Brentuximab vedotin followed by ABVD +/- radiotherapy in patients with previously untreated Hodgkin lymphoma: final results of a pilot phase II study

The past few decades have seen major advances in understanding the pathobiology and clinical management of Hodgkin lymphoma (HL), making it one of the most successfully treated cancers worldwide.[1] At present, more than 90% of patients with early-stage, and up to 80% with advanced-stage disease, are cured with current combined-modality treatment.[2] Nevertheless, some 15% to 30% of all patients respond poorly, fail to respond, or relapse after up-front conventional therapy. These patients have little chance of achieving a durable remission.[3] Moreover, long-term treatment-related toxicities, including second primary malignancies, have emerged as leading causes of morbidity and mortality among these, mostly young, survivors, with a devastating impact on their life expectancy.[4-6] Today, maintaining or improving these outcomes, along with reducing late iatrogenic complications, represents an important challenge for patients with HL.

The recent advent of the anti-CD30 antibody-drug conjugate brentuximab vedotin provides, for the first time, the opportunity to selectively target the malignant Hodgkin and Reed-Sternberg cell populations while virtually sparing normal cells. In the pivotal phase II trial, brentuximab vedotin showed remarkable clinical activity and a manageable safety profile in a subset of heavily pretreated relapsed or refractory HL patients following autologous stem cell transplant; 75% (76 of 102) of patients achieved an objective response and 94% (96 of 102) achieved some tumor reduction.[7] Interestingly, the recent evidence that a proportion of patients responding to brentuximab vedotin still remain in remission after more than four years of follow up has raised the suggestion that they have been cured.[8] Recently, brentuximab vedotin was combined with ABVD within either a concomitant or sequential schedule treatment. In a phase I dose-escalation study of previously untreated HL, the concomitant administration of 1.2 mg/kg brentuximab vedotin with a modified-standard treatment AVD every two weeks proved to be feasible and highly active, yielding 96% complete responses.[9] Notably, the concomitant use of brentuximab vedotin and bleomycin was discouraged because of excessive pulmonary toxicity.

Based on these promising findings, we designed a multicenter, single-arm, pilot phase II study to investigate the role of brentuximab vedotin 1.8 mg/kg for 2 cycles before starting standard treatment with 3 or 6 cycles of ABVD, depending on risk group, with or without radiotherapy (RT), in patients with newly diagnosed stage IA, IIA, and IIIA HL. The primary end point was response rate after brentuximab vedotin before starting ABVD. This was assessed by ^{18}F-fluorodeoxyglucose PET (FDG/PET) scan and defined as a reduction in the now recommended Five Point scale or, if there was no change in Deauville score, as a reduction in standardized uptake value (SUV) intensity compared to maximum basal SUV.[10] Secondary end points were: i) complete response (CR) rate at the end of the full treatment program as defined by Deauville score 1, 2 or 3; ii) 1-year progression-free survival (PFS) measured from the day treatment started to the date of progressive disease; and iii) the safety profile of brentuximab vedotin.

Between April and October 2013, 12 patients were enrolled in our trial and all received the planned 2 cycles of brentuximab vedotin at the full dose of 1.8 mg/kg. Fifty-eight percent of the patients were female (n=7), while 92% (n=11) had stage II disease. Median age was 36 years (Table 1). After the 2 cycles of brentuximab vedotin, 10 patients (83%) achieved a complete metabolic response, and one achieved a partial metabolic response, resulting in an overall response rate (ORR) of 92%. One patient, with stage III disease, did not respond. Following brentuximab vedotin, 10 patients with stage II disease received 3 cycles of ABVD, and one received 4 cycles. Additional RT was delivered to 5 patients. The patient with stage III received 6 cycles of ABVD and no RT. After the full treatment program, the ORR reached 100%, with 11 complete responses and one partial response converting from disease progression. At a median follow up of 12 months, all patients were alive, with 11 still in complete remission, and one relapse. Median 1-year PFS (range 7-16 months) was 92% (95%CI: 55-99). Interestingly, the overall FDG/PET concordance between local and central review process was 92%, with only one case amended from a score of 4 to a score of 2 by the central review panel. The treatment was generally well tolerated, and most common adverse events during brentuximab vedotin therapy were primarily grade 1 or 2, including nausea, vomiting, pyrexia and fatigue. The only grade 3 adverse events were transient and asymptomatic increases in liver transaminases (n=3, 25%) and gamma-glutamyl transpeptidase (n=2, 17%). No grade 4 adverse events were registered. During ABVD with or without RT, grade 3 and 4 neutropenia occurred in 9 patients (75%), but toxicities were transient and resolved with granulocyte colony-stimulating factor support (Table 2).

In this study, 2 cycles of brentuximab vedotin used upfront in treatment-naïve patients with newly diag-

Table 1. Patients' demographic and clinical characteristics (n=12).

Characteristic	N	%
Age, years		
Median	36	
Range	19-70	
Gender		
Male	5	42
Female	7	58
Stage		
II	11	92
III	1	8
ECOG PS		
0	12	100
Albumin		
> 4 gr/dL	8	66
< 4 gr/dL	2	17
NA	2	17
Hemoglobin		
< 10.5 gr/dL	1	8
Lymphocytes		
< 600/mm^3 and/or < 8% WBC	3	25
ESR		
> 50 mL/h	2	17
LDH		
> ULN	3	25

ECOG PS: Eastern Cooperative Oncology Group Performance Status; NA: not assessed; WBC: white blood cells; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase.

nosed HL achieved a rewarding response rate with a favorable safety profile: 92% obtained an objective response, and 83% a complete metabolic response before starting ABVD. In spite of all the limitations of a small study, our data compare favorably to the CR rates previously achieved after either 2 cycles of ABVD in patients with treatment-naïve HL (85.8% and 74.8% for early favorable and unfavorable HL, respectively),[11] or after single-agent treatment with brentuximab vedotin in patients with relapsed or refractory HL (34%)[7] and ALCL (62%).[12] Notably, in our current study, all responding patients maintained their response when treated with ABVD, suggesting that delaying the administration of chemotherapy after brentuximab vedotin is a feasible approach without negative consequences on patients' outcome. Indeed, after a minimum follow-up period of one year, all 11 patients who achieved a complete remission with brentuximab vedotin first and ABVD +/- RT thereafter, maintained their response. There was only one non-responder to brentuximab vedotin. In this patient, disease progression was initially converted to PR by ABVD; however, in spite of this chemotherapeutic approach, the patient again progressed. Overall, the safety profile of the sequential regimen was acceptable. Consistent with previously reported data,[8,9] the most common brentuximab vedotin-related adverse events were generally mild in grade and manageable, while grade 3 events were rare, asymptomatic and transient. Interestingly, only one patient experienced grade 1 peripheral neuropathy. Hematologic toxicities during chemotherapy were as expected, both in terms of frequency and severity, and were well managed with standard supportive care. Notably, the sequential addition of ABVD to brentuximab vedotin did not result in any additional pulmonary toxicity. These data are particularly interesting in the light of recently published long-term results of a pivotal study of brentuximab vedotin[8] showing that heavily pre-treated refractory or relapsed HL patients who respond to brentuximab vedotin can achieve durable remission and favorable survival outcome. In an earlier study up-dated by Gopal *et al.*,[8] 47% of patients achieving a CR remained free from lymphoma after a median follow up of 53.5 months, thus raising expectation of cure for at least a fraction of patients with brentuximab vedotin alone. Interestingly, one factor associated with the likelihood of remaining in remission was a low tumor burden at baseline, further supporting the introduction of brentuximab vedotin earlier in the clinical course of patients with HL. Moreover, we believe that, based on our results, the opportunity to drop bleomycin once a patient achieves a complete metabolic response could be the subject of future study. Although our present study was limited by its small sample size, its single arm design, and short follow-up period, our data compare favorably with the recently published results of a phase II study of front-line brentuximab vedotin monotherapy in 27 HL patients aged 60 years and over.[13] The outstanding single-agent activity of brentuximab vedotin that we observed paves the way for future therapeutic approaches aimed at reducing, or even avoiding, the need for chemotherapy or RT in a patient population for whom the risk-to-benefit ratio of therapies has to be carefully balanced.

In conclusion, the use of brentuximab vedotin as initial treatment of early- or intermediate-stage HL is associated with a very promising anti-lymphoma activity and a very acceptable toxicity profile, warranting further study as a first-line therapy.

Table 2. Common treatment-related adverse events.

Adverse events	Grade 1-2	Grade 3	Grade 4
Neutropenia	–	5	5
Nausea	4	–	–
Increased transaminase	–	3	–
Increased GGT	–	2	–
Pyrexia	3	–	–
Vomiting	2	–	–
Fatigue	2	–	–
Anemia	2	–	–
Erythema	2	–	–
Peripheral neuropathy	1	–	–
Infusion reaction	1	–	–
Cystitis	1	–	–
Edema	1	–	–
Pruritus	1	–	–
Diarrhea	1	–	–
Constipation	1	–	–
Dry mouth	1	–	–
Heartburn	1	–	–
Alopecia	1	–	–
Headache	1	–	–
Hyperuricemia	1	–	–
Hyperglycemia	1	–	–

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References

1. Canellos GP, Rosenberg SA, Friedberg JW, et al. Treatment of Hodgkin lymphoma: a 50-year perspective. J Clin Oncol. 2014;32(3):163-168.
2. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2011. Bethesda, MD: US National Cancer Institute, 2014.
3. Federico M, Luminari S, Iannitto E, et al. ABVD compared with BEA-

COPP compared with CEC for the initial treatment of patients with advanced Hodgkin's lymphoma: results from the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial. J Clin Oncol. 2009;27(5):805-811.
4. Aleman BM, van den Belt-Dusebout AW, Klokman WJ, et al. Long-term cause-specific mortality of patients treated for Hodgkin's disease. J Clin Oncol. 2003;21(18):3431-3439.
5. Hodgson DC. Late effects in the era of modern therapy for Hodgkin lymphoma. Hematology Am Soc Hematol Educ Program. 2011;2011:323-329.
6. van Eggermond AM, Schaapveld M, Lugtenburg PJ, et al. Risk of multiple primary malignancies following treatment of Hodgkin lymphoma. Blood. 2014;124(3):319-327.
7. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol. 2012;30(18):2183-2189.
8. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-1243.
9. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol. 2013;14(13):1348-1356.
10. Meignan M, Barrington S, Itti E, et al. Report on the 4th International Workshop on Positron Emission Tomography in Lymphoma held in Menton, France, 3-5 October 2012. Leuk Lymphoma. 2014;55(1):31-37.
11. Raemaekers JM, Andre MP, Federico M, et al.Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol. 2014;32(12):1188-1194.
12. Pro B, Advani R, Brice P, et al. Four-year survival data from an ongoing pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood. 2014;124(21).
13. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. Blood. 2015;126(26):2798-804.