Hematology

Alternative salvage regimens for relapsed/refractory classical Hodgkin-lymphoma

--Manuscript Draft--

Manuscript Number:	HEM843R1
Full Title:	Alternative salvage regimens for relapsed/refractory classical Hodgkin-lymphoma
Article Type:	Case Report
Keywords:	classical HL, bendamustin, brentuximab-vedotin, rituximab,18FDG-PET/CT
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Abstract:	Objective and importance: Hodgkin-lymphoma (HL) is a well-curable disease. The treatment usually includes combined multiagent conventional chemotherapy and radiotherapy. 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 hemopoetic 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 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 renessaince in the 21th century, it 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 bendamustin (supplemented with or without brentuximab-vedotin) could be a suitable alternative bridging salvage therapy for heavily pretreated HL patient.
Funding Information:	

Alternative salvage regimens for relapsed/refractory classical Hodgkin-lymphoma

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The authors declare no conflict of interest.

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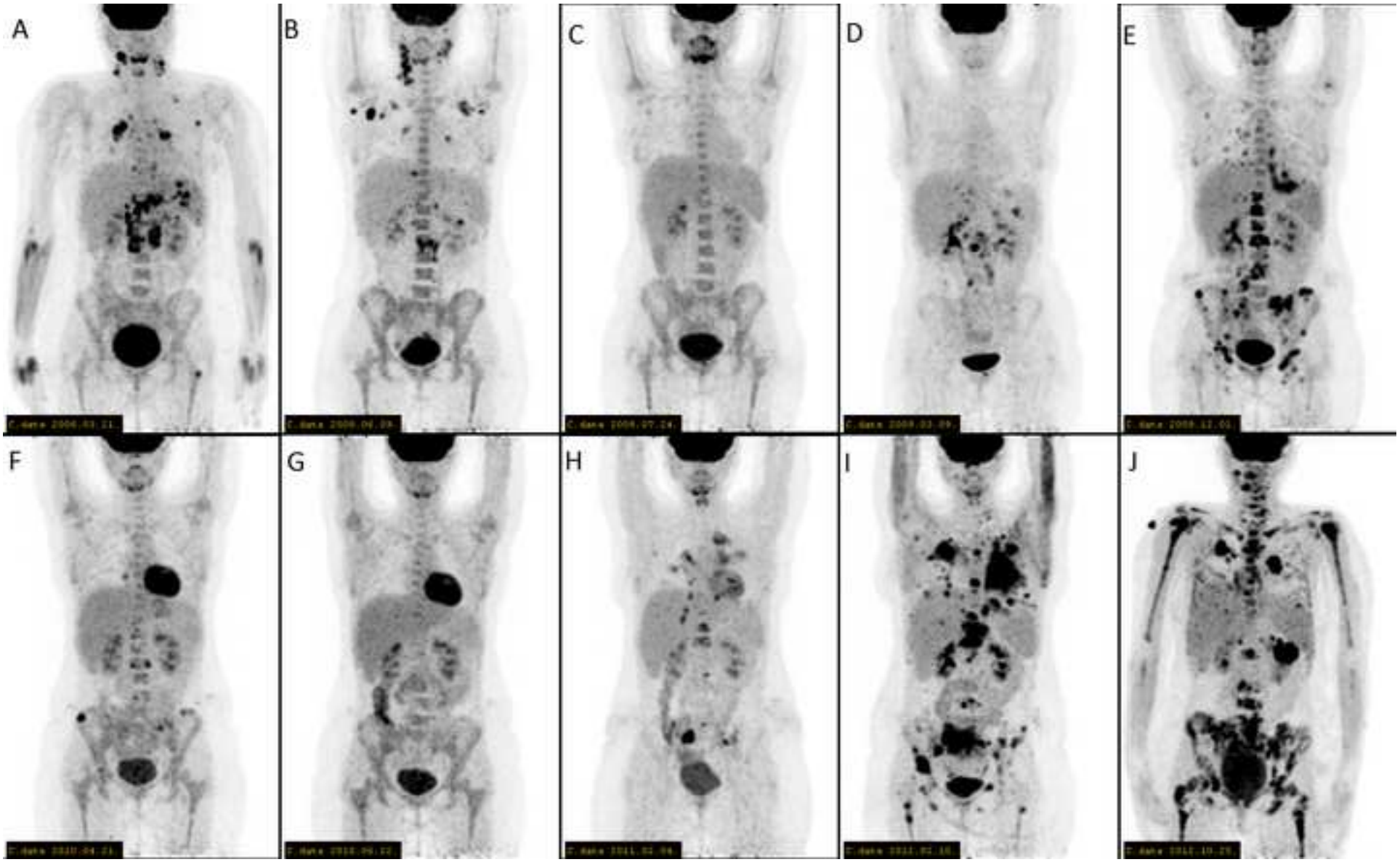

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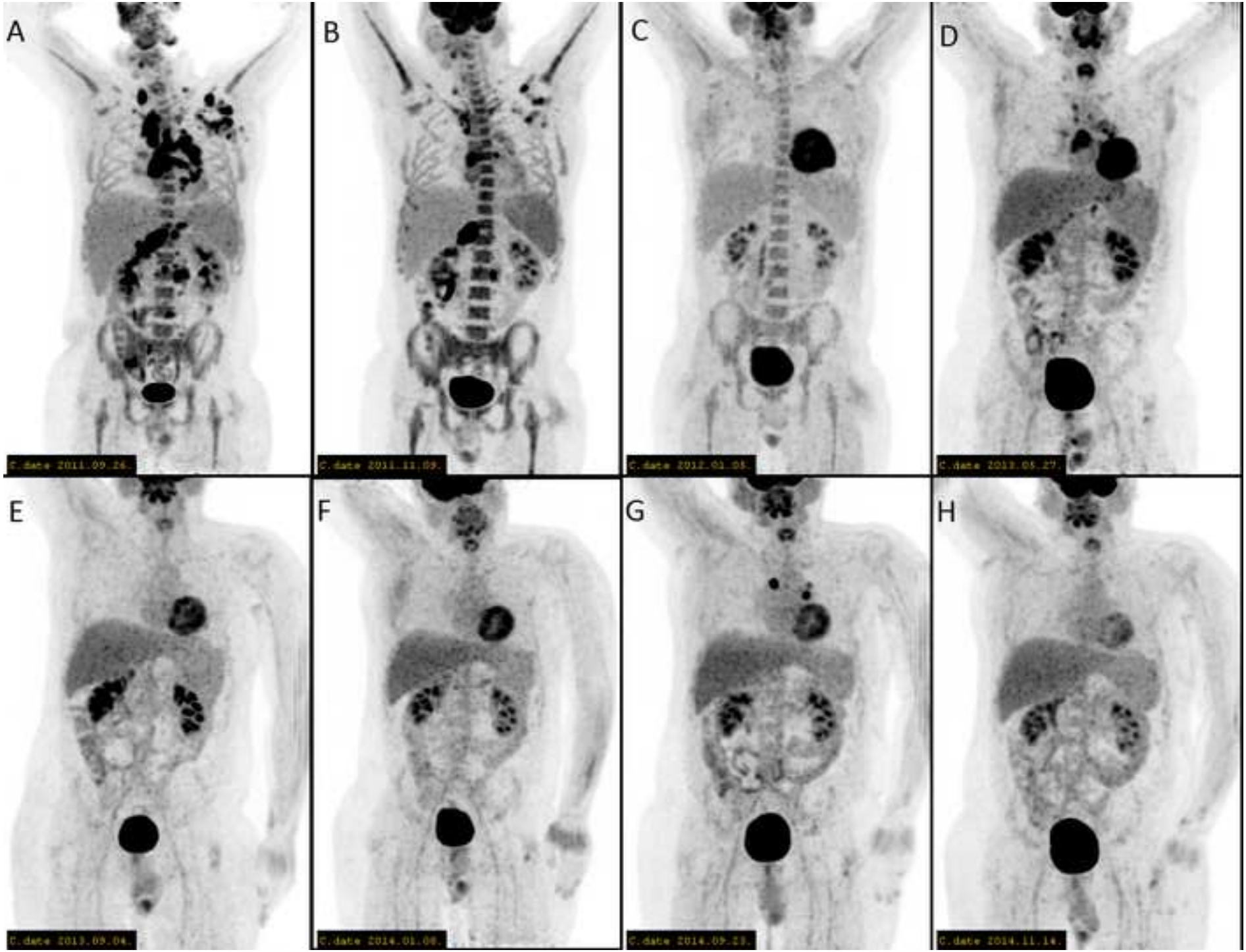

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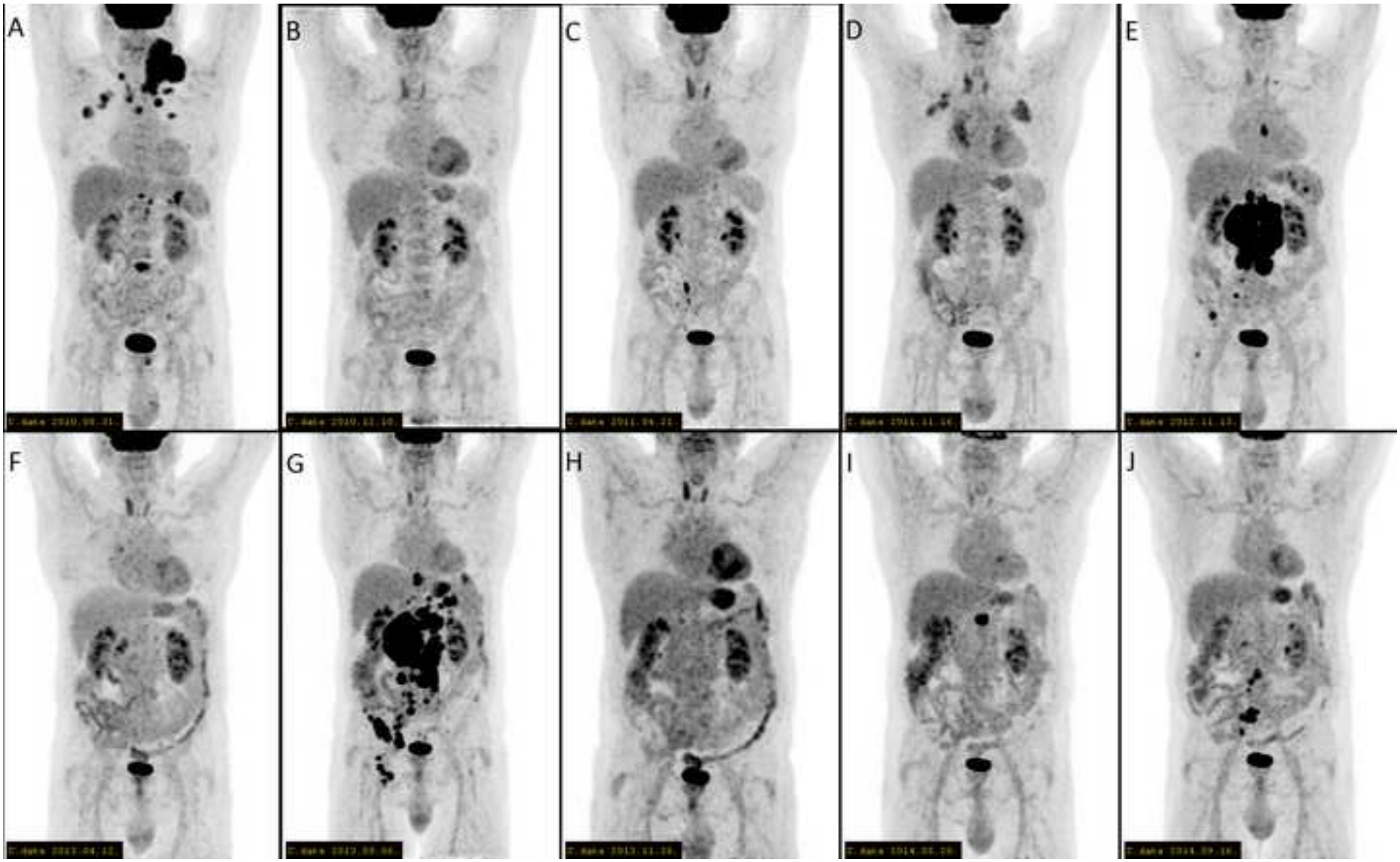

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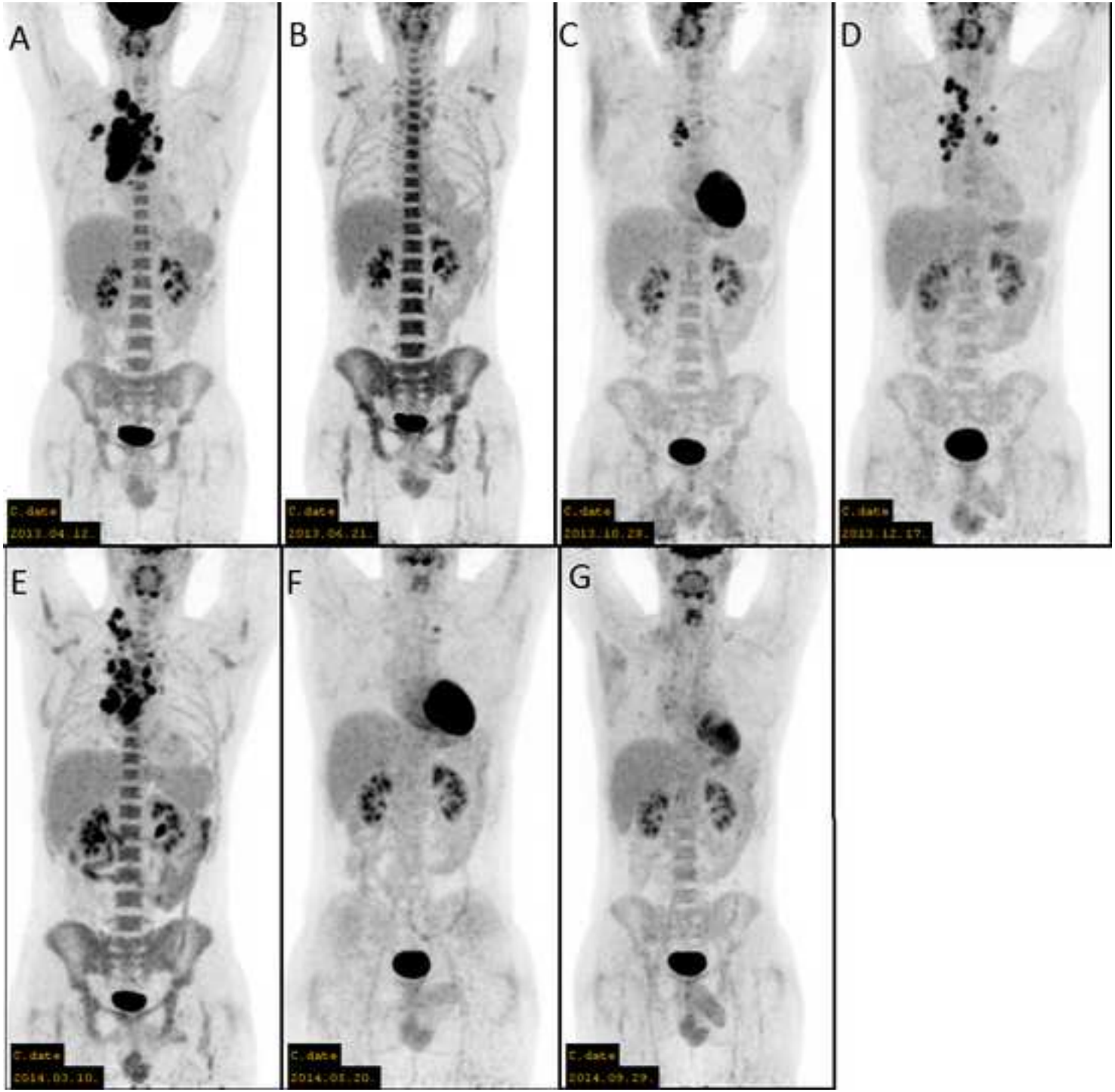

List of figures

Case 1 (1.tiff)

Figure 1. Stage IV relapse (A), Progression after 2 cycles of DHAP (B), CMR after 2 cycles of IGEV (C), Stage IV relapse on the post-Tx scan (D), Further progression without chemotherapy (E), Partial response after 2 cycles of RB (F), CMR after further 4 cycles of RB (G), Stage IV relapse (H), Progression after BV regimen (I), Progression after numerous palliative regimen (J).

Case 1 (2.tiff)

Figure 2. Stage IV relapse (A), Partial response after 2 cycles of DHAP (B), CMR after 2 cycles of IGEV (C), Stage II relapse after BV therapy (D), CMR after 6 cycles of RB (E), CMR without treatment (F), Stage II relapse (G), CMR after 2 cycles of RB (H).

Case 3 (3.tiff)

Figure 3. Primary staging PET/CT stage IV/BE (A), Interim PET/CT scan showed CMR after 2 cycles of ABVD (B), Restaging PET/CT after 6 cycles of ABVD and IFRT, the patient received CMR (C), Pulmonary laesions – infection- (D), Stage IV relapse (E), Partial response after 2 cycles of DHAP (F), Progression after 4 cycles of DHAP (G), Partial response after 2 cycles of RB (H), Localized relapse after 6 cycles of RB (I), Progression after IFRT (J).

Case 4 (4.tiff)

Figure 4. Primary staging PET/CT stage II/BX (A), Interim PET/CT scan showed CMR after 2 cycles of ABVD (B), Restaging PET/CT scan showed progression after 6 cycles of ABVD (C), Further progression without chemotherapy (D), Progression after 2 cycles of DHAP (E), CMR after 2 cycles of RBBV (F), CMR on the post-Tx scan (G)

Introduction

Thanks to risk- and response- adapted treatment strategies, more than 80% of newly diagnosed classical Hodgkin-lympoma (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 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 three years [2]. Treatment options have been quite limited for this subset of patients. The most promising new drugs (mTOR inhibitors, lenalidomide, histone deacetylase inhibitors, 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 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-brentuximab-vedotin 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 8 cycles of adriamycin, bleomycin, vincristine, dacarbasine 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 (Fig1A). After two cycles of salvage dexamethasone, cisplatinum, and cytosine arabinoside therapy (DHAP), the PET/CT showed progression (Fig1B), 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 (Fig1C). 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-cytosin-arabinosid-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 (Fig1D). 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 (Fig1E) therefore, ifosfamide, carboplatine, 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 (Fig1F), and after four further cycles of the RB therapy, she achieved CMR

(Fig1G). 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 recognised (Fig1H), so we started an RB regimen, which had formerly been effective. After 2 cycles of RB therapy, B symptoms were recognised, so the treatment was modified to BV (1.8 mg/kg, every 3 week), as a monotherapy, which resulted in clinically stable disease. In February 2012, further progression appeared after 5 cycles of BV regimen (Fig1I). Numerous palliative chemotherapy regimens (included vinorelbine, dexamethasone, carboplatin) were ineffective (Fig1J) and she died on 01. November 2012.

C**ase 2**

In October 2006, a 34-year-old male was diagnosed with NS subtype of HL, clinical stage III/B. After 6 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 (Fig2A). After 2 cycles of salvage DHAP therapy the PET/CT scan showed partial remission (Fig2B), so the treatment was modified IGEV. He was administered 2 cycles of IGEV regimen, and CMR was detected on the next PET/CT examination (Fig2C). 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 (Fig2D). In June 2013, RB (rituximab 375mg/m2 on day 1; bendamustine 120 mg/m2 on days 1 and 2, each 28 day cycle) rescue therapy was started. After 6 cycles of RB, the next PET/CT examination detected CMR (Fig2E), and the patient was in CMR without chemotherapy in January 2014 (Fig2F). He was referred for an allo-HSCT, but he had only a matched unrelated donor. In September 2014, the control PET/CT evaluted relapse (Fig2G), so we started the RB immunochemoterapy again, which had formerly been effective. After 2 cycles of RB therapy the patient was in excellent clinical condition and the PET/CT also showed CMR (Fig2H). In the hope of maintaining a long-term CR, to additional cycles of RB therapy will be administered and the patient is expected to undergo a haploidentical allo-HSCT with reduced intensity conditioning.

Case 3

In August 2010, a 61-year-old male was diagnosed with stage IV/BE (Fig3A), LR subtype of HL. After administration of 2 cycles of ABVD, the interim PET/CT scan showed CMR (Fig3B). After 6 cycles of ABVD and IFRT (36Gy) the patient achieved CR, which was confirmed by PET/CT scan (Fig3C-3D). In November 2012, after 15 months of CR, B symptoms occurred, so the next PET/CT detected disseminated stage IV relapse (Fig3E). In January 2013, another biopsy sample was taken from a paraaortical 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 2 cycles of DHAP therapy, the PET/CT detected partial response (Fig3F). In September 2013, after 4 complete courses of DHAP the PET/CT scan showed progression (Fig3G), therefore the therapy was changed into RB regimen (rituximab 375mg/m2 on day 1; bendamustine 120 mg/m2 on days 1 and 2, each 28 day cycle), in October 2013. After the administration of 2 cycles of RB regimen, the next PET/CT scan revealed a partial response (Fig3H). A further 4 cycles of RB were given, and the next PET/CT detected a new hypermetabolic mass before the vertebrae XII (Fig3I). Because of the localized relapse, IFRT therapy (30Gy) was recommended. In September 2014, further progression was revealed on the control PET/CT (Fig3J). Considering these results, BV (1.8 mg/kg) plus ICE rescue treatment was started in November 2014**.** In March 2015, after 2 cycles of BV-ICE regimen, a control PET/CT examination is planned.

C**ase 4**

In January 2013, a 21-year-old male was diagnosed with stage II/BX (mediastinal bulky), NS subtype of HL (Fig4A). The interim PET/CT result was almost CMR after receiving 2 cycles of ABVD (Fig4B). In October 2013, after 6 complete courses of ABVD, the restaging PET/CT scan showed a residual mediastinal mass (Fig4C). 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 (Fig4D), so we planned mediastinal lymph node biopsy. Unfortunately, it was refused by the patient again. In January 2014, after 2 cycles of salvage DHAP regimen the next PET/CT verified further progression (Fig4E). Cervical lymph node biopsy confirmed NS subtype of HL. Considering this result, the treatment was modified into RBBV regimen (rituximab 375mg/m2 on day 1; bendamustine 120 mg/m2 on days 1 and 2, each 28 day cycle; 1.8 mg/kg brentuximab-vedotin on day 1). After the administration of 2 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 (Fig4G), 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 [10]. 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) [11]. Radiotherapy as a salvage regimen could be suitable only limited portion of patients. Novel chemotherapeutical and/or targeted treatment strategies are needed to improve survival outcome. Blockade of the programmed death-1 (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 (ORR) were 53% and 87%. Inhibitors of histone deacetylase (HDACi: panobinostat, vorinostat entinostat, mocetinostat) shows favorable clinical activity with documented tumor reduction, but the ORR alone was between 16-27%. Lenalidomide, as a single agent has modest activity in heavily pretreated HL patients, the ORR was between 13-19%. Based on the data above lenalidomide and HDACi, as single agents probably not effective enough in relapse/rectractory HL patients. Some new, phase I-II upcoming trials will investigate the anti-PD-1 antibodies, HDAC inhibitors, 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

1. **Brentuximab vedotin**

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) [12]. The overall response rate (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 allogenic stem cell transplant and treating elderly patients [13]. 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 [4]. 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.

2. **Bendamustine**

After BV, ”old” bendamustine is the second ”new” drug to enter clinical practice with promising efficacy in the past 30 years [14]. 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 [8]. 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 [15]. The definitive proof of activity came from four studies of single agent bendamustine in relapsed/refractory HL [16-19]. 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 [14]. In 2013 Moskowitz et al. reported results of a phase II trial evaluating the activity of single agent bendamustine in

heavily pre-treated patients. In 34 evaluable patients bendamustine was administered in a dose of 120 mg/m2 as a 30-min 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 [16]. Corazzelli et al. published retrospective data with single agent bendamustine in 41 patients. After 2–4 cycles, ORR was 78% and CR was 29%. After 6-8 cycles of complete courses the final ORR was 58%, with 31% CR [17]. Other retrospective clinical trials [18, 19] confirmed these results. It would be useful to find the biological factors that identify the patients who are going to respond.

3. **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 [20]. Based on the new molecular and pathogenetical findings in Hodgkin lymphoma, 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 tumor 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 pre-treated HL patients (with CD20 expression on HRS cells) were enrolled. Rituximab was given IV weekly (375 mg/m^2) for 6 consecutive weeks. The overall response rate was 22% (5 patients, 1 CR, 4 PR), and 36% (8 patients) had stable disease Objective response was seen regardless of CD20 expression on RS cells. [6]. A few case reports are available in the literature documenting the benefit of rituximab in HL [7]

4. **Combination therapy with R-B-BV**

Based on in vitro observations there is a synergism between bendamustine and rituximab [9]. Our data underline that bendamustine-rituximab treatment was an effective and very safe choice for heavily pre-treated patients [21]. Brentuximab vedotin 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 90mg/m^2 bendamustine on days 1 and 2 every 3-weeks for up to 6 cycles. Forty five patients (58% female), with median age of 35 years (range 19-79) were involved in the study. 58% 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 were achieved after 2 cycles of combination therapy The average duration of response for patients who obtained CR was 10.4 months. Related the above mentioned and our results bendamustine (+R+/-BV) based salvage therapy might be helpful for this vulnerable HL population. [22]. Two patients achieved CR (Case1: 11 month and Case2: 15 month), one patient reached PR (Case3: 7 month) with RB regimen. RBBV treatment was successfully administered in one young refractory patient (Case4), who achieved complete remission after this novel treatment and underwent an auto-HSCT. The patient was in CR 17 month (April 2014) ago. The RB(BV) therapy was a very safe regimen in our heavily pre-treated 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 - bendamustin (supplemented with brentuximab-vedotin) can be a less toxic and effective alternative bridging salvage option to achieve complete or good partial remission before auto/allo-HSCT for heavily pre-treated 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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Dear Reviewer,

Thank you very much for the thorough revision of my manuscript. In the following, I would like to present my answers to your questions, as well as the corrections I made based on your suggestions.

1. I have corrected the sentence in the "Discussion" section (paragraph 1, line 8).

Radiotherapy as a salvage regimen could be suitable only for a limited portion of patients. Novel chemotherapeutical and/or targeted treatment strategies are needed to improve survival outcome.

2-3. I have completed the data with toxicity, duration of response (from the start date of RB(BV) regimen) of each patients, and I have also expanded the sentences about feasibility and low toxicity of these regimens in the "Discussion" section.

Two patients achieved CR (Case1: 11 month and Case2: 15 month), one patient reached PR (Case3: 7 month) with RB regimen. RBBV treatment was successfully administered in one young refractory patient (Case4), who achieved complete remission after this novel treatment, and underwent an auto-HSCT. The patient was in CR 17 month (April 2014) ago. The RB(BV) therapy was a very safe regimen in our heavily pre-treated 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.

The text has been completed with the data above in the „Discussion" section, on „Combination therapy with R-B-BV" and in line 10.

4. I have completed the data with the characteristics of the patients and duration of response.

Forty five patients (58% female), with median age of 35 years (range 19-79) were involved in the study. 58% 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%. Related the above mentioned and our results bendamustine (+R+/-BV) based salvage therapy might be helpful for this vulnerable HL population. The average duration of response for patients who obtained CR was 10.4 months.

The text has been completed with the data above in the „Discussion" section, on „Combination therapy with R-B-BV" and in line 8.

5. I have supplemented the text with the results of the new drugs, and comparison with our data.

Blockade of the programmed death-1 (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 (ORR) were 53% and 87%.

Inhibitors of histone deacetylase (HDACi: panobinostat, vorinostat entinostat, mocetinostat) shows favorable clinical activity with documented tumor reduction, but the ORR alone was between 16-27%. Lenalidomide, as a single agent has modest activity in heavily pretreated HL patients, the ORR was between 13-19%. Based on the data above lenalidomide and HDACi, as single agents probably not effective enough in relapse/rectractory HL patients. Some new, phase I-II upcoming trials will investigate the anti-PD-1 antibodies, HDAC inhibitors, 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.

The text has been completed with the data above in the „Discussion" section, on paragraph 1, and in line 9.

6. I have corrected the brentuximab-vedotin dose from "mg/m2" to "mg/kg" in Case3 and Case4.

7. I apologize for the grammatical errors, I have checked and corrected our mistakes again.

Abstract

Objective and importance: Hodgkin-lymphoma (HL) is a well-curable disease. The treatment usually includes combined multiagent conventional chemotherapy and radiotherapy. 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 hemopoetic stem cell transplantation [autoHSCT]), have really unfavourable prognosis. Intervention: For this heavily pretreated subset of HL patients, novel but less toxic treatment strategies should be considered. Brentuximab-vedotin 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 renessaince in the 21th century, it 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 bendamustin (supplemented with or without brentuximab-vedotin) could be a suitable alternative bridging salvage therapy for heavily pretreated HL patient.

Introduction

Thanks to the risk- and response adapted treatment strategies, more than 80% of newly diagnosed classical HL patients can be cured, and they 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 auto-HSCT) can be 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 can not be cured at least with salvage therapy, are expected to have a median survival of less than three years [2]. Treatment options have been quite limited for this subset of patients. The most promising new drugs (mTOR inhibitors, lenalidomide, histone deacetylase inhibitors, 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 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 the 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 (B) [8, 9] Here we report on four heavily pretreated patients who failed to the initial treatment. So far there have been no published data with rituximab–bendamustin-brentuximab-vedotin therapy for the treatment of relapsed/refractory HL patient.

Case1

In March 2007, a 22-year-old female patient was diagnosed with nodular sclerosis (NS) subtype HL, stage II/AX. She was treated with 8 cycles of adriamycin, bleomycin, vincristine, dacarbasine combination(ABVD) and involved field irradiation 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 (Fig1A). After two cycles of salvage dexamethasone-cisplatinum-cytosine/arabinoside(DHAP) therapy, the PET/CT showed progression (Fig1B), so the treatment was modified to ifosfamide-gemcitabine-vinorelbine-prednisone(IGEV) regimen. The administration of two cycles IGEV therapy resulted in complete metabolic remission(CMR) on the next PET/CT, in July 2008 (Fig1C). 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-cytosin/arabinosid-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 (Fig1D). 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, search for an unrelated bone marrow donor was started. In December 2009, the control PET/CT scan showed further progression (Fig1E), therefore ifosfamide-carboplatine-etoposide(ICE), rescue treatment was started, which was intolerable because of side effects (gradeIII-IV myelosuppression). In March 2010, bendamustine-based therapy with additional rituximab(RB) was indicated. The patient adopted dose of bendamustine was 90mg/m2 on the first and second days, and she received 375mg/m2 rituximab on the first day, each 28 day cycles. After two cycles of this regimen, a partial treatment response (PR) was detected on the control PET/CT scan (Fig1F), and after further four cycles of the RB therapy, she achieved

CMR (Fig1G). The patient was expected to undergo an allo-HSCT with reduced intensity conditioning(RIC) as she has only a matched unrelated donor. In February 2011, based on the control PET/CT scan a disseminated relapse was recognised (Fig1H), so we started RB regimen, which was formerly effective. After 2 cycles of RB therapy, B symptoms were recognised, so the treatment was modified to BV (1.8mg/kg, every 3 week), as a monotherapy, which was resulted clinically stable disease. In February 2012, further progression was appeared after 5 cycles of BV regimen (Fig1I). Numerous palliative chemotherapy regimens (included vinorelbine, dexamethasone, carboplatin) were ineffective (Fig1J) and she was died on 01. November 2012.

C**ase2**

In October 2006, a 34–year-old male was diagnosed with NS subtype of HL, with III/B clinical stage. After 6 cycles of ABVD chemotherapy he achieved a complete remission, which was verified with CT. In September 2011, another lymph node biopsy was perfomed and the histological examination revealed lymphocyte rich (LR) subtype of HL, with stage IV/BE (Fig2A). After 2 cycles of salvage DHAP therapy the PET/CT scan showed PR (Fig2B), so the treatment was modified into IGEV. He was administered 2 cycles of IGEV regimen, and CMR was detected on the next PET/CT examination (Fig2C). In March 2012, he underwent an R-BEAM conditioning followed by auto-HSCT. Post-tx maintance therapy was started with BV(1.8mg/kg). In April 2013, after the administration of 16 cycles of BV the control PET/CT scan revealed supradiaphragmatic relapse (Fig2D). In June 2013, RB (rituximab 375mg/m2 on day 1; bendamustin 120mg/m2 on days 1 and 2, each 28 day cycle) rescue therapy was started. After 6 cycles of RB, the next PET/CT examination detected CMR (Fig2E), and the patient was in CMR without chemotherapy in January 2014 (Fig2F). He was referred for an allo-HSCT, but he had only a matched unrelated donor. In September 2014, the control PET/CT evaluated relapse (Fig 2G), so we started the RB again, which was formerly effective. After 2 cycles of RB therapy the patient was in excellent clinical condition and the PET/CT showed also CMR (Fig 2H). In the hope of maintaining a long-term CR, two additional cycles of RB therapy will be administered and the patient is expected to undergo a haploidentical allo-HSCT with RIC.

Case3

In August 2010, a 61–year-old male was diagnosed with stage IV/BE (Fig3A), LR subtype of HL. After administration of 2 cycles of ABVD, the interim PET/CT scan showed CMR (Fig3B). After 6 cycles of ABVD and IFRT(36Gy) the patient achieved CR, which was confirmed by PET/CT scan (Fig3C-3D). In November 2012, after 15 month 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 paraaortical 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 2 cycles of DHAP therapy, the PET/CT detected PR (Fig3F). In September 2013, after 4 complete courses of DHAP the PET/CT scan showed progression (Fig 3G), therefore the therapy was changed into RB regimen (rituximab 375mg/m2 on day 1; bendamustin 120mg/m2 on days 1 and 2, each 28 day cycle), in October 2013. After the administration of 2 cycles of RB regimen, the next PET/CT scan revealed a PR (Fig3H). Further 4 cycles of RB were given, and the next PET/CT detected a new hypermetabolic mass before the vertebrae XII (Fig3I), so because of the localized relapse IFRT therapy(30 Gy) was recommended. In September 2014 further progression was revealed on the control PET/CT (Fig3J). Considering these results, BV(1.8mg/m2) plus ICE rescue treatment was started in November 2014**.** In March 2015, after 2 cycles of BV-ICE regimen, a control PET/CT examination showed partial remission.

C**ase4**

In January 2013, a 21–year-old male was diagnosed with stage II/BX, NS subtype of HL (Fig4A). The interim PET/CT result was almost CMR after receiving 2 cycles of ABVD (Fig4B). In October 2013, after 6 complete courses of ABVD, the restaging PET/CT scan showed a residual mediastinal mass (Fig4C). 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 (Fig4D), so we planned mediastinal lymph node biopsy, unfortunately it was refused by the patient again. In January 2014, after 2 cycles of salvage DHAP regimen the next PET/CT verified further progression (Fig4E). Cervical lymph node biopsy confirmed NS subtype of HL. Considering this result, the treatment was modified into RBBV regimen (rituximab 375mg/m2 on day 1; bendamustin 120mg/m2 on days 1 and 2, each 28 day cycle; 1.8 mg/m2 BV on day 1). After the administration of 2 cycles of RBBV, the next PET/CT scan verified CMR (Fig4F). After R-BEAM conditioning regimen, he underwent a successful auto-HSCT, which was supplemented with mediastinal/neck/supraclavicular region IFRT(36Gy). In September 2014, the post-Tx PET/CT examination detected CMR (Fig4G), 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 remain a great challenge. In case of a localized relapse IFRT might be effective [10]. Josting et al. reported that IFRT seemed to be most beneficial when recurrent disease extends beyond previously unirradiated lymph nodes in those patient who relapse after auto-HSCT (stage I-II relapse, without B symptoms and no extranodal disease) [11]. Radiotherapy, as a salvage regimen could be suitable only limited portion of patients, therefore novel chemotherapeutical and/or targeted treatment strategies are needed to improve survival outcome.

Mechanism of action and the results of clinical trials

1. Brentuximab-vedotin

BV is a targeted therapeutic option for Hodgkin lymphoma 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) [12]. The overall response rate (ORR) was 75%, CR was seen in 34% and PR in 40%. Currently running clinical trials are seeking for role of BV in the first line setting, as well as treating auto-HSCT candidate patients, relapsing after auto-HSCT, bridging to allogenic-HSCT and treating elderly patients [13]. There are a lot of opened questions its overall benefit and its combination possibilities with conventional chemotherapeutic agents, and if so which agent should be combined with it [4]. In addition, combination therapy may intensify side effects, in particular, combining with such agents, like bendamustine, which is also new in the treatment of HL.

2. Bendamustin

After BV, ”old” bendamustin is the second ”new” drug to enter clinical practice with promising efficacy in the past 30 years [14]. 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 [8]. 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 [15]. The definitive proof of activity came from four studies of single agent bendamustine in relapsed/refractory HL [16-19]. These studies also confirmed that, the bendamustine is a safe and effective regimen for patients relapsing after auto-HSCT and an interesting cytoreductive strategy prior to allo-HSCT [14]. 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 patient’s bendamustine was administered in a dose of 120 mg/m2, as a 30-min infusion on days 1 and 2 every 28 days. The ORR was 53%, CR was seen in 33% 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 month. The authors found these results is unfavourable and speculated on the possibility of combining this treatment with other agents that might maintain the response duration [16]. Corazzelli et al. published retrospective data with single agent bendamustin in 41 patients. After 2–4 cycles, ORR was 78% and CR was 29%. After 6-8 cycles of complete courses the final ORR was 58%, with 31% CR [17]. Other retrospective clinical trials [18, 19] confirmed these results. It would be useful to find those biological factors that identify the patients who are going to respond.

3. 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 [20]. Based on the new molecular and pathogenetical findings in Hodgkin lymphoma, it has become clear that the microenvironment plays a critical role in the survival of the malignant HRS cells. HRS cells make up only approximately 1-5% of total tumor bulk in HL, it is thought that perhaps rituximab's effect in vivo may not be due to killing of HRS cells, rather 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/m^2) for 6 consecutive weeks. The overall response rate was 22% (5 patient, 1 CR, 4 PR), and 36% (8 patient) had stable disease Objective response was seen regardless of CD20 expression on RS cells. [6]. A few case reports are avaible in the literature documenting the benefit of rituximab in HL [7]

4. **Combination therapy with R-B-BV**

Based on in vitro observations there is a synergism between bendamustine and rituximab [9]. Our data underline that bendamustine-rituximab treatment was an effective and very safe choice for heavily pretreated patients [21]. 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 90mg/m^2 bendamustine on days 1 and 2 every 3-week up to 6 cycles. The ORR was 94%, and the CR

rate was 82%. The majority of CRs were achieved after 2 cycles of combination therapy. [22] Based on our experience, RB therapy was less toxic, but effective choice for this vulnerable HL population, who relapsed or progressed after at least three lines of chemotherapy, two patient achieved CR, one patient reached PR. RBBV treatment was successfully administered in one young refractory HL patient, who achieved complete remission after this novel treatment, and successfully underwent an auto – HSCT

Conclusion

Rituximab - bendamustin (supplemented with brentuximab-vedotin) can be a less toxic and effective alternative bridging salvage option to achieve complete or good partial remission before auto/allo - HSCT for heavily pretreated HL patient. Further clinical studies might be needed to clarify the correct place of this novel targeted treatment modality in relapsed/refractory HL population. A combination with PD-1 checkpoint inhibitors might improve remission rates and expected sustained response.

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