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To the editor:

Brentuximab vedotin in relapsed primary mediastinal large B-cell lymphoma: results from a phase 2 clinical trial

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Primary mediastinal B cell lymphoma (PMBCL) is a rather infrequent aggressive lymphoma, putatively arising from a transformed thymic B cell. It accounts for <5% of all non-Hodgkin lymphomas and typically affects adolescents and young women in their third or fourth decade of life.[1] PMBCL often should be regarded as a hematological emergency and promptly treated: the initial treatment decision is crucial for the management of this disease.

PMBCL has been recognized as a subtype of diffuse large B-cell lymphoma (DLBCL) since 1994, and it has been regarded as a specific clinical and biological entity since 2001 per World Health Organization classification. Apart from its peculiar clinical presentation and pathological features, PMBCL also displays a unique molecular fingerprint, which clearly distinguishes it from the other DLBCLs and partly overlaps with the molecular profile of nodular sclerosis Hodgkin disease (HD, ie at least one-third of its genes, abnormalities on chromosome 9p and, although weaker, the CD30 expression).[2-5]

Relapse tends to occur early during the posttreatment follow-up, mostly within the first 18 months, involving ~15% to 20% of patients (half of the cases are refractory). Disease at relapse generally behaves aggressively: it may remain confined to the mediastinum or spread to subdiaphragmatic organs. Outcomes for patients with relapsed or refractory PMBCL are generally poorer than those observed for a matched population of DLBCL patients. Overall survival (OS) at 2 years after the first relapse is just half of that seen for DLBCL, even when appropriate salvage treatments (eg, platinum-based or other intensive regimens) and autologous stem cell transplantation (ASCT) are timely applied.[6,7] In addition, adding rituximab to first-line treatment improves outcomes.[8,9]

High-dose treatment and ASCT, however, can influence prognosis, mostly in patients who had partial response (PR) before ASCT: a recent retrospective study from Japan documented a significantly higher OS for transplanted versus not-transplanted patients (67% and 31%, respectively),[10] and a chance of cure can be observed in 40% to 80% of patients with disease that favorably responds to salvage treatment, according to different series.[11-14] However, ~15% of patients with refractory disease remain free of progression after ASCT.[6,11]

Brentuximab vedotin (BV) is a potent anti-CD30 antibody drug conjugate that has been approved in relapsed/refractory HD after ASCT and anaplastic large-cell lymphoma (ALCL). Beyond these consolidated indications, BV has been and is being tested in different settings and for different hematologic diseases with promising results. The CD30 antigen is present in the majority of cases of PMBCL (80%), although it is expressed heterogeneously.[1,5] A recently published phase II trial of BV in patients with relapsed/refractory DLBCL also included 6 patients with PMBCL: a 17% overall response rate (ORR) was observed, and half of the patients maintained disease stability. The responses did not correlate with the quantitative CD30 expression on tumor cells.[15]

Based on these premises, a single-arm, open-label, multicenter, phase II clinical trial evaluating the efficacy and safety of BV as a single agent in patients with relapsed/refractory histologically confirmed $CD30^+$ PMLBCL was conceived and conducted by the Italian Lymphoma Foundation. The study was approved by the institutional review board and the ethical committees and has been performed in accordance with the ethical standards as laid out in the Declaration of Helsinki (EudraCT number: 2012-000735-27, NCT02423291). All patients provided written informed consent.

BV was administered at a dose of 1.8 mg per kg as a single IV infusion on day 1 of each 21-day cycle. Patients who achieved stable disease (SD) or better as assessed by the investigator should receive a minimum of 8, but not >16 cycles of study treatment. Measures of anticancer activity were assessed by using the revised response criteria for malignant lymphoma.[16] Dedicated computed tomography scans were scheduled at baseline and at cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography scans were done at baseline and at cycles 4 and 7. The severity of adverse events (AEs) was graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm). The primary endpoint was ORR;

Table 1. Patient demographics and characteristics at baseline

Characteristic	
Sample size, n	15
Median age at therapy, y (range)	29.3 (19.5-73.4)
Male, n (%)	5 (33.3)
Stage, n (%)	
I/II	7 (46.7)
III	0 (0)
IV	8 (53.3)
IPI, n (%)	
0	1 (6.7)
1	5 (33.3)
2	5 (33.3)
3	4 (26.7)
Systemic symptoms, n (%)	5 (33.3)
Median LDH, U/L (range)	569 (250-3196)
Refractory to most recent therapy, n (%)	32 (74.4)
Median number of previous therapies (range)	3 (1-4)
Prior autologous stem cell transplant, n (%)	8 (53.3)
Prior radiotherapy, n (%)	9 (60.0)

IPI, International Prognostic Index; LDH, lactic acid dehydrogenase.

key secondary endpoints included the complete remission (CR) rate, the duration of response, progression-free survival, OS, and safety.

The safety population consisted of all patients who received ≥1 dose of the study drug, and the efficacy population comprised all patients who had ≥1 postbaseline tumor assessment.

From October 2013 to October 2015, 15 patients were enrolled in 5 Italian centers. The median age of the patients was 29.3 years (range, 19-73 years), 10 of the 15 patients (67%) were females, and 5 of the 15 patients (34%) presented B symptoms. The median number of prior treatments was 3 (range, 1-4 treatments), and 12 (80%) patients had disease that was refractory to the last therapy before BV. All patients previously received rituximab, 8 (53.3%) received ASCT, and 9 (60%) received radiation (Table 1).

The ORR was 13.3% (2/15): 2 patients achieved PR, 1 patient had SD, and the remaining 12 patients had progression of disease (PD). One patient obtained PR after 4 cycles, but then he relapsed at 7th cycle, and 1 patient obtained PR after 7 cycles, underwent allogeneic transplant, and relapsed 3 months later. The other 12 patients showed PD between the second and the seventh cycle. The patient with SD stopped the treatment after cycle 2 for a serious AE not related to BV, namely a grade 5 intestinal perforation, and subsequently died.

Six patients (40%) experienced BV-related AEs, mostly grade 1 or 2: 1 peripheral neuropathy, 1 atrial fibrillation (grade 2, rapidly resolved), 2 ALT and GGT increase, and 2 anemia. One patient experienced BV-related grade 3 fatigue. Hematologic toxicities not BV-related were all grade 1 or 2, except for 2 transient grade 4 granulocytopenia. No pulmonary, renal, vascular, metabolic, or infective toxicities were recorded. Time-to-point events were not estimated due to the limited sample size and the short duration of observations.

Twenty patients were originally planned for the study, but the study coordinator decided to stop the trial early due to drug inefficacy. Based on these results, BV should be considered inactive in the setting of relapsed/refractory PMLBCL: only 13.3% (n = 2) of the patients obtained a PR without any evidence of CR, and the duration of these responses was <3 to 4 months also including a consolidation with allotransplant. Only another experience with BV in relapsed/refractory PMLBCL was reported: the ORR was 17% (only one CR out of 6 patients).[15] This low response rate in PMLBCL was a very unexpected finding because this histologic subtype is typically characterized by high CD30 expression.

In conclusion, BV had a manageable safety profile but very low antitumor activity in patients with relapsed/refractory PMBCL, representing an unusual situation among the $CD30^+$ lymphomas, such as HD, ALCL, cutaneous T-cell lymphoma, and DLBCL, for which the ORR after BV ranges between 30% and 80%. The issue regarding the relation between BV efficacy and the level of CD30 expression is worth additional investigation to elucidate its mechanism and identify eligible patients for BV therapy more effectively, and multidisciplinary efforts are necessary. However, if BV activity is independent of CD30 expression, an alternative mechanism of activity, such as antigen presentation, may offer a rationale for continued exploration in combination.

Although not originally planned, we are now conducting a retrospective post-hoc analysis on CD30 expression in the 15 enrolled patients with the aim of comparing their CD30 expression pattern with those of a matched HL cohort of patients who achieved a response after BV therapy at our institute. Per study protocol, the results of CD30 expression from the most recent postdiagnostic biopsy of relapsed/refractory disease had to be obtained from pathology reports, thus it was not mandatory to repeat a biopsy before BV therapy, and a bias in this analysis could occur. A prospective study may also be needed to test for possible biological resistance.

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Conflicts-of-interest disclosure: P.L.Z. had an advisory role for Takeda Pharmaceuticals. The remaining authors declare no competing financial interests.

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To the editor:

Sinusoidal obstruction syndrome following CD33-targeted therapy in acute myeloid leukemia

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In late December 2016, Seattle Genetics, Inc., announced that the US Food and Drug Administration (FDA) had placed a hold or partial hold on several early-stage clinical trials of vadastuximab talirine (SGN-CD33A) in acute myeloid leukemia (AML) to further evaluate the potential risk of hepatotoxicity with this CD33 antibody–drug conjugate (ADC) when administered before or after allogeneic hematopoietic cell transplantation (HCT).[1] These holds arose from the identification of 6 patients experiencing hepatotoxicity, including several cases of sinusoidal obstruction syndrome (SOS; formerly known as veno-occlusive disease), with 4 resulting deaths. Medical details of these cases have not been provided, and it was not indicated whether SOS was confirmed through liver biopsy and to what degree other causes of liver injury were excluded if the diagnosis was made based on a typical clinical presentation. SOS is a well-recognized and often life-threatening complication following HCT, particularly in individuals undergoing myeloablative conditioning, which damages sinusoidal endothelial cells.[2] Thus, the occurrence of posttransplant SOS after SGN-CD33A exposure does not establish a causal link with this ADC. Still, these recent adverse events involving the liver are reminiscent of the experience with the first-generation CD33-directed ADC, gemtuzumab ozogamicin (GO), when given at the initial dosing of 9 mg/m^2 per dose, and call into question the safety of antibody-based therapeutics targeting CD33, at least in some patients.

In GO, a humanized CD33 antibody is conjugated to a disulfide derivative of calicheamicin-γ_1 via a hydrolyzable linker.[3,4] Free and conjugated calicheamicin caused nonspecific liver toxicity in preclinical testing, and GO was found to be preferentially distributed to the liver.[4] An association between GO and SOS was noted early in the clinic, and a subsequent FDA-requested prospective observational registry showed an SOS rate of around 10%, with a substantial subset of the cases being fatal.[5,6] Histologically, GO-associated liver damage is characterized by sinusoidal injury with extensive sinusoidal fibrosis, stellate cell activation, centrilobular hemorrhage into the space of Disse, and zone 3 hepatocyte necrosis.[7] The exact repair mechanisms after GO-mediated sinusoidal injury are unknown, but a protracted process is indicated by the fact that the association with SOS was particularly strong when GO was administered within 3 to 4 months from allogeneic HCT.[5,8] In animal models of sinusoidal injury marked by loss of sinusoidal endothelial cells, restoration of these cells is dependent on the presence of marrow-derived progenitor cells.[9]

Proposed mechanisms through which GO could damage hepatic sinusoids include exposure to unconjugated calicheamicin circulating in the bloodstream, nonspecific uptake of the ADC by Kupffer cells and liver sinusoidal endothelial cells, or CD33-mediated uptake of GO by 1 or more of the cell populations in the liver that express CD33 (Kupffer cells, sinusoidal endothelial cells, stellate cells).[7,10] It is tempting to consider a CD33-specific mechanism as the primary cause; however, antigen-mediated ADC uptake cannot explain the reported association between SOS (seen primarily after HCT) and prior exposure to inotuzumab ozogamicin (IO), an ADC in which the calicheamicin derivative is linked to a humanized CD22 antibody.[11] The latter suggests the importance of nonspecific (target-independent) hepatic toxicity, with ADCs containing moieties toxic to sinusoidal endothelial cells.

Recent studies with a nonbinding antibody-calicheamicin conjugate containing the same linker payload as GO and IO in cynomolgus monkeys showed loss of sinusoidal endothelial cells early after drug exposure and development of changes consistent with early SOS at later points.[12] Clearance of antibody-bound tumor cells in the liver through antibody-dependent phagocytosis by Kupffer cells is well documented for several antibody-based therapeutics.[13,14] Thus, ADCs, bound or unbound to their target antigen, may be taken up by Kupffer cells via Fc receptors, resulting in liver-dominant off-target delivery of the antineoplastic molecule. In a similar fashion, sinusoidal endothelial cells avidly take up immunoglobulins through endocytic pathways.[15-17] The proposed mechanisms underlying the development of SOS are