Phase I dose-escalation study of brentuximab-vedotin combined with dexamethasone, high-dose cytarabine and cisplatin, as salvage treatment in relapsed/refractory classical Hodgkin lymphoma

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Phase I dose-escalation study of brentuximab-vedotin combined with dexamethasone, high-dose cytarabine and cisplatin, as salvage treatment in relapsed/refractory classical Hodgkin lymphoma: The HOVON/LLPC Transplant BRaVE study

Clinical activity of brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, has been demonstrated in relapsed/refractory classical Hodgkin Lymphoma (R/R cHL) in pivotal phase I and phase II studies.[1,2] Adverse events ascribed to BV as single agent are mostly mild and reversible.[3] Combining BV and chemotherapy prior to high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) might lower the tumor burden and decrease the relapse rate after HDC-ASCT and thus contribute to cure.[4,5]

Brentuximab vedotin has already been combined with standard therapy in a sequential strategy and concurrently with chemotherapy regimens such as ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) before HDC-ASCT,[6-11] and resulted in a CMR rate of more than 75% prior to HDC-ASCT. However, the combination of BV with multi-agent chemotherapy can be associated with significant toxicity.[8,10] Tumor burden reduction by a combination of BV and DHAP treatment is attractive because DHAP by itself is well tolerated in patients with R/R cHL and results in 20% complete remission (CR) and 70% partial remission [PR; based on conventional computed tomography (CT) scanning] and 50-60% metabolic CR (CMR) while stem cell mobilization potential is maintained.[12] In this multicenter, open-label, phase I dose-escalation study, patients aged 18 years or older with a histologically confirmed CD30$^+$ R/R cHL were treated with three cycles of BV-DHAP, followed by HDC (BEAM regimen: carmustine, etoposide, cytarabine and melphalan) with an ASCT rescue.

Brentuximab vedotin was administered at the full dose of 1.8 mg/kg on the first day of each cycle of DHAP, with escalation of the dose of cisplatin and cytarabine. BV was combined with either 75% of the dose cisplatin on day 1 and 75% of cytarabine on day 2 [dose level (DL) 1], 75% cisplatin and 100% cytarabin (DL2) or full dose of all agents (DL3). Full-dose cisplatin was defined as 100 mg/m^2 and full-dose cytarabin was defined as 2 g/m^2 q 12 hours (2 doses). Dexamethasone 40 mg was given at day 1-4. Granulocyte-colony stimulating factor (G-CSF) (Neulasta) 6 mg fixed dose was given subcutaneously on day 5 of DHAP cycles 1 and 3 from DL2 onwards after prolonged neutropenia requiring delay of the next cycle was seen in 2 out of 3 patients treated at DL1. For stem cell mobilization, G-CSF 5 µg/kg was administered twice daily from day 10 of BV-DHAP cycle 2 until stem cell harvest.

Sequential cohorts of 3 patients were treated in a '3+3' dose escalation scheme. Decisions regarding feasibility, dose escalation to the next cohort, and continuation or cessation were based on the occurrence of dose-limiting toxicity (DLT). DLT was defined as either: a) grade 3-4 non-hematologic toxicity, including neurotoxicity with laboratory abnormalities grade equal or greater than 3, only when present for more than two weeks or not returning to grade 0/1; infections only if grade 4; b) all-cause death, with the exception of death due to cHL; c) delay of the second or third cycle of BV-DHAP by more than ten days due to neutropenia, despite use of growth factor prophylaxis. Enrollment at each dose level required a minimum of 3 patients and a maximum of 6 patients. After inclusion of 3-6 patients, inclusion to this particular dose level was discontinued until DLT occurrence had been determined at day 22 after start of cycle 3 for these patients. Dose escalation was stopped as soon as at least 2 patients experienced a DLT or when the highest planned dose level had been reached. Before proceeding to a higher dose level, the DLT data at the preceding dose level were reviewed by the Data Safety Monitoring Board (DSMB).

Table 1. Patients' characteristics.

	All, n=12	DL1, n=3	DL2, n=3	DL3 n=6
Age, years (range)	30.5 (21-56)	32.0 (30-38)	25.0 (24-31)	30.5 (21-56)
Female %	67	67	33	83
ECOG performance status 0 at study entry (%)	100			
Prior therapies (n)				
ABVD	5	1		4
ABVD + RT	4	1	2	1
Escalated BEACOPP	2	1		1
Escalated BEACOPP + RT	1		1	
Diagnosis to 1st BV-DHAP (years)	1.2 (0.7-11.2)	1.2 (1.2-3.3)	1.0 (1.0-1.0)	2.5 (0.7-11.2)
Ann Arbor stage at diagnosis (n)				
I/II	6	1	2	3
III/IV	6	2	1	3
Best response to first-line treatment				
CR	9	3	1	5
PR	2		1	1
Unknown	1*		1	

DL: dose level; ECOG: Eastern Cooperative Oncology Group; ABVD: adriamycin+bleomycin+vinblastine+dacarbazine; RT: radiotherapy; CR: complete remission; PR: partial remission. Values are given as medians (range) or as specified in the table. *No positron emission tomography / computed tomography scan after RT, CR formally not confirmed.

Patients continued with BEAM conditioning preferably within 28 days, but no later than 42 days after start of the third BV-DHAP cycle. Carmustine (BCNU) 300 mg/m^2 was administered on day -7, cytarabine 200 mg/m^2 intravenously daily from day –6 to day –3, etoposide 200 mg/m^2 intravenously daily from day –6 to day –3, and melphalan 140 mg/m^2 intravenously on day –2 before reinfusion of autologous stem cells (day 0). The primary objective was to establish feasibility and the recommended dose level (RDL) of BV in combination with DHAP, administered in a 21-day schedule. Secondary end points included assessment of toxicity, metabolic response rate as assessed by ^{18}F-FDG and computed tomography (positron emission tomography and computed tomography, PET-CT) at the end of induction after three cycles of BV-DHAP, and success rate of autologous peripheral blood stem cell harvest after treatment with BV in combination with DHAP.

Twelve patients with a median age of 30.5 years (range 21-56 years) and histologically proven R/R cHL received BV-DHAP in three escalating dose cohorts. Patients' characteristics are presented in Table 1. Nine patients had previously been treated with ABVD and 3 with escalated BEACOPP. Two patients were refractory to first-line treatment and 10 were in first relapse. The median time from primary diagnosis to the first cycle of BV-DHAP was 1.2 years (range 0.7-11.2 years).

We observed grade 3-4 adverse events in 7 patients; neutropenia grade 4 (n=2, DL1), neutropenia grade 3 and thrombocytopenia grade 4 (n=1, DL3), thromboembolic event grade 3 (n=1, DL 1), elevated transaminases grade 3 (n=1, DL3, resolved), leukocytosis grade 4 (n=1, DL3) and hypokalemia (n=1, DL3). Four patients suffered from grade 1-2 sensory peripheral neuropathy (PNP), which fully resolved in 2 patients. No motor PNP was observed.

Because of prolonged neutropenia in 2 out of 3 patients treated in DL1, which delayed the second BV-DHAP cycle by one week, the protocol was amended to a mandatory pegylated G-CSF (Neulasta) injection after cycles 1 and 3, after which neutropenia has been the cause of cycle delay in only one other patient treated in DL3.

A total of ten serious adverse events (SAEs) occurred in 4 patients, all at DL3. One patient experienced hypokalemia grade 4 as well as acute liver failure grade 4 lasting longer than fourteen days [occurring at 11 days after BV (BV-DHAP cycle 3) and 2 days after initiation of amoxicillin/clavulanic acid]. A liver biopsy showed non-specific toxicity. This patient also experienced atrial fibrillation grade 3 and was treated with cardioversion. These last two SAEs were possibly related to BV and classified as dose-limiting toxicities (n=1, DL3). The same patient experienced fever of unknown origin grade 3, not related to BV (no neutropenia at the time of fever). A second patient exhibited elevated transaminases grade 3 unlikely to be related to BV. A third patient experienced a central venous catheter-related infection grade 3 (not related to BV), varicella zoster reactivation grade 3 after BV-DHAP cycle 3 (no prophylaxis was indicated), and fever of unknown origin grade 3. The fourth patient experienced acute kidney injury grade 3 (resolved) and pneumonitis grade 3 (resolved). These SAEs were considered unlikely to be related to BV treatment.

Three patients were treated at DL1, 3 patients at DL2 and 6 patients at DL3. After three cycles of BV-DHAP, PET CT showed a CMR in 11 out of 12 patients (92%). In the one patient with a persistent FDG-positive mediastinal lesion, a biopsy after BEAM did not show residual Hodgkin lymphoma. This patient also achieved a histologically confirmed CR after second-line treatment.

Stem cell harvest was successful in all patients after one round of stem cell apheresis with a median yield of 5.3x10^6 CD34$^+$ cells/kg (range 3.0-25.9 CD34$^+$ cells/kg). All 12 patients underwent subsequent BEAM chemotherapy and ASCT. Median time to absolute neutrophil recovery recovery was 14.5 days (range 8-43 days). Hereafter, 11 out of 12 patients were in CMR and one patient had a biopsy-proven CR; all remained alive in complete response after a median follow up of 2.0 years (range 1.8-3.0 years).

We report results from a dose-escalation trial of DHAP combined with BV treatment followed by BEAM and ASCT in 12 patients with R/R cHL. The use of BV-DHAP at full dose of all the drugs was considered feasible and resulted in acceptable toxicity, and it is the dose regimen taken forward in the phase II part of the study. The reported acute kidney injury in one patient was most likely attributable to cisplatin in the DHAP treatment. We also observed transient increases in serum transaminase levels possibly related to BV, with one serious adverse event of acute liver failure grade 4. The latter occurred eleven days after initiation of treatment with BV, and the patient had started amoxicillin-clavulanic acid two days prior to the adverse event. Careful follow up of liver function tests in patients treated with BV in combination with DHAP is warranted.

Toxicity results in our study are in line with previous findings that adding BV to standard chemotherapy results in a mild increase in toxicity. However, the observed response rates by PET-CT prior to ASCT and the CR rate of 100% with all patients remaining in complete remission at a median follow up of two years are encouraging.

The phase II part of the study in 60 patients at full doses of all drugs is now ongoing (*clinicaltrials.gov identifier: 02280993*).

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References

1. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010;363(19):1812-1821.
2. 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.
3. De Claro RA, Mcginn K, Kwitkowski V, et al. U.S. Food and Drug Administration approval summary: brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma or relapsed systemic anaplastic large-cell lymphoma. Clin Cancer Res. 2012;18(21):5845-5849.
4. Adams HJ, Kwee TC. Prognostic value of pretransplant FDG-PET in refractory/relapsed Hodgkin lymphoma treated with autologous stem cell transplantation: systematic review and meta-analysis. Ann Hematol. 2016;95(5):695-706.
5. Devillier R, Coso D, Castagna L, et al. Positron emission tomography response at the time of autologous stem cell transplantation predicts outcome of patients with relapsed and/or refractory Hodgkin's lymphoma responding to prior salvage therapy. Haematologica. 2012;97(7):1073-1079.
6. Chen R, Palmer JM, Martin P, et al. Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma. Biol Blood Marrow Transplant. 2015;21(12):2136-2140.
7. Michallet AS, Guillermin Y, Deau B, et al. Sequential combination of gemcitabine, vinorelbine, pegylated liposomal doxorubicin and brentuximab as a bridge regimen to transplant in relapsed or refractory Hodgkin lymphoma. Haematologica. 2015;100(7):e269-271.
8. Garcia-Sanz R, Sureda A, Gonzalez AP, et al. Brentuximab Vedotin Plus ESHAP (BRESHAP) Is a Highly Effective Combination for Inducing Remission in Refractory and Relapsed Hodgkin Lymphoma Patients Prior to Autologous Stem Cell Transplant: A Trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO). Blood. 2016;128(22):1109.
9. Moskowitz AJ, Schoder H, Yahalom J, et al. PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. Lancet Oncol. 2015;16(3):284-292.
10. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. N Engl J Med. 2018;378(4):331-344.
11. LaCasce A, Bociek RG, Matous J, et al. Brentuximab Vedotin in Combination with Bendamustine for Patients with Hodgkin Lymphoma who are Relapsed or Refractory after Frontline Therapy. Blood. 2014;124(21):293.
12. Josting A, Rudolph C, Reiser M, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol. 2002;13(10):1628-1635.