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LETTER TO THE EDITOR

Quick complete response achievement with venetoclax and azacitidine in a case of relapsed disseminated blastic plasmacytoid dendritic cell neoplasm

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Dear Editor,

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and extremely aggressive myeloid malignancy arising from dendritic cell (DC) precursors typically affecting skin and/or bone marrow. Despite excellent complete response (CR) rates with induction chemotherapy, the disease has a marked tendency to relapse and become chemoresistant, with an overall dismal outcome. Frontline treatment with acute myeloid leukemia-like and acute lymphoblastic leukemia-like regimens resulted in disease-free and overall survival advantage, although allogeneic stem cell transplantation appears to be the only therapeutic approach with potential for disease eradication and long-term survivorship [1]. Data on efficacy of specific therapeutic regimens in the relapsed/refractory (R/R) setting are lacking, mainly because of the rarity of this disease entity. Conventional chemotherapy seems to provide only limited and transient clinical benefit [2]. Recently, CD123-directed cytotoxin tagraxofusp has gained FDA approval based on the results of the Phase I/II STML-401-0114 study showing remarkable response rates in both untreated and R/R BPDCN, although median duration of response in the latter setting did not exceed 3 months [3]. The demonstration of peculiar Bcl-2 dependence in BPDCN by Montero et al. [4] prompted exploration of the clinical activity of small molecule Bcl-2 inhibitor venetoclax in R/R disease; DiNardo et al. reported valuable clinical responses with venetoclax in combination regimens in two R/R BPCDN patients [5]. Here we report the clinical case of a patient with disseminated skin relapse of BPDCN achieving a remarkably quick and durable response with venetoclax and azacitidine treatment with a very favorable toxicity profile.

In May 2017, a 64-year-old male patient was diagnosed with disseminated blastic plasmacytoid dendritic cell neoplasm with extensive skin involvement presenting as diffuse, red-brown papules, plaques, and nodules. PET/CT scan revealed an intensely hypermetabolic, enlarged left inguinal lymph node. Bone marrow aspirate revealed blast cell infiltration (30% of bone marrow nucleated cells) with characteristic morphological and immunophenotypical features. Cytogenetic evaluation revealed a normal (46XY) karyotype. Full blood counts and chemistry were within normal ranges.

Patient received induction chemotherapy with hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (hyper-CVAD regimen, course A and B); CR on skin, lymph node, and bone marrow was promptly achieved with cycle 1, with a positive minimal residual disease (MRD, 0.01%) on bone marrow by flow cytometry, probably reflecting the presence of a normal DC counterpart. No central nervous system (CNS) prophylaxis was administered. Due to the unavailability of HLA-identical sibling donors or haploidentical donors, a donor search in the international bone

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marrow donor registries was initiated but was ultimately unsuccessful. Given the unsatisfactory results reported with high-dose chemotherapy and autologous stem cell transplantation, we suggested prosecution of hyper-CVAD chemotherapy, of which our patient was able to complete a total of 3 cycles with persistent CR. Full details about diagnostic clinical and histopathological findings and first-line treatment were previously reported [6]. Patient's tolerance to intensive chemotherapy was overall satisfactory; of note, he experienced several episodes of grade 4 oral and gastrointestinal mucositis and suffered from recurrent grade 3 soft tissues infectious complications (perianal abscess; infected sebaceous cyst). After completion of cycle 3, we decided to proceed with strict clinical follow-up with periodical bone marrow aspirates. The patient stayed in complete remission until September 2018, when a single sovraclavear patch-like lesion made its appearance; a punch biopsy was carried out, and histopathological examination confirmed BPCDN relapse. In December 2018, disseminated skin relapse became evident. Peripheral blood counts and chemistry were unremarkable. A bone marrow aspirate showed the presence of DCs accounting for 0.01% of BM cellularity, again probably reflecting the normal DC compartment. PET/CT scan did not reveal any hypermetabolic foci suggestive for BPCDN localization. Patient was in very good overall conditions; we opted for second-line treatment with venetoclax and azacitidine (venetoclax, 100 mg/d day 1; 200 mg/d day 2; 400 mg/d from day 3; azacitidine 75 mg/m^2 subcutaneously on days 1,2,3,4,5,8, and 9 in 28-day cycles). Tumor lysis syndrome prophylaxis consisted of allopurinol 300 mg/d. No antimicrobial prophylaxis was administered during cycle 1. Treatment initiation was followed by a strikingly quick response leading to nearly complete resolution of all skin lesions by cycle 1 day 14 (Fig. 1). Treatment was very well tolerated and virtually devoid of relevant adverse events. By cycle 3, grade 4 neutropenia appeared (absolute neutrophil count at nadir, 0.140×10^9/L) but was successfully managed with filgrastim support (3–4 30 MU doses per cycle) and levofloxacin 500 mg/d per os until recovery, without any febrile neutropenia episode. Anemia and thrombocytopenia never exceeded grade 2 according to common terminology criteria for adverse events (CTCAE). Patient is currently entering cycle 11 and has been in persistent complete remission, fully transfusion-independent. He is not suffering from any particular therapy-related medical issue, and his quality of life is overall satisfactory. Of note, we have not administered CNS prophylaxis thus far.

R/R BPCDN has traditionally been difficult to manage myeloid malignancy with limited therapeutic options and an overall dismal outcome. The kinetics of response to azacitidine/venetoclax in our patient were particularly striking and certainly different from the clinical behavior commonly seen with hypomethylating agent (HMA) monotherapy. Furthermore, response has proved to be durable with a 8-month follow-up – which compares favorably with other therapeutic approaches. The lack of bone marrow infiltration at relapse might have very well played a major role in improving hematologic tolerability in our moderately pre-treated patient; nonetheless, grade 4 neutropenia occurred in a predictable, cumulative dose-dependent fashion and was easily and successfully managed with filgrastim support. Overall, the association of venetoclax and azacitidine provided an extremely effective platform for achievement of a second CR for our patient, with a rapid onset of response and a very reasonable and manageable toxicity profile; this could be of utmost importance in this patient population, potentially allowing from HSCT bridging while limiting toxicity. Further studies are warranted in order to fully characterize the clinical activity and safety of venetoclax alone and in combinations in R/R BPDCN.

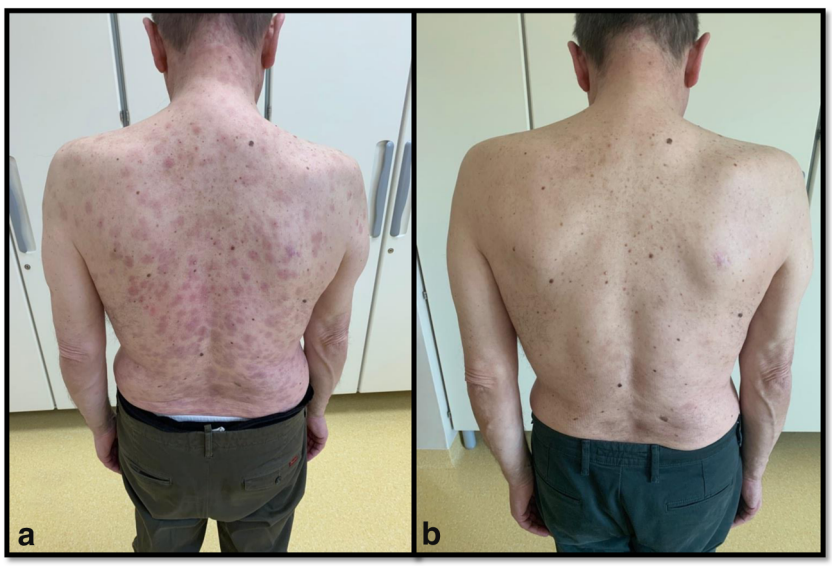

Fig. 1 **a** Overview of skin involvement on posterior trunk at venetoclax/azacitidine initiation (cycle 1, day 1); lesions were mainly of macular/hyperchromic subtype with occasional nodular aspects. **b** Nearly complete clinical resolution of skin involvement as seen at cycle 1 day 14

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.Informed consent.

Informed consent Informed consent was obtained from all individual participants included in the study.

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