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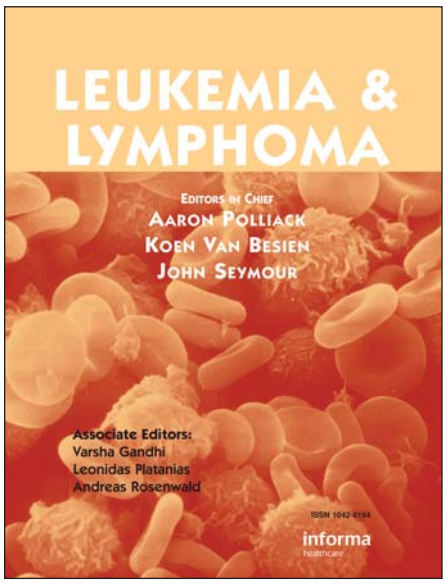

Brentuximab Vedotin (SGN-35) in patients with transplant-naïve relapsed/refractory Hodgkin Lymphoma

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doi:10.3109/10428194.2013.775434

Abstract

Only limited data are available on the role of brentuximab vedotin (SGN-35) in transplant-naïve relapsed or refractory patients with Hodgkin lymphoma (HL). We thus retrospectively analyzed 14 patients with primary refractory or relapsed HL who were treated with brentuximab vedotin as single agent in a named patient program, who had yes received prior high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) due to refractory disease (n=9), comorbidity (n=4) and unknown reasons (n=1). Brentuximab vedotin resulted in an overall response rate of 71% (10/14) with 5 complete responses (CR). Five of those patients with refractory disease and 4 patients with relevant comorbidity responded. Consolidating ASCT (n=4) or allogeneic SCT (n=1) was performed in 5 patients. Median progression-free survival (PFS) was 9 months and the median overall survival (OS) was not reached. These data indicate the therapeutic efficacy of brentuximab vedotin in chemotherapy-refractory transplant-naïve HL patients.

Brentuximab Vedotin (SGN-35) in patients with transplant-naïve relapsed/refractory Hodgkin Lymphoma

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Shortened title: SGN-35 in transplant-naïve Hodgkin lymphoma

Key words: Brentuximab vedotin, Hodgkin Lymphoma, no prior ASCT

Abstract

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INTRODUCTION

In contrast to the results achieved with first line treatment [1,2], the prognosis of Hodgkin Lymphoma (HL) patients with relapsed disease is significantly poorer with about 50% achieving long-term remission when treated with HDCT and ASCT [3,4]. In particular those with refractory disease and older patients with relapsed HL have a dismal prognosis [5-7]. Since sensitivity to second line induction therapy was identified as predictive marker for the outcome after ASCT, even patients with primary progressive disease can benefit from HDCT [8]. An effective reinduction therapy for those suffering from primary progressive and chemotherapy refractory HL should include a non-cross-resistant drug. Since HDCT is associated with significant morbidity and mortality in relapsed older HL patients, new treatment approaches are also warranted in this group [5]. Thus, the availability of a new, better-tolerated and effective reinduction therapy is of key interest especially for those with refractory HL and for relapsed older HL patients.

Brentuximab vedotin (SGN-35) is a new antibody drug conjugate (ADC) which consists of a chimeric anti-CD30 antibody conjugated to four molecules of the synthetic antitubulin chemotherapeutic agent auristatin E (MMAE) [9]. CD30 is abundant on the cell surface of the malignant cells in HL as well as anaplastic large cell lymphoma (ALCL) [10,11]. Brentuximab vedotin has shown impressive anti-tumour efficacy in patients with relapsed HL [8,11]. In the pivotal phase II trial including 102 heavily pretreated HL patients, the overall response rate (ORR) was 75% with a median duration of 5.6 months. Importantly, 34% achieved complete remission (CR) with a median response duration of 20.5 months [12].

Based on these excellent clinical data, the US Food and Drug Administration (FDA) approved brentuximab vedotin for the treatment of HL patients who either failed ASCT or had at least two prior multi-agent chemotherapy regimens and are no candidates for ASCT.

Since there is very limited experience with brentuximab vedotin in those HL patients who fail to achieve a remission before HDCT and in older HL patients who are ineligible to HDCT, we retrospectively analyzed 14 HL patients who were treated with brentuximab vedotin within a named patient program (NPP) and who did not receive HDCT and ASCT prior to brentuximab vedotin treatment.

MATERIALS AND METHODS

Since March 2010, the GHSG and associated centres have treated patients with histologically confirmed refractory or relapsed HL within a named patient program (NPP) initiated by the companies responsible for brentuximab vedotin (Seattle Genetics, Millenium, Takeda). All participants gave written informed consent. Main inclusion criterion was a normal organ function including peripheral blood counts within the normal range. Patients received a 30-minute infusion of brentuximab vedotin dosed at 1.8mg/kg body weight every three weeks. No pre-medication was administered. Toxic events were assessed according to the National Cancer Institute Common Terminology Criteria (CTC) for Adverse Events version 3.0. Upon occurrence of CTC grade 3 toxic events, dose reduction to 1.2mg/kg was recommended. For all patients, staging and restaging computed tomography (CT) was obligatory. The time point of the restaging CT scans was not defined. Response was defined according to the revised response criteria for malignant lymphoma [13].

Exact confidence intervals (CIs) were used where appropriate. OS was defined as the time from the initiation of treatment with brentuximab vedotin to death from any cause and was censored at the date of last information. PFS was defined as time from the initiation of brentuximab vedotin to progression, relapse, or death from any cause, and was censored at the date of last information on remission status. OS and PFS were estimated according to the method of Kaplan and Meier, using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Fourteen patients with primary progressive or relapsed classical HL treated within the NPP without prior HDCT and autologous stem cell transplant were included in the present analysis. The baseline characteristics are presented in Table I. The median age was 45 years (range 24 to 74 years). At initial diagnosis, ten HL patients had stage III or IV disease. Primary progressive disease after first-line treatment was documented in four patients, while another four patients suffered from early and six from late relapse, respectively. The median number of prior chemotherapy regimens was 3 (range 2-6). Nine patients had not received prior HDCT and ASCT due to refractory disease; four patients were excluded from this treatment due to age and comorbidity. The reason for not performing ASCT at first relapse was unknown in one patient.

At initiation of brentuximab vedotin, eight HL patients had stage III or IV disease, and in eight patients extranodal involvement was documented. Prior to treatment with brentuximab vedotin, 11 HL patients had been refractory to their last chemotherapy. Except for one patient, ECOG-status was ≤ 3. The median time between last systemic therapy and initiation of brentuximab vedotin was 2 months (range 1-22).

Treatment Outcome and Survival Rates

Patients received between 2 and 12 courses of brentuximab vedotin (median 4.5). Ten patients (71 %) achieved an objective response including five patients with CR (36%). Five patients with chemo-refractory disease and all patients who did not qualify for HDCT due to age or comorbidity responded to brentuximab vedotin.

After treatment with brentuximab vedotin, five patients underwent HDCT followed by autologous or allogeneic SCT. Two patients proceeded to HDCT and autologous SCT in complete response and were in ongoing CR at the time this report was written. Two patients proceeded to HDCT and autologous SCT in progressive disease; one of them had achieved a complete response after three courses of brentuximab vedotin, in the other patient a stable disease was documented after four courses. Both patients showed signs of progressive disease under continued treatment, and in both a complete response could be documented after HDCT and autologous SCT. One of these patients subsequently underwent reduced-intensity conditioning allogeneic SCT and died of septicaemia three months after allogeneic SCT. In the other patient an ongoing complete response could be documented since HDCT and autologous SCT.

After achieving complete response with brentuximab vedotin, one patient directly proceeded to reduced intensity allogeneic SCT, but eventually developed disease progression and died of progressive lymphoma.

All HL patients who did not receive HDCT at first relapse because of age or comorbidity achieved an objective response including one CR and three PRs. At the time this report was written, these patients were under continuing treatment. Details on response and courses of disease are summarized in Table II.

The median PFS for all patients included in this analysis was 9 months. With ten of the 14 patients being alive at the time of analysis, median OS has not been reached yet. The 12-month estimate for OS was 69% (95%-CI 39% to 100%). Kaplan Meier curves for PFS and OS are shown in Figure 1.

Toxicity

Dose reduction was not necessary and none of the patients had to stop treatment due to toxicity. Peripheral sensory neuropathy grade I/II was documented in four patients; one patient developed grade IV neuropathy after severe septicemia that was thus classified as critical illness neuropathy. Another patient had grade II neuropathy before starting brentuximab vedotin. During treatment, neuropathy worsened to grade III. Severe neutropenia was observed in 4 patients (2

grade III, 2 grade IV). In two of these patients a severe infection was diagnosed and one patient had progressive HL as possible reason for the neutropenia. Two cases of fatigue grade II were documented. No other grade III/IV adverse events were documented. Noteworthy, the older HL patients treated with brentuximab vedotin have not developed any side effects so far.

DISCUSSION

Treatment with brentuximab vedotin resulted in an objective response in 10/14 (71%) HL patients who were HDCT and ASCT naïve due to refractory disease (objective responses in 5/9 patients), comorbidity (objective responses in 4/4 patients) or unknown reason (objective response in 1/1 patient).

Four patients proceeded to HDCT and ASCT, and one patient directly proceeded to HDCT and allogeneic SCT. The median PFS for all patients included in the analysis was 9 months, the estimated 12-months OS for all patients was 69%.

The results of this retrospective analysis suggest that brentuximab vedotin is an effective salvage therapy in chemotherapy-refractory HL patients as well as in older HL patients who do not qualify for HDCT because of comorbidity.

So far, very limited data are available for patients who received brentuximab vedotin before HDCT and stem cell transplantation. In the initial phase I trial reported by Younes et al., twelve patients had not received ASCT prior to brentuximab vedotin treatment. Three of these patients responded to brentuximab vedotin with two complete and one partial remission [14]. In a recently published retrospective analysis of 20 transplant-naïve HL patients treated with SGN-35 within two phase I trials, two complete and four partial responses were reported. Since different schedules and doses of SGN-35 were used in these trials, the results have to be regarded preliminary in terms of efficacy [15]. Similar to our analysis, a recently published retrospective analysis of a single UK centre including twelve HL patients without prior ASCT reported a response rate of 72% with no significant difference to those patients with prior ASCT. In accordance to our analysis, the results of Gibb et al., 2012, indicate that - irrespective of the previous chemotherapy approaches - brentuximab vedotin has significant activity in refractory HL patients [16].

After achieving a response with reinduction therapy, HDCT followed by ASCT has to be regarded as standard of care for patients with primary refractory and relapsed HL [8]. In our analysis, 4/9 HL patients with refractory disease proceeded to HDCT and ASCT after treatment with brentuximab vedotin, and long lasting remissions could be documented in two of these patients achieving CR with brentuximab vedotin. Thus, brentuximab vedotin allowed proceeding to HDCT in some of those patients with chemotherapy refractory HL and might finally result in overcoming their dismal prognosis [8].

Since no standardized restaging schedule was recommended in the NPP, we could not assess the median number of brentuximab vedotin courses required for the best response. After initial response to brentuximab vedotin, 2/14 patients included in our analysis developed progressive disease under continued treatment. The retrospective analysis of Gibb et al., 2012, as well as data of the pivotal phase II trial indicate that it might take not more than four courses to achieve the best response to brentuximab vedotin suggesting to evaluate the response and to decide about HDCT and autologous SCT after the fourth course of brentuximab vedotin [16].

The good anti-tumour activity and tolerability of brentuximab vedotin in HL patients who were ineligible for HDCT due to comorbidity observed in the present analysis also suggests that this drug might be a suitable treatment option for older HL patients. This observation is of special clinical interest regarding the poor outcome and the limited treatment options of older HL patients [5].

In summary, this retrospective analysis indicates that brentuximab vedotin broadens the spectrum of well-tolerated effective reinduction treatment that can be used before HDCT/ASCT in

primary refractory HL patients who might not qualify for this procedure otherwise. Our analysis also suggests that brentuximab vedotin can overcome resistance against conventional chemotherapy in refractory HL. In addition, brentuximab vedotin is also effective and well tolerated in relapsed older HL patients warranting further investigation in prospective clinical trials. Currently, a number of clinical trials evaluating brentuximab vedotin as single agent or in combination with chemotherapy in this setting are being initiated.

Acknowledgements

The authors thank all centers that participated in this data collection, especially M Witzens-Harig, Heidelberg, J. Volk, Hildesheim, J. Potenberg, Berlin, M. Topp, Würzburg, HJ. Steiger, Wiesbaden, M. de Wit, Berlin, H. Ludwig, Wien. In addition we thank all members of the GHSG for the support.

Authorship contributions: SS and AR analyzed data and wrote the manuscript; HG carried out statistical analysis and helped to write the manuscript; AL, SK and UJ, BB, BvT provided patients and corrected the manuscript; DAE and AE analyzed patients and helped to write the manuscript.

Disclosure

Prof. Dr. Andreas Engert: Millenium, Takeda: Research support, honoraria.
Professor Dr. Ulrich Jäger: Advisory Board Takeda.
Dr. Bastian von Tresckow: Millenium The Takeda Oncology Group: Travel grants.
All remaining authors declare no competing financial interests.

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Figure legends

Figure 1: Kaplan-Meier plots and 95% confidence intervals for (A) PFS, (B) OS:

The median PFS was 9 months, the median OS has not been reached.

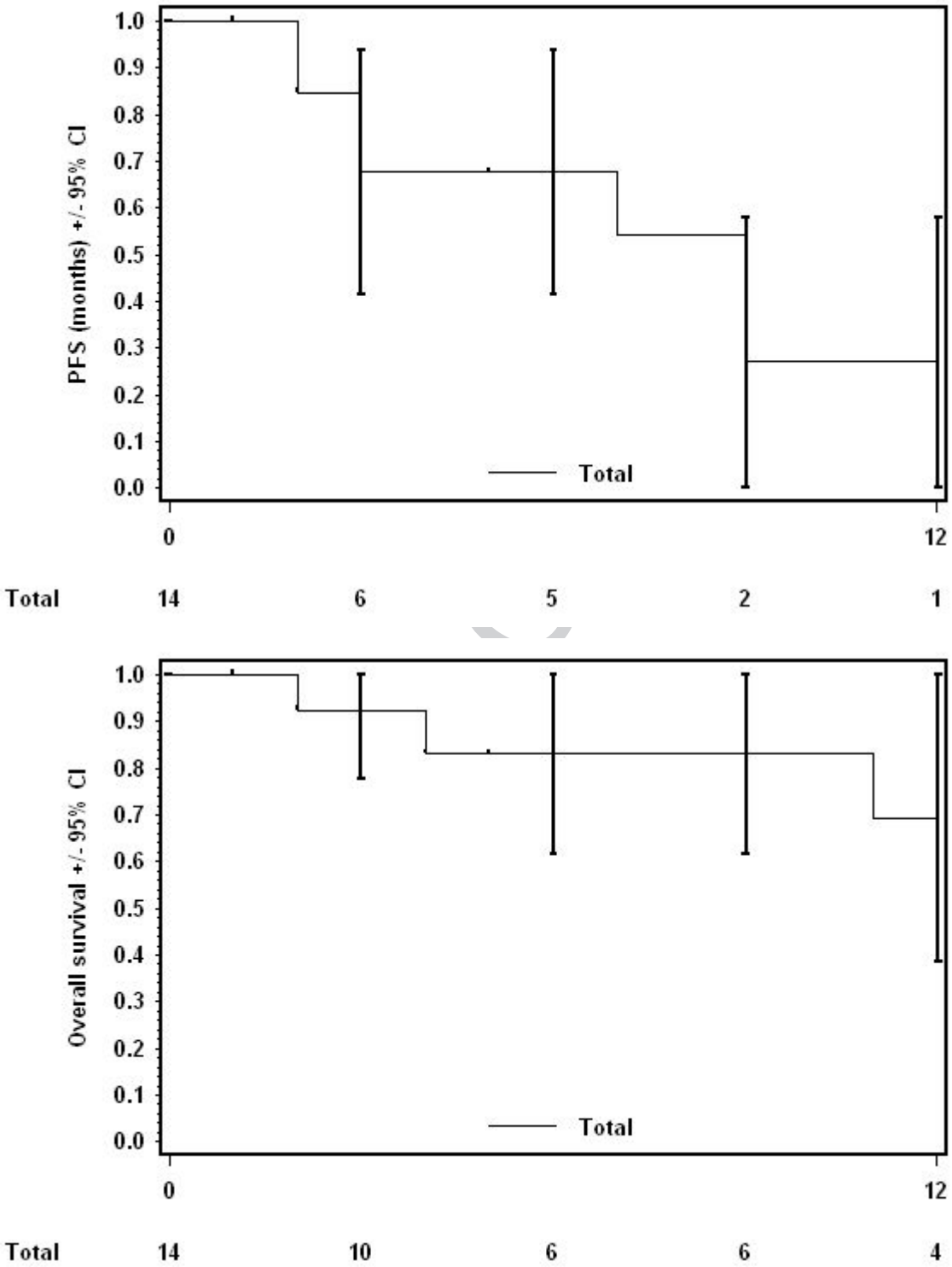

Table I: Patient characteristics.

Pt	Gender	Age	Diagnosis	Primary refractory/ early relapse	Reason for no ASCT at first relapse	Clinical stage at initiation of brentuximab vedotin	ECOG	Previous chemotherapy regimens [n]	Refractory prior brentuximab vedotin	Time between last therapy and start of brentuximab vedotin [months]
1	male	38	HL (NS)	No	Refractory disease	IIB	1	6	Yes	2
2	female	29	HL (NS)	No	Unknown	IIB	1	3	Yes	1
3	male	24	HL (LD)	Yes	Refractory disease	IVB	1	5	Yes	1
4	male	30	HL (NS)	Yes	Refractory disease	IIB	1	3	Yes	1
5	female	68	comp lymphoma (HL CD30 pos.)	Yes	Comorbidity	IIB	3	2	Yes	2
6	female	71	HL (classic)	Yes	Refractory disease	IIIA	2	4	Yes	2
7	male	73	HL (MC)	No	Comorbidity	IIIB	1	2	Yes	2
8	male	36	HL (classic)	No	Refractory disease	IIB	2	2	No	22
9	male	30	HL (classic)	No	Refractory disease	IVB	2	2	Yes	2
10	male	52	HL (classic)	No	Refractory disease	IVB	1	5	Yes	2
11	female	52	HL (classic)	Yes	Refractory disease	IVA	1	2	Yes	3
12	male	72	HL (classic)	Yes	Comorbidity	IIIA	0	3	No	11
13	male	74	HL (MC)	Yes	Comorbidity	IIA	1	2	No	10
14	male	32	HL (classic)	Yes	Refractory disease	IVB	2	4	Yes	1

Table II: Response to brentuximab vedotin and course of disease.

Pt	Best response	SCT after SGN treatment	Progression or relapse (PFS [months])	Death (OS [months])
1	CR	ASCT	No (15)	No (15)
2	CR	ASCT	No (12)	No (12)
3	CR	ASCT	Yes (7)	Yes (11)
4	PD		Yes (3)	Yes (4)
5	PR		No (5)	No (5)
6	SD		Yes (9)	No (15)
7	PR		No (1)	No (1)
8	CR	allogeneic SCT	Yes (9)	Yes (14)
9	SD		No (2)	Yes (2)
10	SD	ASCT	Yes (3)	No (15)
11	PR		No (3)	No (3)
12	PR		No (3)	No (4)
13	CR		No (2)	No (4)
14	PR		Yes (2)	No (2)