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Letter To Blood

Brentuximab vedotin in Relapsed Primary Mediastinal Large B-Cell Lymphoma: Results from a Phase 2 Clinical Trial

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To the editor:

Primary mediastinal B cell lymphoma (PMBCL) is a rather infrequent aggressive lymphoma, putatively arising from a transformed thymic B cell. It accounts for less than 5% of all non-Hodgkin's lymphomas, and typically affects adolescents and young women in their third or fourth decade of life.[1] PMBCL should be often 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 the 1994, and it has been regarded as a specific clinical and biological entity since 2001 by the World Health Organization classification. Apart from its peculiar clinical presentation and pathological features, PMBCL also displays an unique molecular fingerprint, which clearly distinguishes it from the other DLBCLs and partly overlaps with the molecular profile of nodular sclerosis Hodgkin's disease (HD, at least a third of its genes, abnormalities on chromosome 9p and, although weaker, the CD30 expression).[2-5]

Relapse tends to occur early during the post-treatment follow-up, mostly within the first 18 months, involving approximately 15-20% 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 the one seen for DLBCL, even when appropriate salvage treatments (e.g. platinum-based or other intensive regimens) and autologous stem cell transplantation (ASCT) are timely applied.[6,7] To note that adding rituximab to first line treatment improves outcomes.[8,9]

High-dose treatment and ASCT, however, can influence prognosis, mostly in patients who were in 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% - 80% of patients with disease that favorably responds to salvage treatment, according to different series.[11-14] However, about 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 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 included also 6 patients with PMBCL: a 17% overall response rate (ORR) was observed, and half of patients maintained disease stability. 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-positive 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 down in the Declaration of Helsinki (EudraCT number: 2012-000735-27, NCT02423291). All the patients provided written informed consent.

BV was administered at the dose of 1.8 mg/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 investigator should receive a minimum of 8, but no more than 16 cycles of study treatment. Measures of anti-cancer activity were assessed 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. Severity of adverse events (AEs) was graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Primary endpoint was ORR; key secondary endpoints included complete remission (CR) rate, duration of response, progression-free survival, OS, and safety.

The safety population consists of all patients who received ≥1 dose of study drug and the efficacy population comprises all patients who had ≥1 post-baseline tumor assessment.

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

The ORR was 13.3% (2/15): two patients achieved PR, 1 patient had SD and the remaining 12 patients had progression of disease (PD). One patient obtained PR after four

cycles, then he relapsed at 7th cycle, and one patient obtained PR after seven cycles, underwent allogeneic transplant and relapsed three months later. The other 12 patients showed PD between the 2th and the 7th 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 1-2: 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 1-2, except for two transient grade 4 granulocytopenia. No pulmonary, renal, vascular, metabolic, or infective toxicities were recorded. Time-to-point events were not estimated due to limited sample size and short duration of observations.

Twenty patients were originally planned but the study coordinator decided to stop the trial beforehand due to drug inefficacy. On the basis of these results BV has to be considered no active 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 less than 3-4 months (despite a patient underwent subsequently 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 real unexpected finding because this histologic subtype is typically characterized by high CD30 expression.

In conclusion, BV had a manageable safety profile but a real 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 in order to elucidate its mechanism and identify eligible patients for BV therapy more effectively and multi-disciplinary efforts are necessary. On the other hand, 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.

As not originally planned, we are now conducting a retrospective post-hoc analysis on CD30 expression in the 15 enrolled patients with the aim to compare their CD30 expression pattern with the one of a matched HL cohort of patients who achieved a response after BV therapy at our Institute. Since per study protocol results of CD30 expression from the most recent post-diagnostic biopsy of relapsed/refractory disease had

to be obtained from pathology reports, it is not said that the available biopsy was the one performed just before BV therapy and a bias in this analysis could occur. A prospective study could be also needful to test the possible biologic resistance despite target availability.

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Table 1. Patient demographics and characteristics at baseline

	n = 15
Median age at therapy, years (range)	29.3 (19.5-73.4)
Male, n (%)	5 (33.3)
Stage, n (%) - I/II - III - IV	 7 (46.7) 0 (0) 8 (53.3)
IPI, n (%) - 0 - 1 - 2 - 3	 1 (6.7) 5 (33.3) 5 (33.3) 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.

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