Safety and efficacy of brentuximab vedotin as a treatment for lymphoproliferative disorders in primary immunodeficiencies

Primary immunodeficiencies (PID) form a heterogeneous group of more than 350 monogenic inborn errors of immunity. Many PID are associated with an elevated risk of developing lymphoproliferative disorders (LPD), which range from polyclonal polymorphic lymphoproliferation to overt malignant lymphoma.[1] There are no specific treatment guidelines for these rare and heterogeneous clinical entities. Immunotherapy with an anti-CD20 monoclonal antibody (mAb) such as rituximab is frequently used for B-cell LPD (B-LPD). Cytotoxic chemotherapy is associated with a high morbidity rate related to toxicities and infections, in particular in patients with a DNA repair defect disorder.[2] The prognosis for patients with LPD arising in PID (LPD-PID) is usually poor and the therapeutic management needs to be improved.[3] Once a treatment response has been obtained, allogeneic hematopoietic stem cell transplantation (aHSCT) is a curative treatment option for both the LPD and the underlying PID in eligible patients.[4]

Brentuximab vedotin (BV) is an antibody-drug conjugate composed of an antimitotic agent (monomethyl auristatin E) linked to a chimeric anti-CD30 mAb for targeted delivery. This drug is highly effective in a broad range of CD30-positive lymphomas: classical Hodgkin lymphoma (cHL), anaplastic large cell lymphoma (ALCL), T-cell lymphoma, and diffuse large B-cell lymphoma (DLBCL).[5-8] Pediatric experience confirms the data gathered in adult patients.[9] The toxicity profile of BV is acceptable, allowing its use in debilitated and/or older patients.[10] Despite these characteristics, to the best of our knowledge, only two cases of BV use in LPD-PID have been reported.[11,12]

We report our single-center experience of using BV to treat LPD in patients with PID. Adult and pediatric patients treated in the Necker-Enfants Malades Hospital, Paris, France, were retrospectively identified. An independent ethics committee approved the study (CLEA-2019-74). To limit confounding factors, we excluded three patients who received BV simultaneously with chemotherapy or rituximab.

Seven patients (3 females and 4 males) presented a total of 8 LPD treated with BV (P1 had two LPD). Clinical and immunobiological characteristics are shown in *Online Supplementary Tables S1 and S2*, respectively. Six patients had combined immunodeficiency related to *DOCK8, CD27, ITK, ATM* deficiencies (n=1 each), *ADA* deficiency (n=1, treated with enzyme replacement therapy), or a genetically uncharacterized PID (n=1). One patient was diagnosed with X-linked lymphoproliferative type 1 disease (Table 1). LPD appeared at a median age of 15.0 years (range, 5.9-32.7). In two cases (P3 and P6), the LPD treated by BV was a relapse that occurred 0.58 and 2.47 years after the first LPD, respectively (*Online Supplementary Figure S1*). Seven of the eight LPD were at an advanced stage (III or IV), based on a central review of positron emission tomography-computed tomography (PET-CT) and CT scans (staging according to the Lugano classification).[13]

A centralized pathology review was performed, based on the 2016 revision of the World Health Organization classification of lymphoid neoplasms.[14] The histological types were DLBCL, not otherwise specified (n=2), cHL (n=2), anaplastic lymphoma kinase (ALK)$^-$ ALCL (n=2), polymorphic B-cell lymphoproliferation (n=1), and Epstein-Barr virus (EBV)$^+$ mucocutaneous ulcer (n=1). All

Table 1. Characteristics of the lymphoproliferative disorders.

Patient	PID gene	Age at LPD onset (years)	LPD status	PS	Stage	Extranodal involvement	LPD classification	CD30 (%)*	EBV IHC	Clonality	PCR EBV
1	*DOCK8*	9.8	Primary	100	IV	Gut	ALK$^-$ anaplastic large cell lymphoma	100	NA	T-cell	NA
		13.3	Primary	50	III	None	ALK$^-$ anaplastic large cell lymphoma	100	NA	T-cell	NA
2	*ATM*	16.7	Primary	40	II	None	Diffuse large B-cell lymphoma	100	EBER$^-$ LMP1$^-$	B-cell	4.5
3	*ITK*	5.9	Relapse (0.6 years)	30	IV B	Bone marrow	Classical Hodgkin lymphoma	100	EBER$^+$ LMP1$^+$	B-cell	4.8
4	*CD27*	6.0	Primary	50	IV B	Lung	Polymorphic B-cell lymphoproliferation	10-20	EBER$^+$ LMP1$^-$	T-cell	5.8
5	Unknown	30.3	Primary	80	IV B	Lung	Diffuse large B-cell lymphoma	30-40	EBER$^+$ LMP1$^+$	B- and T-cell	3.4
6	*ADA*	27.1	Relapse (2.5 years)	50	IV B	Lung, liver	Classical Hodgkin lymphoma	100	EBER$^+$	Not performed	2.3
7	*SH2D1A*	32.7	Primary	40	IV B	Colon	EBV$^+$ mucocutaneous ulcer	30-40	EBER$^+$	B- and T-cell	6.8

*Percentage of tumor cell expressing membranous CD30. The delay between primary lymphoproliferative disease (LPD) and the relapse is shown in brackets. LPD were staged according to the Lugano Classification. B represent disease-related symptoms: unexplained weight loss > 10% of the body weight, unexplained fever > 38°C, night sweats.[13] PS: Performance status: Lansky score <16 years of age, Karnofsky score ≥16 years of age. PID: primary immunodeficiency; LPD: lymphoproliferative disorder; EBV: Epstein-Barr virus; IHC: immunochemistry; NA: not applicable; PCR: polymerase chain reaction; F: female. M: male; ALK- : anaplastic lymphoma kinase negative; EBER: EBV-encoded small RNAs; LMP1: latent membrane protein 1.

Clinical response	Target lesions: % change	Target lesions: Deauville score	PCR EBV log change
Complete	-64%	1	NA
Complete	-81%	1	NA
Complete	-100%	1	NA
Complete	+07%	5	-1.9
Complete	-86%	2	-5.8
Complete	-66%	3	-3.4
None	New lesions	5	-0.7
Complete	-90%	2	-1.1

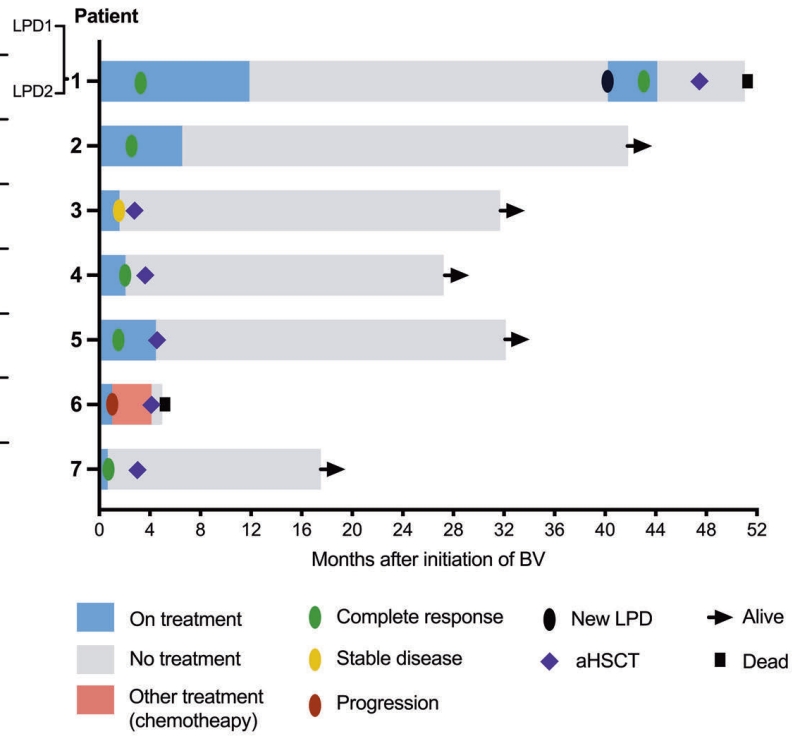

Figure 1. Efficacy of brentuximab vedotin. (Right) Swimmer plot of individual outcome. On the left, summary of clinical response, radiological response of target lesions according to Response Evaluation Criteria in Lymphoma criteria (% change in sum of diameters of target lesions) and metabolic uptake on [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography and polymerase chain reaction (PCR) Epstein Barr virus (EBV) log change for EBV-related B-cell lymphoproliferative disorder (LPD). In three cases, brentuximab vedotin (BV) was started while the LPD was in a partial response after two courses of COP (cyclophosphamide, vincristine and prednisone) for the LPD1 of P1, one injection of rituximab (375mg/m^2) and ten days of steroids for P2, and five injections of rituximab (375 mg/m^2) for P4. In two cases (P3 and P7), the LPD was refractory to rituximab. P1 presented a second LPD, or an immunogenetically evolved relapse, which was not associated with a loss of CD30 expression. The median time to an objective response was 2.6 months (range, 0.56-3.91). However, a clinical improvement was apparent in the first weeks after treatment. aHSCT: allogeneic hematopoietic stem cell transplantation.

LPD were CD30-positive on immunohistochemistry staining (DAKO monoclonal antibody, clone Ber-H2) using a threshold of >5% to define tumor cell CD30 positivity (*Online Supplementary Figure S2*). All but one (DLBCL) B-LPD were EBV-related (evaluated by *in situ* hybridization with the EBER probe and by immunohistochemical measurement of latent membrane protein 1 expression). B-cell clonality (using polymerase chain reaction analysis of immunoglobulin light chain *IGK* and heavy chain *IGH* rearrangements) was identified in all B-LPD analyzed apart from the polymorphic B-cell lymphoproliferation. A clonal *T-cell receptor gamma (TRG)* rearrangement was also identified in three patients, including 2 B-LPD. In P1 (who presented with two ALCL), the presence of a different monoclonal *TRG* rearrangement is compatible with either the presence of two distinct LPD or clonal evolution/emergence of a distinct subclone rather than a relapse of the initial clone.

The rationale for administration of BV was refractory disease (n=3), poor health status (n=2), high cumulative dose of prior cytotoxic chemotherapy (n=2), and the underlying PID (n=1, ataxia telangiectasia, AT). Patients received a median of 4.5 injections (range, 1-16) of BV by LPD at a dose of 1.8 mg/kg every three weeks. In three cases, BV was used as first-line treatment for the LPD (P1-ALCL2, P5 and P6). In five cases, BV was second-line treatment: because of rituximab refractory disease (P3 and P7) or only partial response to first-line treatment [rituximab in P2 and P4 or COP (cyclophosphamide, vincristine, prednisone) in P1-ALCL1]. Detailed individual disease courses are given in the *Online Supplementary Appendix*.

The treatment response was assessed according to RECIL (Response Evaluation Criteria in Lymphoma) criteria.[15] Of the eight LPD, six were in complete response (CR), one in stable disease (SD) and one in progression of disease (Figure 1). P3 had a SD according to RECIL criteria; however, her clinical examination and physical status normalized, and the EBV DNA load decreased by 1.9 log cp/mL. The LPD was considered to be sufficiently controlled to proceed to aHSCT. P6 progressed after two BV injections and was switched to cytotoxic chemotherapy (leading to a CR). The patient subsequently underwent aHSCT but died shortly afterwards of transplant-related complications. The median blood EBV load was significantly lower after BV treatment (2.8 log cp/mL *vs.* 4.7 log cp/mL before treatment; $P<0.05$, two-tailed non-parametric Wilcoxon signed-rank test). EBV DNA was no longer detectable in two cases, including one who had not received rituximab. Illustrative radiological assessments before and after treatment with BV are shown in *Online Supplementary Figure S3*.

Table 2. Adverse events during brentuximab vedotin treatment.

	N. of cases (%) with the event		
	Grade I-II	Grade III	Grade IV
Anemia	4 (50%)	2 (25%)	0
Fever	5 (63%)	0	0
Neutropenia	1 (13%)	1 (13%)	2 (25%)
Thrombocytopenia	3 (38%)	2 (25%)	0
GGT elevation	3 (38%)	1 (13%)	0
Asthenia	2 (25%)	0	0
Elevated liver enzymes	2 (25%)	0	0
Febrile neutropenia	0	1 (13%)	0
Anorexia	1 (13%)	0	0
Nausea	1 (13%)	0	0
Diarrhea	2 (25%)	0	0
Peripheral sensory neuropathy	1 (13%)*	0	0
Ileus	1 (13%)°	0	0
Glucose intolerance	1 (13%)	0	0

* P7 had undergone hemicolectomy 20 years previously for Burkitt's lymphoma. Ileus and grade III cytopenia occurred concomitantly. The ileus resolved, and the cytopenia was corrected in ten days by treatment with colony-stimulating factor. No second-line therapy was needed before allogeneic hematopoietic stem cell transplantation because a complete response was confirmed by positron emission tomography-computed tomography. ° P2 developed peripheral sensorial neuropathy, together with glucose intolerance due to marked bodyweight gain during brentuximab vedotin therapy. Glycemia was equilibrated using oral metformin. Neuropathy regressed (albeit not completely) 36 months after onset. GGT: γ-glutamyltransferase.

Subsequent aHSCT was performed in five cases with a controlled LPD (4 of the 6 CR and P3 in SD) at a median of 1.64 months (range, 3 days-3.1 months) after last BV administration. P1 died of an infection three months after aHSCT, whereas the four remaining patients are alive and relapse-free after a median post-aHSCT follow-up period of 25.7 months (range, 14.5-29.4). In two cases with a CR, aHSCT was not performed in view of the absence of a suitable donor (LPD1 of P1) or the underlying disease (AT in P2). P1 developed a second ALCL or an immunogenetically evolved relapse, based on *TRG* rearrangement profiles, after a 37-month CR (28 months after last BV administration). P2 had a sustained CR at last follow up (36 months after last BV administration). Overall, the median duration of objective response (time interval between the first objective response and disease progression, death or last follow up in remission) was 27.54 months (range, 0-39).

Treatment-emergent adverse events (AE) (regardless of their relationship with BV) were assessed using Common Terminology Criteria for Adverse Events v5.0. Six of the eight treatment courses featured at least one AE (Table 2), the two most frequent were anemia (n=6) and fever (n=5). Four patients presented one or more grade III AE [anemia (n=2), thrombocytopenia (n=2), neutropenia (n=1), febrile neutropenia (n=1) and γ-glutamyltransferase elevation (n=1)], and two presented a grade IV event (neutropenia). No characterized or severe infection occurred. Two patients discontinued BV treatment due to an AE: P7 after the first injection (grade II ileus and grade III cytopenia), and P2 after nine injections (grade II peripheral sensorial neuropathy, which had improved significantly at last follow up).

In summary, our results indicate that BV can be an effective first- or second-line treatment approach for selected CD30-positive LPD in patients with PID. This unconventional approach was implemented because of: (i) the patients' poor general condition; (ii) their underlying disease; or (iii) the high-risk features of LPD [all but one case were advanced (stage III/IV) LPD, and the disorder had relapsed and/or was treatment-refractory in four cases]. The treatment-emergent AE observed in our population were consistent with those previously reported and were manageable.[5-9]

In view of the rarity and diversity of LPD-PID, there are no recommendations regarding the treatment and the response evaluation of these conditions. Guidelines on management of LPD in immunocompetent hosts have not been validated in LPD-PID and those applied in post-transplant LPD are not transposable. Treatment aims in LPD-PID, in addition to controlling the LPD, need to avoid additional infectious risk and toxicities in order to bridge patients to transplant in optimal condition. Indeed, aHSCT represents definitive treatment of both LPD and PID. Our result shows that BV could be effective in this context, since it demonstrated a good tolerance profile in our small population. The level of remission required to proceed to aHSCT is subject to debate.[4] Interestingly, P3 underwent aHSCT with SD following RECIL criteria, despite significant clinical and virological responses, and showed good long-term control of the LPD. Some patients are not eligible for aHSCT because of the nature of the underlying condition or their poor general condition.[2] In such cases, BV could represent a well-tolerated therapeutic approach which may allow prolonged responses. The optimal utilization of BV (patient selection, optimal treatment regimen, and concomitant or sequential use of anti-CD20 mAb in CD20-positive LPD) has yet to be defined. Because dedicated prospective trials are unrealistic for these infrequent, heterogeneous conditions, we believe that pilot observational studies, despite their limitations, are important for setting up further multicenter observational studies. These should be designed to tailor the treatment options and optimize the position of BV within the treatment hierarchy.

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