Combining Brentuximab Vedotin with dexamethasone, high-dose cytarabine, and cisplatin (BV-DHAP) as salvage treatment in paediatric relapsed or refractory classical Hodgkin lymphoma: two case reports.

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Abstract

Hodgkin Lymphoma (HL) is a common malignancy in adolescents. For relapsed/refractory disease many regimens have been proposed and novel agents are increasingly used. Brentuximab Vedotin (BV) is an antiCD30 antibody-drug conjugate used as single agent or in combination with classical regimens mainly in adults, while limited is the experience in paediatrics. We report here on two boys with aggressive and high-risk relapsed HL, successfully treated with the BV plus DHAP regimen as induction salvage treatment. Our experience provides initial real-world evidence on the use of BV-DHAP as first-line salvage therapy for high-risk relapsed/refractory HL and expands the current therapeutic choices.

Introduction

Hodgkin Lymphoma (HL) is one of the most commonly occurring malignancies in adolescents and young adults, curable in the majority of cases. Unfortunately, a subgroup of patients do not enter remission with front line therapy or relapse after initial response to therapy (R/R cHL). In such cases, treatment options are different regimens of chemotherapy, radiotherapy, high-dose chemotherapy plus autologous stem cell transplantation (HDCT/ASCT), and immunotherapy[1,2]. Many regimens have been proposed[1] and recently novel agents are increasingly involved in order to achieve a better response without increasing the toxicity burden. Brentuximab Vedotin (BV) is an antibody-drug conjugate combining the anti-CD30 monoclonal antibody with the monomethyl auristatin-E. Studies are evaluating the combination of BV with classical regimens mainly in adults, while limited is the experience in paediatrics.

Recently a phase II study[3] investigated for the first time BV plus the DHAP regimen as salvage therapy in adults, with encouraging results. The experience with this regimen in children or adolescent has not been described so far.

Results

We report here on two boys with high-risk relapsed HL, successfully treated with the BV-DHAP regimen as induction salvage treatment.

Case Description n.1

A 15-year-old boy presented classical-HL, advanced stage (IVB) and started treatment according to the EuroNet-PHL-C2 protocol, TL-3. After two OEPA cycles, the PET/CT scan for the early response assess-

ment (ERA) showed partial metabolic response (pMR) with Deauville Score (DS) 5. He went on with 4 DECOPDAC-21 cycles. Late response assessment (LRA) PET/CT scan showed slight residual uptake in the mediastinum, requiring mediastinal residual node radiotherapy (28.8 Gy). The three-month follow-up CT scan showed pulmonary nodules (19mm diameter); the PET/CT revealed high metabolic uptake in the lungs and in multiple supra-diaphragmatic adenopathies. After repeated biopsies, insufficient to confirm the suspect of relapsed disease, the pulmonary biopsy confirmed the diagnosis of R/R cHL. According to the EuroNet-PHL recommendations[1], this patient was candidate to HDCT/ASCT. Considering published data in adults[3], we decided to take a chance on salvage induction chemotherapy regimen adopting the BV plus DHAP regimen (figure 1) followed by HDCT/ASCT. The boy collected successfully hematopoietic stem cells after one cycle. After 2 cycles, the interim PET/CT revealed complete metabolic response (cMR), DS2. After 4 BV-DHAP the PET/TC showed no pathological uptake. The patient then proceeded to HDCT/ASCT. Hematological toxicity grade 3-4 was reported without any particular adverse event (AE) during the BV-DHAP administration. Considering the high- risk disease, BV consolidation program (12 doses) was added. The boy is in complete remission and good clinical conditions at 36-month follow-up.

Case Description n.2

A 13-year-old boy was diagnosed with cHL stage IIBE, bulky disease, extranodal involvement of pleura and enrolled in the EuroNet-PHL-C2 study, TL-3. The ERA-PET, after 2 OEPA, showed pMR with DS-5. Four DECOPDAC-21 cycles were performed and the LRA-PET showed the complete disappearance of the pathological uptake. One month later, the patient presented Covid-19 and, shortly after, enlargement of left axillary lymphnodes. The excisional biopsy showed no evidence of the disease. However, because of the persistence of the axillary lymphadenopathy, high fever and deteriorated clinical conditions, a new biopsy confirmed relapsed cHL, stage IVB (bone marrow involvement). Based on our previous experience, considering the high risk of the disease, the patient started with BV-DHAP as salvage therapy. The clinical conditions recovered. The interim PET/CT evaluation showed pMR, DS-3; the BM trephine confirmed absence of HL, and stem cell apheresis was successfully performed. The patient proceeded with two further cycles of BV-DHAP. At this moment the disease assessment showed persistent pMR. With the aim to obtain complete metabolic response before HDCT/ASCT, and taking into account the good clinical conditions of the patient, 2 cycles of BV-Bendamustine[4] regimen were delivered. Haematological toxicity grade 3-4 without any particular adverse event was reported. The pre-ASCT PET/TC scan evaluation showed a cMR and the boy proceeded to HDCT/ASCT. Considering the features of high-risk disease, the patient started consolidation treatment with 12 doses of BV. At the time of this writing, after 12-month follow-up, the boy is in good clinical conditions free of disease.

Discussion

The standard of care, both in adults and paediatric patients, for risk R/R cHL is the HDCT/ASCT[1]. Achieving cMR before the HDCT/ASCT has been demonstrated as the most impactful factor affecting DFS and OS[5,6,7,8,9]. For this reason, identifying the best rescue therapy represents the most important challenge. There is no "gold standard" chemotherapy regimen because no randomized trials have been done on children or adolescent; the overall response rates (ORR) of salvage regimens vary between 70% and 90%[1,10].

The DHAP regimen has been extensively studied as rescue therapy in high-risk Hodgkin and non-Hodgkin lymphomas with optimal relationship between efficacy and toxicity, in particular ORR of 88% (21% CR, 67% PR) in R/R cHL has been reported[11,12,13]. Novel agents like BV have gained an increasing role in R/R cHL. The use of BV as single agent for the salvage therapy is reported in adults with ORR of 75%, CR 34%, with manageable toxicity[14]. Better results have been achieved combining classical chemotherapy regimens and BV[1]. Despite the widespread use of BV in adults and the large number of prospective and retrospective studies, there are few data on efficacy and safety in paediatrics. The initial experience of BV in pediatric patients with R/R cHL showed 47% ORR[15]. A retrospective multicentric italian real-life study on 66 young patients demonstrated the efficacy of BV single agent or combined with chemotherapy in R/R cHL with manageable toxicity[16]. Recently the combination regimen of BV-bendamustine in pediatric patients reported ORR of 81%[17]. In adults the phase II HOVON/LLPC Transplant BRaVE study investigated the

combination BV plus DHAP achieving cMR in 42/52 (81%) evaluable patients and pMR in 5 (10%), with ORR of 90%. After a median follow-up of 27 months, the 2-year PFS by intention-to-treat was 73.5%, and the 2-year OS was 94.9%[3]. This combination has not been investigated in the pediatric setting, so far. In our experience the BV-DHAP regimen resulted highly effective. The patients we reported on were both characterized by rapid progression and high burden of disease leading to a stage IVB bulky disease in about a two-month lapse. Considering the high-risk disease, our previous experience with DHAP and the encouraging data of BV-DHAP in adults we decided to adopt this regimen. We gained disease control and cMR before the HDCT/ASCT. Furthermore, monitoring haematological toxicity, liver and renal function, ototoxicity and neurotoxicity we found a lower rate of AEs than reported in adults. Both patients did not experience any important AE, exception for a grade II/III neutropenia, and a mild hepatotoxicity. None of these events was likely to cause treatment discontinuation. We then decided to start maintenance with BV following the results of the AETHERA trial[18]. This choice was also possible because of the low degree of toxicity shown during the previous cycles.

In conclusion, in our experience in two adolescent patients with R/R cHL, the BV-DHAP regimen resulted highly effective to obtain mCR prior to HDC/ASCT in very high risk and aggressive disease. Patients should be closely monitored for toxicity, especially hematological toxicity. Our experience provides initial practical and real-world evidence in favour of the use of BV-DHAP as first-line salvage therapy for high-risk relapsed/refractory HL. This regimen expands the currently existing therapeutic choices making BV-DHAP a suitable salvage therapy.

Conflict of interest

None of the authors has any conflicts of interest to declare.

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LegendsFigure 1 Schematic overview of the BV-DHAP regimen. Drugs with their dosage are indicated on the left. Cycles were delivered every 21 days

Table 1 Clinical characteristics of the two patients

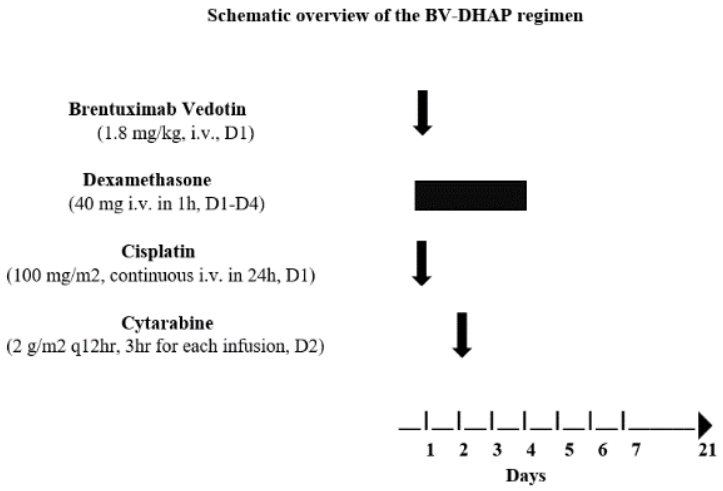

FIGURE 1 Schematic overview of the BV-DHAP regimen. Drugs with their dosage are indicated on the left. Cycles were delivered every 21 days.

Note: Granulocyte colony-stimulating factor (G-CSF) was given at a dose of 5µg/kg from day 4 until day 13 to respect the dose-intensity.

TABLE 1 Clinical characteristics of the two patients

	Patient 1
Ann Arbor stage at diagnosis	IVB
Prior therapies	2 OEPA+4 DECOPDAC-21 and RT
Time to relapse	4 months
Ann Arbor stage at relapse	IVB
Risk factors at relapse*	Early relapse after more than 4 cycles of first line chemothe
Salvage treatment	4 BV-DHAP followed by HDCT/ASCT
Medium time of delivering (days) of chemotherapy**	21-23
Best response at salvage treatment	CR
Follow up (DFS)	36 months

*Risk factors according to the EuroNet-PHL criteria

** According to hematological recovery (Absolute neutrophil count $>1x10^9$/L and platelets count $> 1x10^9$/L)