Alternative salvage regimens for relapsed/refractory classical Hodgkin’s lymphoma

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Objective and importance: Hodgkin’s lymphoma (HL) is a well-curable disease. The treatment usually includes combined multiagent conventional chemotherapy and radiotherapy. One-fifth of the patients need repeated treatments because of relapse or primary progressive disease. Those HL patients, who cannot be cured at least with salvage therapy (including autologous haemopoietic stem cell transplantation (auto-HSCT)), have really unfavourable prognosis.

Intervention: For this heavily pretreated subset of HL patients, novel but less toxic treatment strategies should be considered. Brentuximab-vedotin (BV) is a novel targeted treatment option, which was administered after the failure of two different regimens in patients, who were ineligible for auto-HSCT or after the failure of auto-HSCT. Moreover, there are favourable data with chemotherapeutical regimens supplemented with rituximab not only in relapsed but also in newly diagnosed classical HL patients. Bendamustine, an almost forgotten 50-year-old drug, lives its renaissance in the twenty-first century, which can be administered in refractory HL as well. Combination of the ‘new’ and ‘old’ drugs might be also helpful.

Conclusion: Our data suggest that rituximab plus bendamustine (supplemented with or without BV) could be a suitable alternative bridging salvage therapy for heavily pretreated HL patients.

Keywords: Classical HL, Bendamustine, Brentuximab-vedotin, Rituximab, ¹⁸FDG-PET/CT

Introduction

Thanks to risk- and response-adapted treatment strategies, more than 80% of newly diagnosed classical Hodgkin’s lymphoma (HL) patients can be cured, and are expected to be long-term survivors. HL remains a challenging disease in those patients, who progress or relapse after first-line therapy.¹ Salvage regimens (including autologous haemopoietic stem cell transplantation (auto-HSCT)) can cure approximately 50% of relapsed/refractory patients. Auto-HSCT can be effective if it is performed in complete or very good partial remission. Those HL patients who cannot be cured at least with salvage therapy are expected to have a median survival of less than 3 years.² Treatment options have been quite limited for this subset of patients. The most promising new drugs (mammalian target of rapamycin inhibitors, lenalidomide, histone deacetylase inhibitors (HDACi), programmed death 1 (PD-1) blockers) are available only in clinical trials for the treatment of relapsed/refractory HL.³,⁴ It has been a great challenge to manage those HL patients who are waiting for auto- or allogeneic (allo)-HSCT, but are not in complete remission. A suitable new option is anti-CD30 targeting with brentuximab-vedotin (BV), which was approved for the therapy of auto-HSCT failure or after failure of two regimens in patients who were not candidates for transplantation.⁵ There are growing numbers of promising results with chemotherapeutical regimens supplemented with rituximab not only in relapsed but also in newly diagnosed classical HL patients.⁶,⁷ Moreover, there are favourable data with the application of a ‘new–old’ drug called bendamustine.⁸,⁹ Here we report on four heavily pretreated patients whose initial treatment failed. So far there have been no published data with rituximab–bendamustine–BV therapy for the treatment of relapsed/refractory HL patients.

Case 1

In March 2007, a 22-year-old female patient was diagnosed with nodular sclerosis (NS) subtype HL, stage II/AX. She was treated with eight cycles of adriamycin, bleomycin, vincristine, and dacarbazine combination (ABVD) and involved field radiation therapy (IFRT). Complete remission was verified with CT in
January 2008. In April 2008, stage IV/B relapse was recognized, which was confirmed by PET/CT (Fig. 1A). After two cycles of salvage dexamethasone, cisplatinum, and cytosine arabinoside therapy (DHAP), the PET/CT showed progression (Fig. 1B), so the treatment was modified to ifosfamide, gemcitabine, vinorelbine, and prednisone (IGEV) regimen. The administration of two cycles of IGEV therapy resulted in complete metabolic remission (CMR) on the next PET/CT in July 2008 (Fig. 1C). In August 2008, a successful CD34+ stem cell harvesting was performed. In October 2008, a rapid progression of the lymphoma was recognized, so total body irradiation was applied before the R-mini-BEAM (rituximab–carmustine–etoposide–cytosine arabinoside–melphalan) conditioning. The auto-HSCT was performed on 18 October 2008. In March 2009, disseminated relapse was detected on the 100 days post-transplantation (post-Tx) PET/CT scan (Fig. 1D). However, as she was in a good clinical condition, no chemotherapy was given, but she was referred for an allo-HSCT, and in the lack of a human leukocyte antigen identical sibling, the search for an unrelated bone marrow donor was started. In December 2009, the control PET/CT scan showed further progression (Fig. 1E) therefore, ifosfamide, carboplatin, and etoposide (ICE) rescue treatment was started, which was intolerable because of side effects (grade III–IV myelosuppression). In March 2010, bendamustine-based therapy with additional rituximab (RB) was initiated. The patient received a dose of bendamustine of 90 mg/m² on the first and second days, and she received 375 mg/m² rituximab on the first day of each 28-day cycle. After two cycles of this regimen, a partial treatment response was detected on the control PET/CT scan (Fig. 1F), and after four further cycles of the RB therapy, she achieved CMR (Fig. 1G). The patient was expected to undergo an allo-HSCT with reduced intensity conditioning (RIC) as she had only a matched unrelated donor. In February 2011, based on the control PET/CT scan a disseminated relapse was recognized (Fig. 1H), so we started an RB regimen, which had formerly been effective. After two cycles of RB therapy, B symptoms were recognized, so the treatment was modified to BV (1.8 mg/kg, every 3 weeks), as a monotherapy, which resulted in clinically stable disease. In February 2012, further progression appeared after five cycles of BV regimen (Fig. 1I). Numerous palliative chemotherapy regimens (included vinorelbine, dexamethasone, and carboplatin) were ineffective (Fig. 1J) and she died on 1 November 2012.

Case 2
In October 2006, a 34-year-old male was diagnosed with NS subtype of HL, clinical stage III/B. After six cycles of ABVD chemotherapy he achieved complete remission, which was verified with CT. In
September 2011, another lymph node biopsy was performed and the histological examination revealed lymphocyte-rich (LR) subtype of HL, stage IV/BE (Fig. 2A). After two cycles of salvage DHAP therapy the PET/CT scan showed partial remission (Fig. 2B), so the treatment was modified IGEV. He was administered two cycles of IGEV regimen, and CMR was detected on the next PET/CT examination (Fig. 2C). In March 2012, he underwent an R-BEAM conditioning followed by auto-HSCT. Post-Tx maintenance therapy was started with BV (1.8 mg/kg). In April 2013, after the administration of 16 cycles of BV the control PET/CT scan revealed supradiaphragmatic relapse (Fig. 2D). In June 2013, RB (rituximab 375 mg/m² on day 1; bendamustine 120 mg/m² on days 1 and 2, each 28-day cycle) rescue therapy was started. After six cycles of RB, the next PET/CT examination detected CMR (Fig. 2E), and the patient was in CMR without chemotherapy in January 2014 (Fig. 2F). He was referred for an allogeneic transplantation. In September 2014, the control PET/CT evaluated relapse (Fig. 2G), so we started the RB immunotherapy again, which had formerly been effective. After two cycles of RB therapy the patient was in excellent clinical condition and the PET/CT also showed CMR (Fig. 2H). In the hope of maintaining a long-term complete remission (CR), two additional cycles of RB therapy will be administered and the patient is expected to undergo a haploidentical allo-HSCT with RIC.

Case 3
In August 2010, a 61-year-old male was diagnosed with stage IV/BE (Fig. 3A), LR subtype of HL. After administration of two cycles of ABVD, the interim PET/CT scan showed CMR (Fig. 3B). After six cycles of ABVD and IFRT (36 Gy) the patient achieved CR, which was confirmed by PET/CT scan (Fig. 3C and D). In November 2012, after 15 months of CR, B symptoms occurred, so the next PET/CT detected disseminated stage IV relapse (Fig. 3E). In January 2013, another biopsy sample was taken from a para-aortic lymph node. The histology revealed mixed cellularity subtype of HL, so DHAP salvage treatment was started. An auto-HSCT was planned, but the patient refused the procedure. After two cycles of DHAP therapy, the PET/CT detected partial response (Fig. 3F). In September 2013, after four complete courses of DHAP the PET/CT scan showed progression (Fig. 3G), therefore the therapy was changed into RB regimen (rituximab 375 mg/m² on day 1; bendamustine 120 mg/m² on days 1 and 2, each 28-day cycle),
in October 2013. After the administration of two cycles of RB regimen, the next PET/CT scan revealed a partial response (Fig. 3H). A further four cycles of RB were given, and the next PET/CT detected a new hypermetabolic mass before the vertebrae XII (Fig. 3I). Because of the localized relapse, IFRT therapy (30 Gy) was recommended. In September 2014, further progression was revealed on the control PET/CT (Fig. 3J). Considering these results, BV (1.8 mg/kg) plus ICE rescue treatment was started in November 2014. In March 2015, after two cycles of BV–ICE regimen, a control PET/CT examination is planned.

**Case 4**

In January 2013, a 21-year-old male was diagnosed with stage II/BX (mediastinal bulky), NS subtype of HL (Fig. 4A). The interim PET/CT result was almost CMR after receiving two cycles of ABVD (Fig. 4B). In October 2013, after six complete courses of ABVD, the restaging PET/CT scan showed a residual mediastinal mass (Fig. 4C). IFRT therapy was recommended, but the patient refused it. Considering the patient’s good clinical condition, watchful waiting was chosen. In November 2013, the next PET/CT detected progression (Fig. 4D), so we planned mediastinal lymph node biopsy. Unfortunately, it was refused by the patient again. In January 2014, after two cycles of salvage DHAP regimen the next PET/CT verified further progression (Fig. 4E). Cervical lymph node biopsy confirmed NS subtype of HL. Considering this result, the treatment was modified into RBBV regimen (rituximab 375 mg/m² on day 1; bendamustine 120 mg/m² on days 1 and 2, each 28-day cycle; 1.8 mg/kg BV on day 1). After the administration of two cycles of RBBV, the next PET/CT scan verified CMR (Fig. 4F). After R-BEAM conditioning regimen, the patient underwent a successful auto-HSCT, which was supplemented with mediastinal/neck supraclavicular region IFRT (36 Gy). In September 2014, the post-Tx PET/CT examination detected CMR (Fig. 4G), BV maintenance treatment was started. In April 2015, based on physical examination, laboratory findings, and simple imaging procedures, the patient was still in CR.

**Discussion**

The management of classical HL relapse after a second-line treatment (including auto-HSCT) or primary refractory disease still remains a great challenge. In the case of a localized relapse IFRT might be effective. Josting et al. reported that IFRT seemed to be most beneficial when recurrent disease extends beyond previously unirradiated lymph nodes in those patients who relapse after auto-HSCT (stage...
I–II relapse, without B symptoms and no extranodal disease). Radiotherapy as a salvage regimen could be suitable only for limited number of patients. Novel chemotherapeutical and/or targeted treatment strategies are needed to improve survival outcome. Blockade of the PD-1 pathway seems to be promising. Pembrolizumab and nivolumab are two anti-PD-1 antibodies, phase I clinical trials were evaluating the activity in relapsed/refractory HL. The overall response rates (ORRs) were 53 and 87%. HDACi (panobinostat, vorinostat, entinostat, and mocetinostat) show favourable clinical activity with documented tumour reduction, but the ORR alone was between 16 and 27%. Lenalidomide, as a single agent, has modest activity in heavily pretreated HL patients, the ORR was between 13 and 19%. Based on the data above lenalidomide and HDACi, as single agents, probably were not effective enough in relapse/refractory HL patients. Some new, phase I–II upcoming trials will investigate the anti-PD-1 antibodies, HDACi, lenalidomide alone and in combination in heavily pretreated HL (which are available on the website http://clinicaltrials.gov). Related to the above mentioned results RB(BV) could be a suitable alternative salvage option for relapsed or primary refractory HL patients.

Mechanism of action and the results of clinical trials

BV

BV is a targeted therapeutic option for HL patients. This drug provides significant improvement compared to conventional polychemotherapy. In 2012, Younes et al. reported favourable results of a large, phase II trial evaluating the activity of BV in heavily pretreated relapsing or refractory HL after auto-HSCT (BV dose was 1.8 mg/kg every 3 weeks). The ORR was 75%, CR was seen in 34% of patients, and PR in 40%.
Currently running clinical trials are seeking the role of BV in a first-line setting, as well as treating autologous stem cell transplant candidate patients, relapsing after auto-HSCT, bridging to allogeneic stem cell transplant, and treating elderly patients. There are a lot of open questions about its overall benefit and its combination possibilities with conventional chemotherapeutic agents, and if combination is possible which agent should be combined with it. In addition, combination therapy may intensify side effects, in particular, combining with such agents, as bendamustine, which is also new in the treatment of HL.

**Bendamustine**

After BV, ‘old’ bendamustine is the second ‘new’ drug to enter clinical practice with promising efficacy in the past 30 years. Bendamustine is a unique cytostatic agent with structural similarities to alkylating agents and purine analogues, but it is non-cross-resistant with alkylating agents and other drugs either *in vitro* or *in vivo*. Bendamustine is characterized by its bifunctional action, since it induces apoptosis due to its p53-dependent alkylating activity, with a DNA-damaging effect that is more pronounced and longer-lasting than that of other alkylating agents. The definitive proof of activity came from four studies of single agent bendamustine in relapsed/refractory HL. These studies also confirmed that bendamustine is a safe and effective regimen for patients relapsing after auto-HSCT and an interesting cytoreductive strategy prior to allo-HSCT. In 2013 Moskowitz *et al.* reported results of a phase II trial evaluating the activity of single agent bendamustine in heavily pretreated patients. In 34 evaluable patients bendamustine was administered in a dose of 120 mg/m² as a 30-minute infusion on days 1 and 2 every 28 days. The ORR was 53%, CR was seen in 33% of patients, and PR in 19%. In those HL patients who relapsed within 3 months after auto-HSCT, no evaluable response was detected. The median duration of response was 5 months. The authors found these results unfavourable and speculated on the possibility of combining this treatment with other agents that might maintain the response duration. Corazzelli *et al.* published retrospective data with single agent bendamustine in 41 patients. After two to four cycles, ORR was 78% and CR was 29%. After six to eight cycles of complete courses the final ORR was 58%, with 31% CR. Other retrospective clinical trials confirmed these results. It would be useful to find the biological factors that identify the patients who are going to respond.

**Rituximab**

Rituximab is a monoclonal antibody directed against the cell-surface marker CD20. In a study, Rassidakis *et al.* reported classic HL Reed–Sternberg (HRS) cells expressed CD20 in 22% of 598 patients studied. Based on the new molecular and pathogenetical findings in HL, it has become clear that the microenvironment plays a critical role in the survival of malignant HRS cells. HRS cells make up only approximately 1–5% of total tumour bulk in HL. It is thought that perhaps rituximab’s effect *in vivo* may not be due to killing of HRS cells, rather it may be secondary to eliminating surrounding reactive B cells, leading to a decrease in cytokine and chemokine secretion, therefore targeted therapies against the microenvironmental CD20 positive polyclonal B cells and the putative HRS stem cells may increase the response rate and the survival of the HL patients. There are promising reports on the administration of rituximab in relapsed classical HL. In a study from M.D. Anderson Cancer Center, 22 heavily pretreated HL patients (with CD20 expression on HRS cells) were enrolled. Rituximab was given IV weekly (375 mg/m²) for 6 consecutive weeks. The ORR was 22% (five patients, one CR, four PR), and 36% (eight patients) had stable disease. Objective response was seen regardless of CD20 expression on RS cells. A few case reports are available in the literature documenting the benefit of rituximab in HL.

**Combination therapy with R–B–BV**

Based on *in vitro* observations there is a synergism between bendamustine and rituximab. Our data underline that bendamustine–rituximab treatment was an effective and very safe choice for heavily pretreated patients. BV and bendamustine have independent mechanisms of action and are highly active with manageable safety profiles when administered as single agents to patients with HL who relapse after auto-HSCT (BV: 34% CR, bendamustine: 33% CR). Patients received 1.8 mg/kg BV on day 1 with 90 mg/m² bendamustine on days 1 and 2 every 3 weeks for up to six cycles. Forty-five patients (58% female), with median age of 35 years (range 19–79), were involved in the study. Fifty-eight per cent of patients had relapsed disease and 42% of patients had primary refractory disease. The CR rate was 82% of patients and the overall objective response rate (CR+PR) was 94%. The majority of CRs was achieved after two cycles of combination therapy. The average duration of response for patients who obtained CR was 10.4 months. Related to the above mentioned and our results bendamustine (+R±BV)-based salvage therapy might be helpful for this vulnerable HL population. Two patients achieved CR (Case 1: 11 months and Case 2: 15 months), one patient reached PR (Case 3: 7 months) with RB regimen. RBBV treatment was successfully administered in one young refractory patient (Case 4), who achieved complete remission after this novel treatment.
and underwent an auto-HSCT. The patient was in CR 17 months (April 2014) ago. The RB(BV) therapy was a very safe regimen in our heavily pretreated HL group, who relapsed or progressed after at least three lines of chemotherapy. The patients had no notable treatment-related side effects. There are no published data on trials with RB(BV) regimen, except our case report on RB therapy.

**Conclusion**

Rituximab–bendamustine (supplemented with BV) can be a less toxic and effective alternative bridging salvage option to achieve complete or good partial remission before auto-salvage option to achieve complete or good partial remission. There are no published lines of chemotherapy. The patients had no notable group, who relapsed or progressed after at least three treatments.

Rituximab–bendamustine can be a very safe regimen in our heavily pretreated HL patients. Further clinical studies might be needed to clarify the correct place of this novel targeted treatment modality in relapsed/refractory HL populations. A combination with PD-1 checkpoint inhibitors might improve remission rates and expected sustained responses.

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