

Case Report

Frontline Clofarabine and Cytarabine combination for plasmacytoid blastic dendritic cell neoplasm

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Abstract

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare hematological cancer usually involving skin and/or bone marrow. Recent molecular evidence suggests that BPDCN originates from the myeloid lineage. Short-term responses to conventional treatments underline the need for new therapies in this disease. We present the case of a 55-year-old woman with therapy-related leukemic-phase BPDCN who experienced a six month remission following clofarabine and cytarabine combination therapy. Intensive anthracyclin-based regimen and stem-cell transplant (SCT) were excluded due to pre-existing severe cardiac dysfunction. Relapse occurred after six month of complete remission and the patient died from thrombocytopenia-induced intracranial bleeding. For elderly or young BPDCN patients not eligible for intensive regimen or in relapsed/refractory disease, clofarabine-based therapy appears as an option.

Keywords : Clofarabine, Cytarabine, blastic plasmacytoid dendritic cell neoplasm.

Introduction

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) is a rare and aggressive hematological malignancy derived from plasmacytoid dendritic cells, recognized as a separate entity since the 2008 WHO classification (1). This disease is usually revealed by skin lesions (brownish to violaceous infiltrated 'bruise-like' patches, plaques or tumors), possibly associated to splenomegaly, lymphadenopathy, and variable bone marrow or blood involvement (2, 3). A minority of patients presents with pure leukemic disease (4). Phenotypic characterization usually shows positivity for CD4, CD56, CD123, blood dendritic cell antigen (BDCA)2, T-cell leukemia/lymphoma (TCL)1 and B-

cell chronic lymphocytic leukemia/lymphoma (BCL)11A expression (5). A range of cytogenetic alterations are reported in BPDCN with a predominance of deletions involving chromosomes 5q (72%), 12p and 13q (64%), 6q (50%), 15q (43%) and 9 (28%) (6). The prognosis is dismal with a median overall survival longer than twelve month in case of pure skin involvement (3, 7) and a few month only in leukemic forms of BPDCN (4).

Case report

A 55-year-old woman presented with anemia and alteration of general state. She had history of resolved hepatitis B virus infection, Hashimoto's thyroiditis and

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diabetes mellitus treated by oral route. She also had stage III EBV-positive diffuse large B cell lymphoma involving thyroid gland, successfully treated by 6

cycles of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) combination followed by two cycles of high dose methotrexate and

Figure 1A

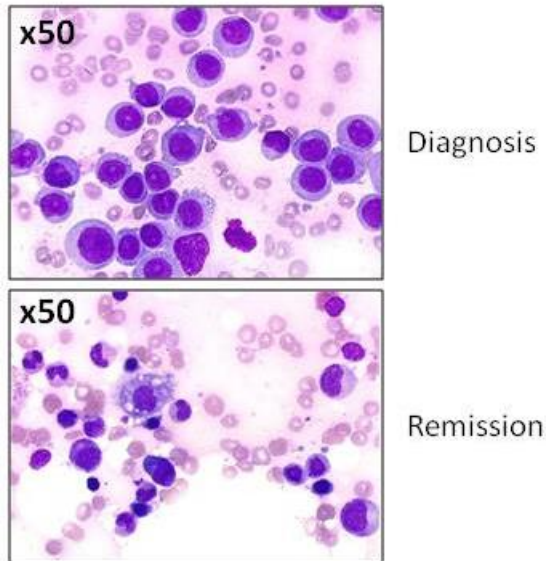


Figure 1B

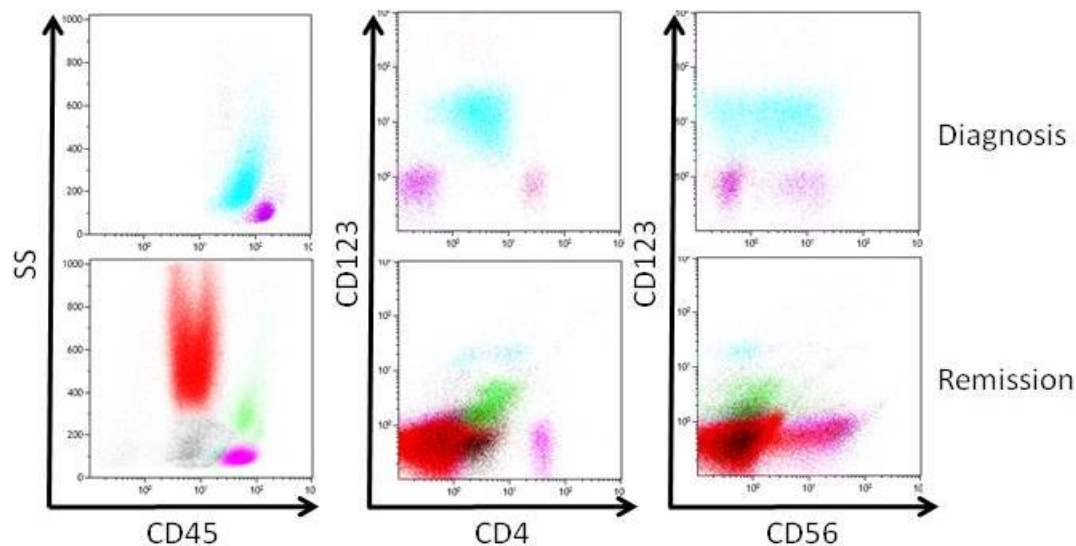


Figure 1. Biological assessment of diagnosis and Minimal Residual Disease. 1A, May-Grunwald-Giemsa staining from bone marrow smear done at diagnosis and after induction therapy, observed under optic microscope (x50 magnification); 1B, Multiparameter flow cytometry assessment of minimal residual disease. SS: Side Scatter. The turquoise dots correspond to BPDCN bone marrow detection at diagnosis and after cytological remission (90% and 0,4% of the total leukocyte count, respectively). All antibodies used were purchased from Beckman Coulter (Brea, CA).

four cycles of Etoposide and Holoxan. She developed anthracycline-induced severe cardiac dysfunction six months after treatment as diagnosed by echocardiography showing global hypokinesia and decreased right ventricular ejection fraction (20% compared to 60% before chemotherapy). Physical examination showed gingival hyperplasia but no adenopathy or splenomegaly and no skin lesion. White blood cell count was $4,9 \times 10^9/l$ including 43% medium to large blastic cells; hemoglobin and platelets were 71 g/l and $56 \times 10^9/l$, respectively. Other routine tests were normal, except for lactate dehydrogenase level measured at 942 U/l (range, 200-400U/l). Bone marrow smear showed 93% blastic cells harboring peripheral microvacuoles (Figure 1A). Blood and bone marrow phenotype was CD45+dim CD4+ CD56+ CD123+ bright CD38+ CD13+ CD11b+ HLA-DR+ while common B-cell lineage (CD19, CD20, CD24, CD79A), T-cell lineage (CD2, CD3, CD5, CD7, CD8), NK-cell lineage (CD16 and CD57) and MPO were negative. Blast cells also expressed CD33, CD117 and CD36 antigens. The standard karyotype done on bone marrow cells was normal. Accordingly, the patient was diagnosed with therapy-related Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN). Due to anthracycline-induced cardiac dysfunction, she was given clofarabine 40 mg/m², cytarabine 1000 mg/m² and dexamethasone 10 mg total dose for five consecutive days. She developed pulmonary aspergillosis, chronic disseminated candidiasis, ischemic cerebrovascular accident and grade IV therapy-related adverse events including clofarabine-related acute hepatitis, palmoplantar erythrodysesthesia and mucositis. She reached morphological complete remission with low minimal residual disease (0,4% of total leukocytes, Figure 1B). Six months after remission, a relapse occurred attested by gingival hypertrophy and ulcerated tumor of the soft palate, circulating blast cells, pancytopenia and disseminate intra-vascular coagulopathy. The patient died soon after salvage therapy initiation (high dose methotrexate and L-asparaginase) due to refractory thrombocytopenia-induced intracranial bleeding (Figure 2).

Discussion

No treatment guidelines are available for BPDCN as yet. High-response rates (41 to 100%) are achieved with anthracyclin-based lymphoma-like or various form of acute leukemia-like regimens. However, short-term

remissions and constant relapses underline the need for new and efficient consolidation strategies. Allogenic stem-cell transplantation (SCT) performed after a first remission currently represents the only possibility for long-term survival (median overall survival: 21 to 38,5 months) (7-10), and reduced-intensity SCT is also an option (median survival: 13 to 86 month) (11). Our current case is to our best knowledge, the first report of clofarabine use for BPDCN. Clofarabine is a purine analog combining the most favorable pharmacokinetic properties of both fludarabine and cladribine while reducing their potential for dose-limiting toxicity. This drug showed efficacy in acute myeloid leukemia (AML) patients with age-related limitation for intensive therapy and also in relapsed or refractory AML in younger patients (12-14). Because of severe cardiac dysfunction, intensive anthracyclin-based regimen and SCT were excluded in our patient. We aimed to treat her with a clofarabine-based AML-like regimen, which induced a complete remission. To explain the importance of therapy-related side effects, we hypothesized that previous chemotherapy given for lymphoma and diabetes contributed to immune dysfunction and related infections. Concomitant use of dexamethasone to reduce clofarabine-induced side effects may also have contributed to immunodeficiency. We used AML-like regimen based on an expected reduced toxicity compared to intensive ALL-like treatments and due to recent evidence of genetic lesions in *IKAROS* family of genes (*IKZF1*, *IKZF2*, *IKZF3*), *HOXB9*, *UBE2G2*, *ZEB2* and *TET2* genes – mostly documented in myeloid neoplasms - in BPDCN (15). Achievement of a six-month-length remission in our patient following clofarabine-based treatment is similar to the observations made in leukemic-phase patients treated with intensive regimens (excluding SCT) (4, 7). We suggest that clofarabine/cytarabine combination may be an option in unfit BPDCN patients or in case of relapsed/refractory disease to allow subsequent SCT.

Abbreviation list

BPDCN: Blastic Plasmacytoid Dendritic Cell Neoplasm
 SCT: stem-cell transplant
 WHO: world health organization
 EBV: Epstein-Barr virus
 AML: acute myeloid leukemia
 ALL: acute lymphoblastic leukemia

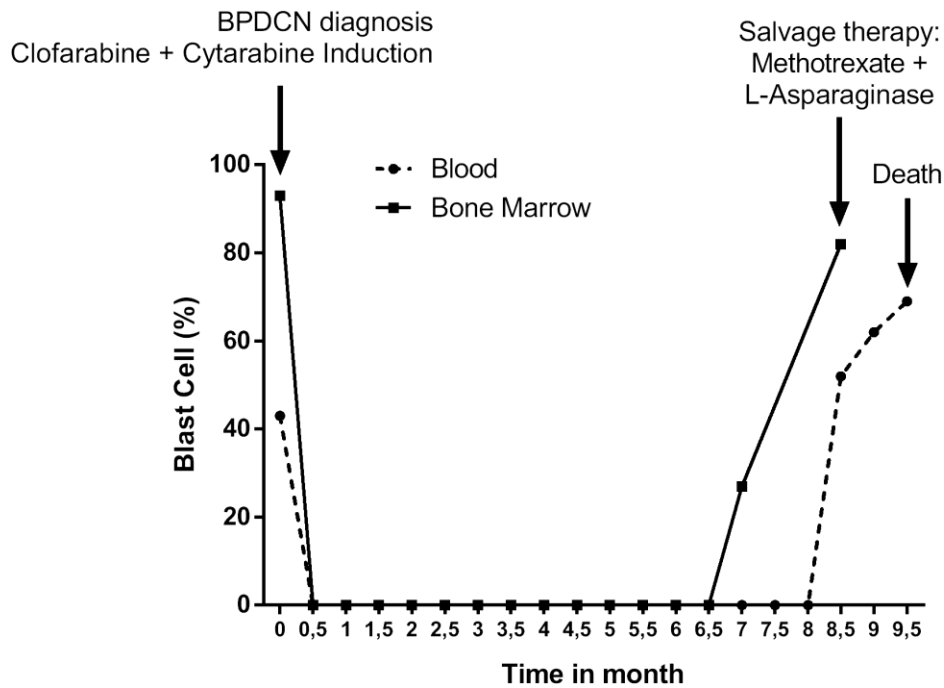


Figure 2. Disease evolution following clofarabine and cytarabine treatment.

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