Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma. The Hellenic experience

Maria K. Angelopoulou | Theodoros P. Vassilakopoulos | Ioannis Batsis | Ioanna Sakellari | Konstantinos Gkirkas | Vasiliki Pappa | Panagiota Giannoulia | Ioannis Apostolidis | Christos Apostolopoulos | Paraskevi Roussou | Panayiotis Panayiotidis | Maria Dimou | Marie-Christine Kyrtonis | Maria Palassopoulou | Georgios Vasilopoulos | Maria Moschogiannis | Christina Kalpadakis | Dimitrios Margaritis | Alexander Spyridonidis | Eurydiki Michalis | Konstantinos Anargyrou | Panagiotis Repousis | Eleuthera Hatzimichael | Zoi Bousiou | Elias Poulakidas | Dimitrios Grentzelias | Nikolaos Harhalakis | Gerassimos A. Pangalis | Achilles Anagnostopoulos | Panagiotis Tsirigotis

1 Department of Hematology, Laikon General Hospital, National and Kapodistrian University of Athens, Athens, Greece
2 Hematology and Bone Marrow Transplantation Department, General Hospital of Thessaloniki Papanikolaou, Thessaloniki, Greece
3 2nd Department of Internal Medicine, Faculty of Medicine, ATTIKON General University Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece
4 Department of Hematology, Evaggelismos General Hospital, Athens, Greece
5 Third Department of Medicine, “Sotiria” General Hospital of Thoracic Diseases, Hematology Unit, National and Kapodistrian University of Athens, Medical School, Athens, Greece
6 1st Department of Propedeutic Internal Medicine, Laikon General Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece
7 Department of Hematology, Larissa University Hospital, University of Thessalia, Larissa, Greece
8 Department of Hematology, Athens Medical Center, Athens, Greece
9 Department of Hematology, Heraklion University Hospital, University of Crete, Heraklion, Greece
10 Department of Hematology, Democritus University of Thrace Medical School, Alexandroupolis, Greece
11 Bone Marrow Transplantation Unit, University of Patras, Patras, Greece
12 Department of Clinical Hematology, “G.Gennimatas” Athens General Hospital, Athens, Greece
13 Department of Hematology, Air Force Hospital, Athens, Greece
14 Department of Hematology, Metaxa Hospital, Piraeus, Greece
15 Department of Hematology, Ioannina University Hospital, University of Ioannina, Ioannina, Greece
16 Department of Hematology, 401 Military Hospital of Athens, Athens, Greece
17 Hygeia General Hospital, Athens, Greece

Correspondence
Maria K Angelopoulou, MD, PhD, Associate Professor in Hematology, Medical School, Department of Hematology, Laikon General Hospital, National and Kapodistrian University of Athens, 17, Agiou Thoma Street, 11527, Athens, Greece.
Email: mkangelop@gmail.com

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2017 The Authors Hematological Oncology Published by John Wiley & Sons Ltd
Abstract
This retrospective study aimed to describe the Hellenic experience on the use of brentuximab vedotin (BV) in relapsed/refractory (R/R) Hodgkin lymphoma (HL) given within its indication. From June 2011 to April 2015, ninety-five patients with R/R HL who received BV in 20 centers from Greece, were analyzed. Their median age was 33 years, and 62% were males. Sixty-seven patients received BV after autologous stem cell transplantation failure, whereas 28 patients were treated with BV without a prior autologous stem cell transplantation, due to advanced age/comorbidities or chemorefractory disease. The median number of prior treatments was 4 and 44% of the patients were refractory to their most recent therapy. The median number of BV cycles was 8 (range, 2-16), and the median time to best response was the fourth cycle. Fifty-seven patients achieved an objective response: twenty-two (23%), a complete response (CR), and 35 patients (37%), a partial, for an overall response rate of 60%. Twelve patients (13%) had stable disease, and the remaining twenty-six (27%) had progressive disease as their best response. At a median follow-up of 11.5 months, median progression-free survival and overall survival were 8 and 26.5 months, respectively. Multivariate analysis showed that chemosensitivity to treatment administered before BV was associated with a significantly increased probability of achieving response to BV ($P = .005$). Bulky disease ($P = .01$) and response to BV ($P < .001$) were significant for progression-free survival, while refractoriness to most recent treatment ($P = .04$), bulky disease ($P = .005$), and B-symptoms ($P = .001$) were unfavorable factors for overall survival. Among the 22 CRs, 5 remain in CR with no further treatment after BV at a median follow-up of 13 months. In conclusion, our data indicate that BV is an effective treatment for R/R HL patients even outside clinical trials. Whether BV can cure a fraction of patients remains to be seen.

KEYWORDS
autologous stem cell transplantation, brentuximab vedotin, Hodgkin lymphoma, prognostic factors, relapsed/refractory

1 | INTRODUCTION
Salvage chemotherapy followed by high-dose therapy and autologous hematopoietic stem cell transplantation (ASCT) is the treatment of choice for relapsed/refractory (R/R) Hodgkin lymphoma (HL) patients.\textsuperscript{1-3} This therapeutic strategy can provide long-term disease control in approximately 50% of R/R patients.\textsuperscript{4,5} For patients who relapse after ASCT, conventional chemotherapy options are usually unsatisfactory, and their outcome is rather dismal with a median overall survival (OS) of 2 years.\textsuperscript{6,7} Relapsed disease after ASCT is considered incurable, unless allogeneic transplantation is applied. However, very few patients can achieve this goal, since refractory disease often hampers the benefit of this procedure.

Brentuximab vedotin (BV) is an antibody-drug conjugate targeting the CD30 antigen expressed on the surface of the malignant cells and leading to G2/M cell cycle arrest through disruption of the microtubule network.\textsuperscript{8,9} A multicenter phase II trial of BV in patients with HL recurring after ASCT demonstrated an overall response rate (ORR) and complete response (CR) rate of 75% and 34%, respectively,\textsuperscript{10} with a median progression-free survival (PFS) extending to 9.3 months.\textsuperscript{11} Based on this study, accelerated approval was granted by the US Food and Drug Administration in 2011 to BV, while the European Medicines Agency approved BV in October 2012 for R/R CD30+ HL patients following ASCT or following at least 2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option.

Herein, we present the Hellenic experience with BV in patients with R/R HL outside clinical trials, reflecting everyday clinical practice. Furthermore, we wanted to report the pattern of its use, to identify possible prognostic factors and investigate whether a fraction of patients can achieve long-term disease control with BV as the sole treatment.

2 | METHODS
This was a retrospective multicenter study among 20 centers in Greece aiming to collect data on patients with R/R HL treated with BV. Between June 2011 and April 2015, one hundred patients received BV within its indication. The study was approved by the Institutional Review Board of the participating hospitals. All patients had histologically confirmed R/R CD30+ HL and had received at least 2 cycles of BV, either due to disease progression after ASCT or after at least 2 prior therapies if ASCT was not indicated because of advanced age, insufficient stem cell collection, or chemoresistant disease. Two coordinating centers (Laikon and Attikon Hospitals) collected the data through a detailed form completed by the treating physicians and reviewed by the coordinators (MKA, PT). Five patients were excluded from this analysis, 3 due to insufficient data and 2 due to a histologic diagnosis of gray-zone lymphoma. Thus, 95 patients were finally analyzed.

BV was administered as a 30-minute infusion at the dose of 1.8 mg/kg of body weight every 3 weeks for a maximum of 16 cycles. The dose was capped to 180 mg for patients over 100 kg. Primary refractory disease was defined as no CR or relapse within 3 months of first line therapy. Early and late relapse were defined as relapse within or beyond 12 months after the end of first-line treatment, respectively. Bulky disease was defined as a mass measuring >10 cm in its transverse diameter. All patients underwent baseline assessments including physical examination, routine laboratory tests, and radiological examinations prior to BV. Response assessment was based on the revised response criteria for malignant lymphoma.\textsuperscript{12} However, radiologic tests were not centrally reviewed for a strict definition of response to be applicable. The treating physicians used computed tomography and/or positron emission tomography/computed tomography scans for response assessment according to their practice and test availability. The best response and the cycle after which best response was documented were recorded. The primary endpoint of the study was PFS, whereas ORR and OS were secondary endpoints.

2.1 | STATISTICS
PFS was defined as the time from BV initiation to progression, relapse, or death of any cause. For PFS estimation, patients without disease
progression after BV were censored at the time of last follow-up or at the time of subsequent treatment. OS was measured from the time of BV initiation to death of any cause. PFS and OS along with 2-sided 95% confidence interval (CI) were estimated using the Kaplan-Meier method. Survival functions were compared using the log-rank test. Significant variables at $P < .05$ in the univariate analyses were evaluated in multivariate analyses. The following covariates were entered in the multivariate analysis model: age at BV initiation, gender, number of treatments administered before BV (<3 vs > 3), response to initial treatment (primary refractory disease vs early relapse vs late relapse), response to the last chemotherapy regimen administered before BV (chemosensitive vs chemorefractory), disease stage (I/II vs III/IV), bulky disease, extranodal involvement and B-symptoms at BV initiation, previous ASCT, and response to BV (CR vs partial response [PR]) vs no response. Multivariate analysis for response to BV was performed by using a multiple logistic regression model, while for PFS and OS, a Cox proportional hazard model was used. Analysis of the data was performed using Medcalc and R software.

3 | RESULTS

3.1 | Patients' characteristics

Patients' median age at BV initiation was 33 years. More than half of them were primary refractory to first line treatment, whereas 19% and 24% had early and late relapse, respectively. Among the 95 patients, 67 received BV after ASCT failure, whereas in 20, BV was administered as salvage chemotherapy due to resistant disease with the intention to proceed to ASCT. Eight patients were considered ineligible for ASCT due to advanced age and/or poor performance status and received BV as third or more salvage. At the time of BV initiation, 2/3 had advanced disease stage, more than 1/3 had B-symptoms, and almost half of them had extranodal involvement. In addition, 15% had bulky disease. The median time from diagnosis and ASCT to BV initiation was 35 months (6-287) and 18 months (3-108), respectively. The median time from the first documented relapse post ASCT to BV initiation was 8 months (range, 1-81). Table 1 depicts patients' characteristics from the pivotal phase II study and 5 other published series of patients reporting their national experience in comparison to ours.

3.2 | Response to BV

The median number of BV cycles was 8 (range, 2-16). The exact timing of response assessment was not predefined. However, the median cycle number for best response achievement was the fourth (range, 2-12).

Among 95 patients, 57 achieved an objective response: twenty-two (23%), a CR, and 35 patients (37%), a PR, for an ORR of 60%. Twelve patients (13%) had stable disease and the remaining twenty-six (27%) had progressive disease (PD) as their best response. Table 2 depicts efficacy of BV in published series including the present study. Prognostic factor univariate analysis for response revealed that less pretreated patients (<3 prior treatments), with nonbulky disease, the ones who received BV after ASCT and those who were chemosensitive to their last prior treatment to BV responded significantly better (Table 3). By multivariate analysis, only chemosensitivity to last prior treatment remained significant ($P = .005$): Patients who were sensitive to their last prior chemotherapy achieved an ORR of 75% vs 40% for those who were chemorefractory (Table 4).

3.3 | Progression-free survival and Overall survival

At a median follow-up time of 11.5 months, disease progression was observed in 62 of 95 patients, while 21 of 95 patients expired after treatment with BV. The median PFS and OS were 8 months (95% CI, 5-9) and 26.5 months (95% CI, 20-31), respectively, with a 2-year OS reaching 67% (Figure 1).

| TABLE 1 | Patients’ characteristics from the present analysis in comparison with the pivotal phase II study and other published series |
| Characteristics | Phase II Study | Germany | Italy | Asia | Turkey | France | Greece |
|-----------------|---------------|---------|-------|------|--------|--------|--------|
| Number of points | 102           | 45      | 65    | 22   | 58     | 240    | 95     |
| Male sex, %     | 53            | 49      | 52    | 68   | 64     | 65     | 62     |
| Primary refractory disease | 71 | 62      | 69    | 55   | 49     | 49     | 57     |
| Prior ASCT, %   | 100           | 87      | 88    | 77   | 80     | 59     | 70     |
| Prior allo-SCT, % | 0        | 4.6     | 2     | 15   | 2.1    |        |        |
| Median number of prior treatments (range) | 3.5 (1-13) | 4 (2-12) | 4 (2-13) | NR | 4 (2-7) | 3 (1-13) | 4 (1-9) |
| Refractory to prior last treatment, % | 42 | 64      | 80    | NR   | 72     | 56     | 44     |
| Median time (months) from diagnosis to BV treatment (range) | 40 (12-220) | 48 (10-180) | NR | 41 (14-199) | NR | 31 (3-336) | 35 (6-287) |

Disease characteristics at BV treatment:

|                          | Phase II Study | Germany | Italy | Asia | Turkey | France | Greece |
|--------------------------|---------------|---------|-------|------|--------|--------|--------|
| Advanced clinical stage/B-symptoms, % | NR/NR | 73/44 | NR/45 | 95/68 | 78/47 | NR/NR | 63/36 |
| Bulky disease, %         | NR            | 4⁴     | NR    | NR   | NR     | NR     | 15     |
| Extranodal involvement, % | NR      | 73     | NR    | 64   | NR     | NR     | 45     |
| ECOG PS ≤1, %            | 100           | 82      | 77    | 45   | 80     | NR     |        |

Abbreviations: allo-SCT indicates allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; NR, not reported; PS, performance status.

⁴Bulky mediastinum.
For PFS, the following factors proved significant by univariate analysis: number of prior treatments (<3 vs >3), refractoriness to most recent treatment, bulky disease at initiation of BV, prior ASCT, and response to BV (Table 3). By multivariate analysis, the factors that remained significant for PFS were bulky disease ($P = .01$) and response to BV ($P < .001$) (Table 4). The median PFS for patients with bulky was 3 vs 9 months for those with nonbulky disease (Figure 2A). Responders to BV proved to have a significantly superior prognosis with a median PFS of 12 months compared with 3 months for nonresponders (Figure 2B). PFS did not differ significantly between complete and partial responders (median PFS, 14 and 11 months, respectively, $P = non-significant$, Figure 2C).

**TABLE 2** Outcome after BV in comparison with the pivotal phase II study and other published series

| Characteristics                      | Phase-II Study | Germany | Italy | Asia | Turkey | France | Greece |
|--------------------------------------|----------------|---------|-------|------|--------|--------|--------|
| BV cycles: # (range)                 | 9 (1-16)       | 7 (1-12) | 8 (3-16) | 5 (1-18) | 7 (2-18) | 6 (1-16) | 8 (2-16) |
| Cycle of response evaluation         | 2, 4, 7, 10, 13, and 16 | NR | 3 and 8 | every 1-2 cycles | 2, 5, and ≥6 | 4 | 3 or 4 |
| Median time to response              | 5.7 wks*       | NR | NR | NR | 0.9 mo | NR | 4 cycles |
| ORR/CR, %                            | 75/34          | 60/22 | 71/22 | 73/18 | 64/27 | 60/34 | 60/23 |
| SD, %                                | 22             | 29 | 17 | 18 | 8 | 8 | 13 |
| PD, %                                | 3              | 11 | 12 | 5 | 29 | 28 | 27 |
| Median time of follow-up (months)    | 33             | NR | 13.2 | NR | NR | 16 | 11.5 |
| median PFS (months)                  | 9.3            | 8 | 6.8 | 5.7 | 7 | 6.8 | 8 |
| median OS (months)                   | 40.5           | NR | NR | NR | NR | NR | 26.5 |
| OS, %                                | 3 y, 47        | 1 y, 83 | 1 y, 75 | 1 y, 67 | 1 y, 71 | 2 y, 58 | 2 y, 67 |

*Median time to CR: 12 weeks.

Abbreviations: BV, brentuximab vedotin; CR, complete response; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; SD, stable disease.

**TABLE 3** Univariate prognostic factor analysis

| Characteristic                           | Response | P | PFS | OS |
|------------------------------------------|----------|---|-----|----|
| Sex (female vs male)                     | 62 vs 59 | NS | 9 vs 6 | NS | 28 vs 27 | .049 |
| B-symptoms (no vs yes)                   | 64 vs 53 | NS | 8 vs 6 | NS | 26 vs 16 | <.001 |
| Number of previous treatments (≤3 vs >3) | 69 vs 49 | .058 | 9 vs 5 | .01 | NR vs 27 | NS |
| Refractory to most recent treatment (no vs yes) | 75 vs 40 | <.001 | 9 vs 4 | .005 | 28 vs 26 | .008 |
| Bulky disease (no vs yes)                | 65 vs 21 | .014 | 9 vs 3 | <.001 | 27 vs 10 | <.001 |
| Extranodal involvement (no vs yes)       | 67 vs 55 | NS | 9 vs 6 | NS | 27 vs 26 | .057 |
| Prior ASCT (yes vs no)                   | 69 vs 39 | .009 | 9 vs 4 | .007 | 27 vs NR | NS |
| Response to BV (yes vs no)               | NA       | NA | 12 vs 3 | <.001 | 28 vs 26 | NS |
| CR to BV (yes vs no)                     | NA       | NA | 14 vs 4 | <.001 | NR vs 26 | .014 |

Abbreviations: ASCT indicates autologous stem cell transplantation; BV, brentuximab vedotin; CR, complete response; NA, not applicable; NR, not reached; NS, nonsignificant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

**TABLE 4** Multivariate prognostic factor analysis

| Response to BV (multiple logistic regression) | Odds Ratio | 95% CI | P |
|----------------------------------------------|------------|--------|---|
| Response to previous treatment before BV (Chemosensitive vs chemorefractory) | 0.22 | 0.07-0.65 | .005 |

| Progression-Free Survival (Cox proportional hazard analysis) | Hazard Ratio | 95% CI | P |
|-------------------------------------------------------------|--------------|--------|---|
| Bulky disease (yes vs no)                                  | 2.28         | 1.18-4.38 | .01 |
| Response to BV (yes vs no)                                 | 0.08         | 0.04-0.16 | <.001 |

| Overall Survival (Cox proportional hazard analysis) | Hazard Ratio | 95% CI | P |
|----------------------------------------------------|--------------|--------|---|
| Response to previous treatment before BV (Chemosensitive vs chemorefractory) | 0.32 | 0.10-0.98 | .04 |
| Bulky disease (yes vs no)                           | 4.62         | 1.57-13.64 | .005 |
| B-symptoms (yes vs no)                              | 5.52         | 1.95-15.62 | .001 |

Abbreviation: BV indicates brentuximab vedotin.
Male gender, refractoriness to most recent chemotherapy prior to BV, bulky disease, extranodal involvement, B-symptoms, and failure to achieve CR with BV were identified as poor prognostic factors for OS by univariate analysis (Table 3). Factors that remained significant for OS by multivariate analysis were refractoriness to most recent treatment ($P = .04$), bulky disease ($P = .005$), and B-symptoms ($P = .001$) (Table 4). Median OS for nonresponders to the last previous treatment before BV was 26 months for non-responders vs 28 for responders. Patients with bulky disease and B-symptoms had a median OS of 10 and 16 months, respectively compared with 27 and 26 months for those with nonbulky disease and absence of B-symptoms, respectively (Figure 3).

### 3.4 Treatment after BV

Among the 95 patients included in the study, 67 received BV after ASCT and 28 without a preceding ASCT. Among the 67 patients who received BV after ASCT, 22 received further chemotherapy for subsequent relapse/progression, 18 underwent allogeneic stem cell transplantation (allo-SCT), 22 received no further treatment, 2 were treated with radiotherapy, and 1 with a second ASCT, while the remaining 2 patients were still under BV treatment at the time of the present analysis. Among the 18 patients who underwent allo-SCT after BV, the majority (14 of 18) were alive without evidence of active disease. On the contrary, among the ones who received subsequent chemotherapy and those who did not receive any further treatment, only 2 of 22 and 8 of 22, respectively, had not developed PD at the time of the present analysis.

There were 28 patients who received BV without a previous ASCT. Among these, 8 patients were not eligible for ASCT due to advanced age or poor performance status, while in the remaining 20 patients, BV was administered in an effort to achieve disease control.
with intent to proceed to ASCT. Eight of these 20 patients did not have an objective response to BV and were considered as noneligible for auto-SCT by the treating physician, while 2 other patients who achieved CR and PR after BV refused any further treatment. Therefore, BV was used as a bridge to ASCT in 10 of 20 patients. They received a median number of 4 cycles before ASCT, and 3 of 10 achieved a response (PR). Six of them are currently alive without evidence of disease at a median time of 8 months (3-17) after ASCT, while 4 progressed shortly thereafter (between 2 and 6 months post ASCT).

3.5 | Outcome of complete responders to BV

In total, 22 of 95 patients achieved CR after BV. Ten of 22 CRs relapsed at a median time of 9 months (range, 8-20) after the initiation of BV. The median number of BV cycles administered to this group of patients was 10 (range, 8-16). Two complete responders received 10 and 16 BV cycles and underwent allo-SCT thereafter. Five patients completed a median number of 15 BV cycles (range, 9-16) and remain in CR with no further treatment at a median follow-up of 13 months (range, 8-17). Finally, the remaining 5 CRs are still on BV after a median of 3 months (range, 2-9). Figure 4 depicts the outcome the 12 patients who remain in CR.

4 | DISCUSSION

This retrospective multicenter Greek study confirms that BV is effective in everyday clinical practice, outside clinical trials.

Our series is the second largest one compared to other national reported experiences.14-18 Our patients’ characteristics were comparable to the ones among the other series. The Asian series had a higher percentage of patients with advanced clinical stage both at diagnosis and before BV and a higher proportion of patients with B-symptoms prior to BV initiation.14 The Italian and Turkish series reported a higher percentage of patients being refractory to the most recent treatment before BV.15,16 Our study included a relatively lower percentage of patients with extranodal involvement at BV initiation.

Our results are in accordance with the other national experience studies with an ORR of 61% including 23% CR.10,14-18 In our series, PD was relatively common (27%) in concordance to the Turkish and the French series who also reported a PD rate of 29% and 28%, respectively.16,18 Notably, in the pivotal phase II trial and the Asian series, who both reported extremely low rates of PD, response was assessed frequently.10,14 Since responses are observed early in the course of treatment, it is likely that frequent response assessments may catch early, short-living responses, thus minimizing the rate of PD primarily. This is further suggested by the fact that PFS is more or less similar across studies. Our study reflects real life, where response assessments are not prospectively defined and are performed less frequently. Even so, our results are in agreement with the published literature regarding the rapidity of response. We observed best response at a median time of 4 cycles that coincided with the most frequently applied cycle of first disease evaluation. The same observation was made by the French investigators.18 In the Italian series, they also observed the best response after the 3rd compared with the 8th cycle.15 The retrospective nature of the study

![Figure 3](image-url) Prognostic factors for overall survival: A, Response to most recent treatment prior to brentuximab vedotin (BV; chemosensitive vs chemorefractory). B, Bulky disease at BV initiation, (yes vs no). C, Presence of B-symptoms at BV initiation (yes vs no). CR indicates complete response; PD, progressive disease; PR, partial response; SD, stable disease

![Figure 4](image-url) Outcome of complete responders to brentuximab vedotin (BV)
and the fact that response assessment was done according to the treating physicians represent a limitation. Thus, response rates should be viewed with caution in this setting, while PFS is a more realistic endpoint.

With the aforementioned limitations, we found that chemosensitivity to the most recent treatment before BV was an independent favorable factor for response achievement. The number of previous regimens and older age (>60 y) were identified as significant factors for response by the Turkish and French studies.

Regarding PFS, there is agreement that response to BV is a favorable factor. In our analysis, there was no significant difference between CR and PR, while PFS was dramatically inferior for nonresponders. This finding is different from the one from the pivotal study, where CRs had a significantly better outcome compared with PRs. This difference might reflect the poor discrimination between CR and PR outside the clinical trial setting. In addition, the German experience identified primary refractory disease/early relapse and refractoriness to the most recent treatment as additional prognostic factors for PFS. In our series, refractoriness to the most recent treatment was significant in the univariate analysis, but was obscured in the multivariate setting by response to BV and bulky disease. Our study is the only one denoting the poor prognostic significance of bulky disease at the time of BV initiation for PFS. Bulk proved to be significant for OS as well, along with refractoriness to most recent therapy before BV and the presence of B-symptoms. This observation is similar to the one of the pivotal trial: The authors found that the sum of the products of the longest perpendicular dimensions of the previously identified dominant lymph node masses was an independent factor for OS, along with age and performance status.

Another issue that has not been clarified yet, is the need for consolidation with allo-SCT in BV responders. It is clear that patients respond rapidly to BV, crudely after 4 cycles. The French investigators revealed that ORR at the end of BV treatment cycles was dramatically lower than that ORR at the end of BV treatment cycles was dramatically lower than that observed after a median of 4 cycles, with PD increasing from 28% to 54%. These data indicate that the decision to proceed to allo-SCT should be taken early during treatment. Whether BV can cure a fraction of patients remains to be seen.

5 CONCLUSION

Brentuximab vedotin is an effective treatment for R/R HL patients after failure of ASCT, not only within clinical trials but also in everyday clinical practice. The decision for further consolidation with a transplant should be taken early during treatment. Whether BV can cure a fraction of patients remains to be seen.

REFERENCES

1. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone marrow transplantation in relapsed and resistant Hodgkin’s disease: results of a BNLI randomised trial. Lancet. 1993;341(8852):1051–1054.
2. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin’s disease: a randomised trial. Lancet. 2002;359(9323):2065–2071.
3. Vassilakopoulos TP, Angelopoulou MK, Siakantaris MP, et al. Brentuximab vedotin in first relapse following chemotherapy or combined modality therapy: analysis of outcome and prognostic factors after conventional salvage therapy. Eur J Haematol. 2002;68(5):289–298.
4. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin’s lymphoma registered in the database of the German Hodgkin’s lymphoma study group. J Clin Oncol. 2001;19(7):2026–2032.
5. Sureda A, Arranz R, Iriondo A, et al. Autologous stem-cell transplantation for Hodgkin’s disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. Clin Oncol. 2001;19(5):1395–1404.
6. Moskwowitz AJ, Peralez MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158–163.
7. Kalyanannisid P, Voutiadou G, Baltadakis I, et al. Outcomes of Hodgkin’s lymphoma patients with relapse or progression following autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012;18(3):451–457.
8. Offazoglu E, Kissler KM, Sievers EL, Greval IS, Gerber HP. Combination of the anti-CD30–auristatin-E antibody-drug conjugate (SGN-35) with chemotherapy improves antitumour activity in Hodgkin lymphoma. Br J Haematol. 2008;142(1):69–73.
9. Vassilakopoulos TP, Angelopoulou MK. Advanced and relapsed/refractory Hodgkin lymphoma: what has been achieved during the last 50 years. Semin Hematol. 2013;50(1):4–14.

10. 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.

11. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase II study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236–1243.

12. Cheson BD, Pfistner B, Juweid ME, et al. International harmonization project on lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579–586.

13. Kaplan ES, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457–481.

14. Yang QM, Hong JY, Ko YH, et al. Brentuximab vedotin for relapsed or refractory CD30+ Hodgkin lymphoma: a multicenter analysis from Asia. Onco Targets Ther. 2014;7:1717–1722.

15. Zinzani PL, Viviani S, Anastasia A, et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica. 2013;98(8):1232–1236.

16. Salihoglu A, Elverdi T, Karadogan I, et al. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey. Ann Hematol. 2015;94(3):415–420.

17. Rothe A, Sasse S, Goergen H, et al. Brentuximab vedotin for relapsed or refractory CD30+ hematologic malignancies: the German Hodgkin Study Group experience. Blood. 2012;120(7):1470–1472.

18. Perrot A, Monjanel H, Bouabdallah R, et al. Lymphoma Study Association (LYSA). Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French named-patient program. Haematologica. 2016;101(4):466–473.

19. Chen R, Palmer JM, Tsai NC, et al. Brentuximab vedotin is associated with improved progression-free survival after allogeneic transplantation for Hodgkin lymphoma. Biol Blood Marrow Transplant. 2014;20(11):1864–1868.

20. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2016;128(12):1562–1566.

21. 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.

22. Chen R, Palmer J, Martin P, et al. Post transplant outcome of a multicenter phase II study of brentuximab vedotin as first line salvage therapy in relapsed/refractory HL prior to AHCT. Blood. 2015;126(23):519 abstract.

23. Moskowitz AJ, Schoder H, Yahalom J, et al. PET-adopted sequential salvage therapy with brentuximab vedotin followed by augmented ifosfamide, 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.

24. Onishi M, Graf SA, Holmberg L, et al. Brentuximab vedotin administered to platinum-refractory, transplant-naive Hodgkin lymphoma patients can increase the proportion achieving FDG PET negative status. Hematol Oncol. 2015;33(4):187–191.

25. García-Sanz R, Sureda A, Alonso-Alvarez S, et al. Evaluation of the regimen brentuximab vedotin plus ESHAP (BRESHAP) in refractory or relapsed Hodgkin lymphoma patients: preliminary results of a phase I-II trial from the spanish group of lymphoma and bone marrow transplantation (GELTAMO). Blood. 2015;126(23):582 abstract.

26. LaCasce AS, Bociek G, Sawas A, et al. Brentuximab vedotin plus bendamustine: a highly active salvage treatment regimen for patients with relapsed or refractory Hodgkin lymphoma. Blood. 2015;126(23):3982 abstract.

27. 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):269–271.

How to cite this article: Angelopoulou MK, Vassilakopoulos TP, Batsis I, et al. Brentuximab vedotin in relapsed/refractory Hodgkin lymphoma. The Hellenic experience. Hematological Oncology. 2018;36:174–181. https://doi.org/10.1002/hon.2383