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Venetoclax to treat relapsed blastic plasmacytoid dendritic cell neoplasm: A case-report and review of literature

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare hematological malignancy which particularly affects elderly patients. To date, there is no standardized therapeutic approach. Patients are usually treated with ALL/lymphoma-type or AML-type chemotherapy. With chemotherapy, prognosis is still poor, and median overall survival often remains inferior to 2 years [1]. The limitations of chemotherapy can be overcome by targeting oncogenic pathways that are investigated in BPDCN. Targeted therapies are currently under development with promising results [2]. For example, tagraxofusp is a human interleukin 3 fused to truncated diphtheria toxin and has shown promising response rates which seems to improve overall survival [3] in BPDCN. Recent studies show that BPDCN survival depends on the anti-apoptotic protein BCL-2, which is highly expressed in BPDCN compared to normal plasmacytoid dendritic cells. As a consequence, sensitivity to venetoclax, a BCL2 inhibitor, has been demonstrated *in vitro*, but also *in vivo* [4]. Some authors have recently reported the clinical efficacy of venetoclax, as a single agent [5,6] or in combination with chemotherapy [7,8] in relapsed BPDCN and in front-line treatment in one case.

Here we present the case of a 77 years-old man who was diagnosed with cutaneous blastic plasmacytoid dendritic cell neoplasm in April 2018. This patient also suffers from other severe comorbidities such as ischemic cardiomyopathy, chronic obstructive bronchitis due to smoking, arterial hypertension, hypercholesterolemia, chronic alcoholism, and untreated low-grade myelodysplasia RAEB type 2. To establish the diagnosis of BPDCN, the patient underwent a skin biopsy which revealed blastic plasmacytoid dendritic cell infiltration with high BCL2+ staining. As part of the clinical work-up, the patient underwent a bone marrow biopsy and a CT-scan, which showed no evidence of other extension. The patient's case was discussed in a multidisciplinary cancer conference (MCCs), mini−CHOP regimen was chosen as front-line chemotherapy (cyclophosphamide 375 mg/m^2 at D1, doxorubicine 25 mg/m^2 at D1, vincristine 1 mg at D1, prednisone 40 mg/m^2/day from D1 to D5) and was administered for 8 cycles (from June to November 2018). There was no response to this treatment, as the patient presented persistent skin lesions; one in the left popliteal fossa which appeared after the 6th cycle, and other lesions appeared on the patient's face, chest, upper limbs and lower left limb during the last cycle. The main skin lesions at the end of mini−CHOP treatment can be seen in Fig. 1. A second-line strategy was then decided after MCCs, and consisted of venetoclax alone, and was administered from December 2018, at the dose of 20 mg per day. Venetoclax ramp-up dose followed this escalation: 20 mg per day for 17 days, 50 mg per day for 10 days, 100 mg per day for 7 days, 200 mg per day for 7 days, then 400 mg per day in order to prevent tumor lysis syndrome. It was decided not to increase the dose above 400 mg/day, which is the efficient dose for sensitive lymphomas like chronic lymphocytic leukemia and the dose commonly used in the other reported cases of venetoclax in BPDCN. After three months of treatment, no severe adverse events were noted, no transfusion or antibiotic support was needed. No tumor lysis syndrome occurred at any dose. The patient only reported a fluctuating grade 2 asthenia (according to the common terminology criteria for adverse events) and an oral mycosis. The patient showed complete recovery of some skin lesions (face, chest and upper limbs) which contrasted with some lesions which remained stable (lower limbs) while the largest lesion behind the left knee completely recovered after one month of treatment, but then appeared again and progressed (Fig. 1). Local radiotherapy was then initiated to stop the progression of the left knee skin lesion. Because of this dissociated response, venetoclax was stopped before radiation therapy and replaced by bendamustine at the dose of 50 mg/m^2/day for 2 days every month.

The few clinical studies on patients with relapsed or refractory BPDCN show that venetoclax seems relevant in this situation. Therapeutic responses seem more effective on skin lesions than on medullar infiltration, as shown in Table 1. In this case, mini−CHOP as a wide-spread lymphoma-type front-line chemotherapy was not efficient in treating BDPCN cutaneous lesions. In contrast, this response was dissociated under venetoclax, skin lesions decreased rapidly at treatment initiation, with best responses appearing after one month but relapsing immediately after, although our patient only presented a cutaneous extension of BPDCN. Mechanisms of resistance and of relapse under venetoclax in BPDCN are unclear. It may be due to the loss of overexpression of BCL2 in the tumor cells, which has not been proven in this case. Further reports are warranted to answer this question. In previous studies, complete remission occurred mainly in patients treated with a combination including venetoclax. Responses seem less effective when used as single agent, suggesting that venetoclax may increase sensitivity of BPDCN to chemotherapy. In this case, the patient was treated with venetoclax alone, in order to limit the potential hematological toxicity of a combined treatment, particularly because the patient presented a myelodysplatic syndrome. Moreover, a hypomethylating agent was not associated with venetoclax because there was no evidence of additional benefits in treating BPDCN at that time, and there were no criteria to treat the patient's myelodysplasia too. Our patient was treated with rosuvastatine for cardiovascular reasons.

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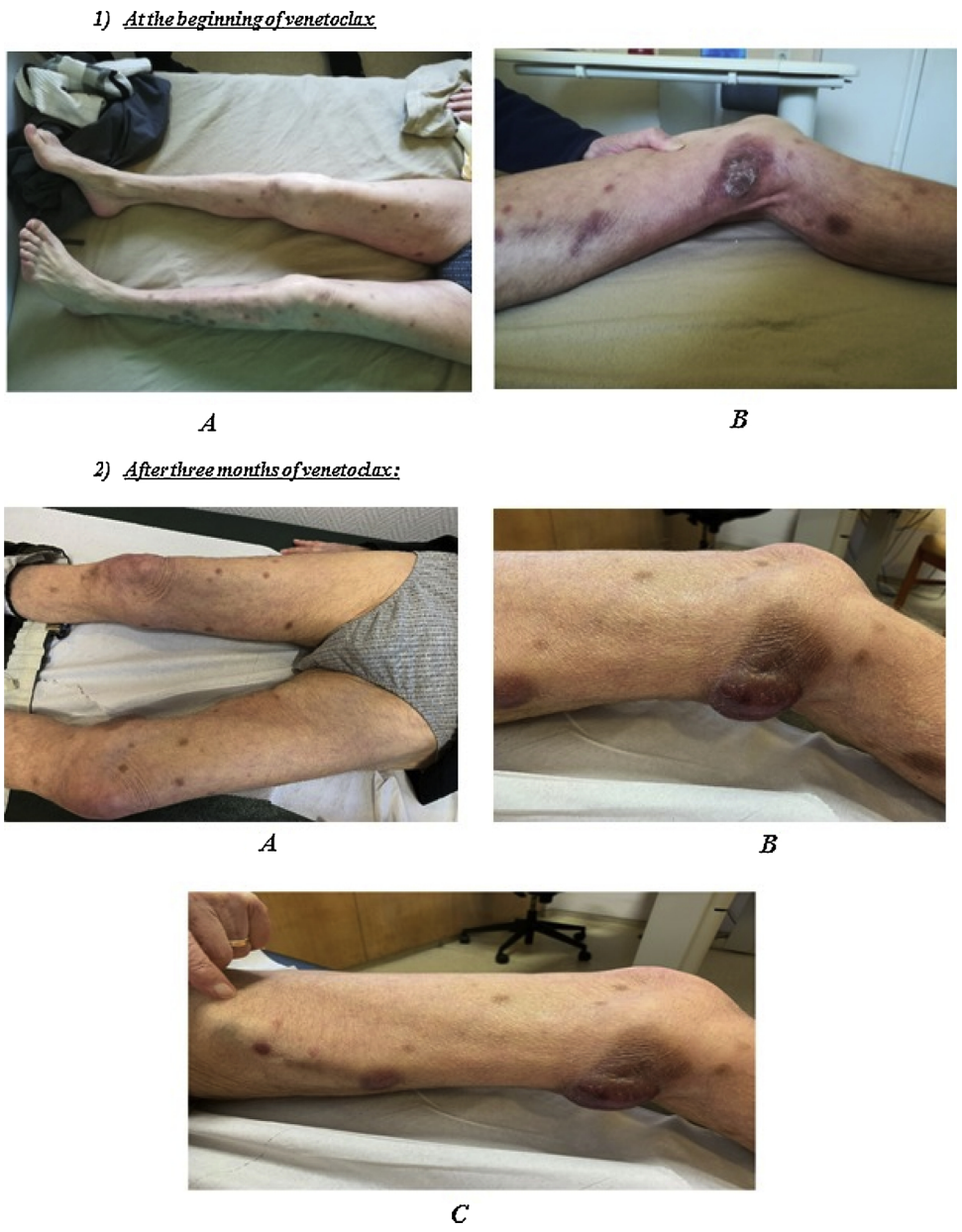

Fig. 1. The main skin lesions after mini CHOP treatment and after venetoclax (pictures to be compared: 1A *versus* 2A; 1B *versus* 2B and 2C).

Certain studies show that the use of statins may enhance the therapeutic response, which could modify our results and will require further explorations.

Venetoclax in BPDCN is well tolerated. To our knowledge, no major or fatal adverse events occured in this situation. Tumor lysis syndrome was not reported at any dose, even in the absence of dose escalation. These results are surprising because this syndrome is present in other hematological malignancies where venetoclax is now prescribed or under development (chronic lymphocytic leukemia, acute myeloid leukemia). Further, our patient benefited from a complete hospital discharge for several months. Therefore, venetoclax seems to be adapted in the treatment of BPDCN in the elderly, avoiding chemotoxicity and repeated hospitalizations.

A recent report indicates that venetoclax penetrates in cerebrospinal fluid and may be effective in managing central nervous system involvement [9], which is a frequent dissemination of BPDCN.

Gathering all these recent findings, a phase 1 clinical trial with a phase 2 expansion phase is currently recruiting to find the safest dose of venetoclax, and to study its efficacy and its tolerance in a larger group of patients with untreated or relapsed BPDCN (NCT03485547).

This case suggests also that anti-CD123 targeted therapies like tagraxofusp could be combined with venetoclax, to induce a more effective and prolonged response.

In conclusion, current cumulating experiences show that venetoclax seems safe, effective and adapted in treatment of BPDCN, especially in elderly patients with skin involvement.

Table 1
Current assessment of efficacy and safety of the use of venetoclax in BPDCN.

Reference	N	Age (years)	Associated treatments	Previous treatments	Extension of lesions	Duration of treatment	Dose	Best results	Tolerance
Montero et al., Cancer discovery 2017	2	#1: 80	No	#1 : HOP, anti-IDH2, anti-IL3R	#1 and #2 : bone marrow, lymph nodes, skin	#1 : 6 weeks (death)	#1 : weekly dose escalation (20-50-100-200-400 mg daily	1 : partial response on skin and lymph node lesions, no hematologic response	#1 : intracranial hemorrhage grade 5, thrombopenia
		#2 : 73		#2 : hyperCVAD, anti-IL3R, decitabine		2 : 12 weeks (progression)	#2 : weekly dose escalation (50-100-200-400 mg daily)	#2 : very good partial response on lymph nodes and skin ; partial hematologic response	#2 : 0
Grushchak et al., Medicine 2017	1	65	No	CHOP 2 cycles then ASCT	Skin only	> 10 months, no progression	400 mg daily	Complete response after 5 months	Infrequent chills, mild diarrhea grade 1
Di Nardo et al., AJH 2017	2	#1: 73	Yes (not precised)	#1 : 2 lines (not precised)	Bone marrow, lymph nodes, skin	–	–	#1 : major response on PET/CT and skin ; partial hematologic response	
		#2 : 76		#2 : 4 lines (not precised)				#2 : major response on skin	
Agha et al., NEJM 2018	1	62	No	Bortezomib-simvastatin	Skin, lymph nodes, bone marrow	–	400 mg daily	Complete remission on PET/CT and bone marrow biopsy exceeding 1 year	
Pemmaraju et al., NEJM 2019	3	–	Hyper-CVAD	Front-line in 1 patient, not precised in the 2 others	–	–	–	Complete remission	–
Micol et al., NEJM 2019	1	45	Cytarabine + idarubicin (3+7 induction)	2 cycles of idarubicin + asaparaginase + high-dose methotrexate	Skin only	–	–	Complete remission (day 45)	–

A greater number of patients and prospective trials are needed to assert that venetoclax could be used as a reference therapy in BPDCN, alone or in combination.

Declaration of Competing Interest

None.

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