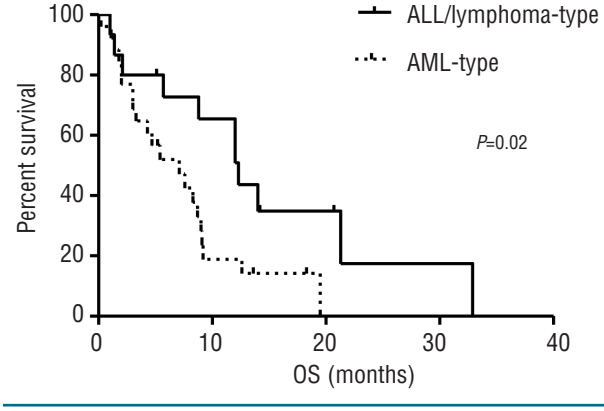

Figure 3. Overall survival (OS) according to types of induction therapy. The median OS was 12.3 months (range 1-32.9) in patients who received an ALL/lymphoma-type regimen and 7.1 months (range, 0.2-19.5) in those treated with an AML-type regimen (P=0.02).

involvement at onset is rarely reported:[20,21] in our study 23% of patients had no cutaneous manifestations at diagnosis, and among them only two developed skin lesions during progression of the disease. We found frequent neuromeningeal involvement (16%), both at diagnosis and at relapse, as in other studies in which the incidence of CNS disease ranged from 9% to 26%.[9,22] These data suggest that systematic preventive intrathecal chemotherapy is indicated in the treatment of disease in addition to intensive chemotherapy, because the CNS could be a persistent blast-cell sanctuary.

It is not surprising that four of our cases had a prior MDS; this finding confirms the observation of a French group that described two cases of MDS among 23 patients.[9] The Hellenic Dendritic Cell Leukemia Study Group reported two cases of secondary BPDCN among 22 patients.[22] In our population, six patients had a previous malignancy (14% of the whole population examined), although in two cases (1 breast cancer and 1 ALL) the latency between the two malignancies was longer than 15 years, so it is probably more correct to consider BPCDN as a second, rather than a secondary, neoplasm.

As for the cytogenetic profile, previous studies reported that two-thirds of patients with BPDCL have an abnormal karyotype: complex karyotypes are common but specific chromosomal aberrations are lacking.[15,23,24] In our series cytogenetic analysis confirmed that most patients had unfavorable cytogenetics (48%), among which complex karyotype was a distinctive feature. Moreover, as recently found,[25] no patients had *NPM1* mutations. Of interest, among 14 cases examined in our series, three had *FLT3*-ITD mutations. The detection of this mutation is a real novelty and difficult to interpret. The central review of cases showed that none of the patients with *FLT3*-ITD had had a previous MDS or a myeloproliferative disorder, so we can consider that they are cases of real BPDCN. As already reported, *FLT3*-ITD has been observed in all subtypes of AML, particularly in acute promyelocytic leukemia and those patients with normal karyotype, as our patients.[26] However, the occurrence of this mutation in BPCDN is debated; Jardin *et al.* did not find the mutation in any of 15 BPCDN cases, while a previous study showed that *FLT3*-ITD could also be expressed by dendritic cells.[27,28] At present no other clinical studies have supported our observation, but this is probably because the *FLT3*-ITD mutation was not searched for in large numbers of cases of BPDCN. If our finding is confirmed, it would indicate that FLT3 inhibitors could be a potential therapy for these patients. The expression of *FLT3*-ITD in some cases and a previous myelodysplastic phase in other cases suggest the myeloid origin of the neoplastic clone of BPDCN.

At present, there is no consensus on the optimal treatment of BPDCN. The available studies are retrospective and different treatments were used: the majority of patients received multi-agent chemotherapy, according to ALL or AML schedules, while a few cases underwent allogeneic HSCT.[9,22,27-34] The response rates and survival of the patients in the main previous studies are summarized in Table 4, in which we report the largest published series on adult and pediatric populations with at least five cases of BPDCN.[9,16,22,29-31] It emerges that BPDCN is quite sensitive to chemotherapy initially, with complete response rates ranging from 53% to 89%. However, the prognosis is poor, even for patients reaching complete remission. The median survival in the different series ranged from 12 to 27 months, with longer overall survival reported for series including pediatric cases or patients with exclusively cutaneous disease. Generally patients treated with an

Table 4. Results of the main series of BPDCN reported in the literature.

Reference	Treatment	N. of patients	Complete Remission Rate*	Relapse	Median OS (months, range)	Notes
Feuillard J. *et al.*, 2002[9]	ALL/lymphoma-type AML-type Palliative/none Total	15 6 2 23	12 CR 6 CR 0 18 CR (86%)	15/18 (83%)	12 (3-96)	Adult and pediatric population
Jegalian AG. *et al.* 2010[16]	ALL-type	9	8 CR (89%)	1/8 (12%)	23 (1-156)	Pediatric population
Tsagarakis NJ. *et al.*, 2010[22]	ALL/lymphoma-type AML-type Palliative or unknown Total	13 6 3 22	12 CR 3 CR 0 15 CR (79%)	6/15 (40%)	15 (6.6-23.4)	Adult population
Dalle S. *et al.*, 2010[29]	ALL/lymphoma-type AML-type Radiotherapy Palliative/none Total	26 12 5 4 47	14 CR 5 CR 4 CR 0 23 CR (53%)	n.r.	16.7 (1-54)	Adult and pediatric population; patients with only cutaneous involvement also included
Hashikawa K. *et al.*, 2011[30]	ALL/lymphoma-type AML -type Radiotherapy None or unknown Total	13 4 4 5 26	10 CR 1 CR 3 CR n.r. 14 CR (67%)	11/14 (78%)	12.7 (1-42)	Adult and pediatric population; patients with only cutaneous involvement also included
Dietrich S. *et al.*, 2011[31]	ALL /lymphoma-type AML-type Total	4 2 6	4 CR 1 CR 5 CR (83%)	4/5 CR (80%)	21 (6-82)	Adult population

**percentage calculated on the number of patients treated with chemotherapy and/or radiotherapy. OS: overall survival; ; n.r.: not reported; CR: complete remission.*

ALL/lymphoma-type regimen had better survival outcomes than those who received AML-type treatment; in a study by Tsagarakis *et al.* the complete remission rate was 79% and all patients who received ALL-type therapy achieved complete remission.[22] Although the therapeutic regimens used in our series were very heterogeneous, our experience confirmed those results, documenting a relative superiority of ALL/lymphoma-type therapy with regards to complete remission rate and better survival, both for patients treated with CHOP and for those given more aggressive regimens such as hyper-CVAD. This suggests that the neoplastic cells are initially sensitive to chemotherapeutic agents typically active against lymphoblasts, such as steroids, vincristine, and asparaginase. On the other hand, the high relapse risk observed in patients who initially respond and the myeloid lineage derivation of blastic dendritic cells suggest that the addition of more myeloid-focused strategies, such as high-dose cytarabine, could be useful in this disease, at least as a bridge to transplantation.

The poor outcome of patients affected by BPDCN justifies the use of transplant procedures, but the efficacy of these need to be investigated in clinical trials and the role of allogeneic HSCT remains to be defined. The only available data published in detail derive from small series of patients or single case reports, most showing that intensive therapy for acute leukemia increased the rate of complete remissions, but only myeloablative treatment with allogeneic HSCT during the first remission resulted in the chance of a significant improvement in overall survival, especially in younger patients.[22,27,29,31-34] In the French analysis by Dalle *et al.*, among 47 patients with BPDCN, ten were transplanted during the management of their disease (9 allogeneic transplants, 1 autologous transplant; median age 38 years); the transplanted patients had a significantly longer survival (31.3 months) than that of the non-transplanted patients (median of only 12 months).[29] Moreover, Dietrich *et al.* described four patients who underwent allogeneic HSCT, of whom two were allografted in remission and were alive and disease-free at 57 and 16 month post-transplant. Because all the patients in that study were older than 50 years, the conditioning regimen was of reduced intensity. The results provide evidence that allogeneic HSCT is also feasible in elderly patients and may result in sustained remission.[31]

The median overall survival of our allogeneic HSCT recipients was 22.7 months, which was significantly longer than that of the non-transplanted patients. The transplanted patients were younger and three of them were in first complete remission of disease.

Regardless of the type of treatment, the unfavorable prognosis reported for BPDCN was confirmed in our series, with the median overall survival (8.7 months) of the patients in our series being worse than that reported in the literature, perhaps because our population consisted exclusively of patients with the leukemic form of the disease.

In conclusion, BPDCN with bone-marrow involvement is a rare disease, with a dismal prognosis, behaving like acute leukemia with high-risk features. Its diagnosis is not easy and requires expert physicians, both clinicians and histopathologists. Effective therapies have not been established yet. Younger patients who receive high-dose chemotherapy with allogeneic HSCT have a better outcome, but the majority of patients are too old or unfit to undergo this intensive therapeutic approach, so alternative strategies must be considered, combining ALL-like plus AML-like protocols and early intrathecal prophylaxis, given the frequent occurrence of CNS involvement. In some fit patients older than 50 years, allogeneic HSCT in the course of first complete remission can be considered, even with non-myeloablative conditioning regimens. Future studies are warranted to support this strategy.

Appendix – Co-authors

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Funding

This work was partially supported by grants from the Italian Ministry for University and Scientific Research (Fondi Ateneo Linea D-1 2011–2012) and by the AIRC (Italian Association for Cancer Research)

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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