Brentuximab vedotin prior to allogeneic hematopoietic cell transplantation in classical Hodgkin lymphoma: a retrospective study of the EBMT Lymphoma Working Party

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ABSTRACT

Rationale: Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate. Preliminary data suggest that BV might improve outcomes after allogeneic stem cell transplantation (SCT) for Hodgkin lymphoma (HL) when used as pre-transplant salvage therapy.

Patients and Methods: Between 2010 and 2014, 435 adult patients underwent an allogeneic SCT for classical HL at EBMT participating centers. We compared the outcomes of 217 patients who received BV prior to allogeneic SCT with that of 218 patients who did not receive BV. The median follow-up for survivors was 41 months.

Results: Patients in the BV group were younger (median age: 30 versus 33 years), but more heavily pretreated (median pre-allograft treatment lines: 4 vs 3). The two groups were comparable in terms of disease status, performance status, comorbidities, prior autologous SCT, type of donor, conditioning and *in vivo* T cell depletion. In multivariate analysis, pre-allograft BV had no impact on acute graft versus host disease (GVHD), non relapse mortality, cumulative incidence of relapse, progression free survival or overall survival (OS) but significantly reduced the risk of chronic GVHD (hazard ratio=0.67; 95%CI=0.47-0.96; p=0.03). Older age, poor performance status, use of pre-transplant radiotherapy and active disease at SCT adversely affected OS.

Conclusion: Patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, BV may improve the outlook of allogeneic SCT by helping to put otherwise refractory patients in a more favorable disease status facilitating allotransplant success.

INTRODUCTION

Hodgkin lymphoma (HL) is a curable disease with 5-year progression free survival (PFS) exceeding 80% with standard first line therapy. For primary refractory or relapsed disease after first line treatment, second line salvage chemotherapy followed by autologous stem cell transplantation (SCT) is considered the standard of care, resulting in sustained disease control in more than half of the patients.[1-4] For patients who relapse after autologous SCT, the median survival is 24 months, and allogeneic SCT represents the only curative modality.[5-7].[8]

The success of allogeneic SCT in relapsed/refractory HL is dependent on a number of factors including tumor sensitivity to salvage therapy before transplantation.[9-12] Unfortunately, a significant number of patients with relapsed/refractory HL have chemo-resistant disease and have received multiple lines of therapy. Therefore, novel monoclonal antibodies such as brentuximab vedotin (BV) or checkpoint inhibitors are increasingly used as a bridge to transplant.[13]

BV is an anti-CD30 monoclonal antibody linked by a protease-cleavable linker to monomethyl auristatin E, a microtubule-disrupting agent. This antibody-drug conjugate is approved for the treatment of classical HL in relapse either after autologous SCT or after two lines of combination chemotherapy in transplant ineligible patients. [14-16] The pivotal phase II study using single-agent BV in relapsed/refractory HL revealed an overall response rate of 75%, with 34% complete responses, and a median remission duration of 20 months for complete responders.[16] Side effects are relatively modest, the most clinically significant one being reversible peripheral neuropathy, which often prohibits long term BV therapy. The AETHERA randomized trial recently demonstrated that maintenance with BV after autologous SCT significantly improved PFS in high risk HL patients.[17]

Preliminary data suggests that BV may improve the results of allogeneic SCT for HL when used as a bridging agent.[18-21]. However, the impact on long-term outcomes remains unknown. In this study we aimed at assessing the impact of pre-transplant BV on a subsequent allogeneic SCT by comparing the outcome of patients who received BV before allogeneic SCT with that of patients who did not receive BV before allogeneic SCT, using a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

PATIENTS AND METHODS

Study design and data collection

This is a retrospective registry-based multicenter analysis. Data were provided and approved for this study by the Lymphoma Working Party (LWP) of the EBMT. EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive stem cell transplantations and follow-up once a year. Audits are routinely performed to determine the accuracy of the data. Since

January 1 2003, all transplant centres have been required to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975. Eligibility criteria for this analysis included adult patients (age >18 years) with classical HL who received a first allogeneic SCT between 2010 and 2014 from an HLA matched related or unrelated donor with bone marrow (BM) or G-CSF-mobilized peripheral blood (PB) stem cells. Patients who received cord blood, mismatched or haploidentical stem cells and tandem transplants were excluded.

Variables collected included recipient and donor age and gender, date of diagnosis, lines and detailed type of therapy prior to allogeneic SCT, response to each individual treatment line, previous autologous SCT, date, duration and number of doses of BV, disease status at transplant (complete remission, partial remission or active disease), performance status and comorbidity index, transplant related-factors including conditioning regimen, immunosuppression (*in vivo* T-cell depletion vs. none), GVHD prophylaxis, stem cell source (BM or PB) and donor type. Active disease was defined as not being in CR or PR with stable disease, primary induction failure, primary refractory, or disease progression. For patients who received additional treatment after allogeneic SCT, we also collected the date of BV administration, additional cellular therapy, and additional immunotherapy or chemotherapy.

Definitions

Histological diagnosis was based on local review and patients were staged according to the Ann Arbor system. Disease status at transplantation was classified as chemosensitive disease including all patients who had shown at least a partial remission (PR), chemoresistant disease including patients with primary refractory disease, refractory relapse or untreated relapse. Patients who survived more than 90 days after allo-SCT without evidence of tumor were classified as having experienced complete remission (CR). PR was defined as a ≥ 50% reduction of all pre-transplantation measurable disease for at least 1 month. Patients achieving less than 50% tumor reduction were considered non-responders. Intensity of conditioning regimens was defined as previously published.[16]

Statistical analysis

Endpoints included PFS, overall survival (OS), non relapse mortality (NRM), cumulative incidence of relapse (CIR) and acute and chronic GVHD. All outcomes were measured from the time of allogeneic SCT. PFS was defined as survival without relapse or progression; patients alive without relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous relapse. Surviving patients were censored at the time of last contact. The probabilities of OS and PFS were calculated by using the Kaplan-Meier estimator. The probabilities of acute and chronic GVHD, NRM, and relapse were calculated by using the cumulative incidence estimator to accommodate competing risks. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For acute and chronic GVHD, death without the event was the

competing risk. For all prognostic analyses, continuous variables were categorized and the median used as a cut-off point. Univariate comparisons were performed using the log-rank test for PFS and OS, and the Gray's test for cumulative incidences. Chronic GVHD was analyzed as a time-dependent variable. A Cox proportional hazards model was used for multivariate regression. Factors known to influence the outcome and factors associated with a p value less than 0.10 with any endpoint by univariate analysis were included in the model. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes.

All analysis were performed using R version 3.1.1 with the R packages survival version 2.38, cmprsk version 2.2-7 and Hmisc version 3.16-0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients' characteristics

Altogether, 435 patients met the eligibility criteria for this study. 218 patients had not received BV prior to allogeneic SCT (no BV group), and 217 had received BV as salvage therapy before allogeneic SCT (BV group). Of the 217 BV-exposed patients, in 152 patients (70%) BV was the most recent regimen before allogeneic SCT (bridge-to-transplant), whilst it was followed by another salvage regimen in 22 patients (10%). In the remaining 43 patients, the start date of BV was not indicated. Patients' characteristics are listed in Table 1. 341 patients (78%) had a prior autologous SCT. Patients in the BV group had received a median of 5 doses (1-18). Maximum response to BV was complete remission (CR: 34%), partial remission (PR: 41%) and stable disease (SD: 21%). This maximal response was achieved after a median of 4 cycles of BV (1-16). Median time from start of BV to allogeneic SCT was 179 days (Q1 127; Q3 287)

Transplant characteristics

Transplant characteristics are listed in Table 2. Sixty patients in the BV and 30 in the non BV group received BV after allogeneic SCT, predominantly for relapse after allogeneic SCT, after a median of 12 and 22 months post transplant, respectively.

Effect of salvage BV prior to allogeneic SCT on transplant outcomes

In univariate analysis, prior use of BV had no effect on either engraftment (Table 3; Figure 1A), or on the incidence and severity of acute GVHD (Table 3; Figure 1B). Indeed, the cumulative incidence of day +100 acute GVHD grade II-IV was 22% in the BV group vs 28% in the non BV group. Conversely, there was a lower incidence of chronic GVHD in the BV group with a 37% cumulative incidence at 2 years versus 44% in the non BV group, although this was not statistically significant (Table 3; Figure 1C; p=0.06). Finally, pre-transplant BV was associated with a significantly higher 2-year CIR (48% versus 35%) (Figure 2A), but had no significant effect on the 2-year cumulative incidence of NRM (14% versus 18%), PFS (38%

versus 47%) or OS (70% versus 63%). The median follow-up for survivors was 41 months (interquartile range/IQR 28-55 months).

Multivariate analysis

In multivariate analysis, pre-allograft BV had no significant effect on acute GVHD, NRM, CIR, PFS, or OS, but significantly reduced the incidence of chronic GVHD (Table 4). Use of pre-transplant radiotherapy adversely affected chronic GVHD and OS, poor performance status (Karnofsky score < 90) adversely affected PFS and OS, older age (>40 years) adversely affected acute GVHD, NRM, PFS and OS, whereas active disease status at the time of allogeneic SCT adversely affected chronic GVHD, CIR, NRM, PFS and OS, and a higher number of treatment lines increased the incidence of cGVHD (Table 4).

DISCUSSION

Reduced intensity conditioning followed by allogeneic SCT is an effective treatment modality for HL patients who relapsed or progressed after autologous SCT. However, the success of this treatment modality is largely dependent on the tumor being sensitive to salvage therapy before transplantation.[10] Unfortunately, patients with relapsed/refractory disease have already received multiple lines of therapy and are quite difficult to salvage. Preliminary data from small series suggest that pre-transplant salvage therapy with BV might improve outcomes after allogeneic SCT for HL.[18-20]

Our study included a high-risk population: 78% of the patients had received a prior autologous SCT (of note, some of the patients had received more than one autologous SCT before allogeneic SCT) and the median number of prior treatment lines was 4. Of note, patients on the BV group were more heavily pre-treated than patients in the non BV group, with 69% of the patients in the BV group having received 4 or more lines of therapy including BV versus 40% in the non BV group. As most of the patients in this study received BV as last treatment before allogeneic SCT, one could argue that BV allowed these high-risk patients to obtain a response good enough to proceed to SCT. Multivariate analysis showed that pre-allograft salvage therapy with BV did not affect acute GVHD, NRM, CIR, PFS or OS. These results are in disagreement with previous reports from Chen suggesting that the use of BV as a bridge to allogeneic SCT improves post transplant outcomes.[19] However, all patients in our series were transplanted from 2010 to 2014, whereas in Chen et al. study patients who did not receive BV study were transplanted from 2003 and 2009, implying that general improvements in SCT technology rather than BV itself might have contributed to the superior outcome of the BV group in that study.

Interestingly, we clearly show that pre-allograft salvage therapy with BV significantly decreased the cumulative incidence of chronic GVHD in multivariate analysis. This was despite the fact that 31% of patients in the BV group received post transplant DLI versus only 17% in the non-BV group. While there is no clear explanation for this effect, it may be due to the immunomodulatory effects of BV which need to

be further studied. In this context, BV has been shown to induce remission in rheumatoid arthritis. [23] CD30 is a cell membrane protein of the tumor necrosis factor superfamily expressed on activated CD3+ T cells and upregulated in T cells when exposed to allogeneic antigens. Mallard et al reported that the absolute number of CD30+ lymphocytes is significantly higher in the dermal infiltrate of the skin of the patients with acute GVHD, compared with those without it, indicating that the accumulation of cytotoxic and activated CD30+ T cells reflected an activated immune status in the skin of the patients with acute GVHD.[25] Chen et al showed that patients with acute GVHD have a higher percentage of CD30 expressing CD8+ T cells with the difference especially pronounced in the central memory subset (CD8+ CD45RO+ CD62L+).[26]

One important limitation of our retrospective registry study is the risk of selection bias. Ideally, this question should be answered by a prospective randomized trial comparing allogeneic SCT after prior salvage with or without BV. However, this type of study is ethically questionable because of the limited alternative options in these often chemoresistant patients.

In conclusion, and in contrast to previous much smaller studies, patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, patients with BV-induced remissions prior to transplant do not worse than chemosensitive patients, implying that BV can improve the outlook of allogeneic SCT by helping to put otherwise refractory patients in a more advantageous disease status as a prerequisite for a successful allotransplant. The decrease in chronic GVHD is an interesting finding that needs to be further studied in the setting of allogeneic SCT, even beyond HL.

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Contributing centers by decreasing number of patients enrolled in the study:

Conflict of Interest

A Bazarbachi, M Mohty, A Sureda and xxxx received research support and lectures honoraria from Takeda whose product is discussed in this work. The other authors do not have any conflicts of interest. No financial support was provided for this work.

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FIGURE LEGENDS

Figure 1: Effect of pre-transplant BV salvage on post transplant engraftment, acute and chronic graft versus host disease. (A) Cumulative incidence of engraftment, (B) Cumulative incidence of chronic graft versus host disease.

Figure 2: Effect of pre-transplant BV salvage on post transplant outcomes (A) Cumulative incidence of non-relapse mortality, (B) Cumulative incidence of relapse, (C) Progression free survival, (D) Overall survival.

Table1: Patients' Characteristics

Variable	No Brentuximab N (%)	Brentuximab N (%)	P
N	218	217	
Age at allogeneic SCT median (range)	33 (18-71)	30 (18-68)	0.04
Female	82 (38)	89 (41)	0.53
SCT-Comorbidity Index	0 (0-6)	0 (0-6)	0.93
Karnofsky score 90, 100	158 (73)	161 (77)	0.37
Lines before SCT median (range)	3 (1-9)	4 (1-12)	<0.001
4 or more treatment lines	71 (40%)	123 (69%)	<0.001
First line treatment ABVD	156 (72)	158 (73)	0.8
Second line			0.82
DHAP	43 (20)	44 (20)	
ESHAP	30 (14)	19 (9)	
ICE	15 (7)	26 (12)	
IGEV	23 (11)	28 (13)	
Radiotherapy before transplant	104 (48)	105 (48)	0.96
Prior autologous SCT	171 (78)	170 (78)	1
Disease status at SCT			0.44
Not available (N)	1	2	
Active Disease	76 (35)	91 (42)	
CR>1	102 (47)	89 (41)	
PR>1	39 (18)	35 (16)	
Median interval from diagnosis to allogeneic SCT (months, range)	31 (11-336)	35 (7-23)	0.02
Median follow up for alive patients (months, range)	50 (42-60)	32 (25-41)	<0.001

Abbreviations: SCT= allogeneic stem cell transplant; ABVD= Adriamycin, bleomycin, vinblastine and dacarbazine; CR= complete response; PR= partial response; SD= stable disease; DHAP= dexamethasone, high dose cytarabine and cisplatin; ESHAP= etoposide, solumedrol, high dose cytarabine and cisplatin; ICE= ifosfamide, carboplatin and etoposide; IGEV= ifosfamide, gemcitabine and vinorelbine.

Table2: Transplant characteristics

Transplant Characteristics	No Brentuximab N (%)	Brentuximab N (%)	P
Patients	**218**	**217**	
Median year of SCT	**2011**	**2013**	**<0.001**
Number of this SCT			**0.59**
First	**45 (21)**	**41 (19)**	
Second	**160 (73)**	**159 (73)**	
Third	**12 (6)**	**17 (8)**	
Fourth	**1 (0)**	**0 (0)**	
Non myeloablative or reduced intensity conditioning	**169 (78)**	**163 (75)**	**0.53**
No TBI	**174 (80)**	**170 (78)**	**0.79**
ATG	**55 (25)**	**54 (25)**	**1.00**
No ATG	**163 (75)**	**163 (75)**	
Donor type			**0.74**
MRD	**136 (62)**	**131 (60)**	
MUD	**82 (38)**	**86 (40)**	
Stem cell source			**1.00**
BM	**44 (20)**	**43 (20)**	
PB	**174 (80)**	**174 (80)**	
Treatment post-transplant			
DLI	**38 (17)**	**67 (31)**	**0.002**
Median time from SCT to DLI (months, range)	**10 (3-37)**	**10 (0-58)**	**0.78**
BV post-transplant	**30**	**60**	**<0.001***
Median months from SCT to BV	**22 (3-36)**	**12 (4 days-52 months)**	**0.10**
Number of post SCT BV doses			
Missing	**9**	**12**	
Median (range)	**8 (1-16)**	**5 (1-16)**	**0.02**
Median duration of BV post SCT (days-range)	**178 (1-632)**	**101 (1-507)**	**0.06**

***** Gray's test for cumulative incidence of BV post administration taking into account competing risk of death

Abbreviations: SCT= allogeneic stem cell transplant; TBI= total body irradiation; ATG= anti-thymocyte globulin; MRD= matched related donor; MUD= matched unrelated donor; BM= bone marrow; PB= peripheral blood; DLI= donor lymphocytes infusion; BV= brentuximab-vedotin.

Table3: Transplant outcomes

Transplant outcomes	No Brentuximab N (%)	Brentuximab N (%)	P
Patients	218	217	
Engrafted	210 (99)	208 (98)	0.69
Acute GVHD			
Grade I	39 (18)	38 (18)	
Grade II	42 (19)	33 (15)	
Grade III	13 (6)	8 (4)	0.52
Grade IV	7 (3)	7 (3)	
Unknown grade	6 (3)	4 (2)	
2 year NRM	18 (13-24)	14 (10-19)	0.26
2 year CIR	35 (29-42)	47 (40-54)	0.01
2 year PFS	47 (41-54)	38 (32-45)	0.12
Chronic GVHD			
Yes	102 (49)	83 (40)	0.06
No	106 (51)	127 (60)	
2-year OS	63 (57-70)	70 (64-76)	0.15
Deaths	96 (44)	85 (39)	
Cause of death			0.78
SCT related	48 (50)	43 (51)	
Relapse/progression	41 (43)	39 (46)	
Other	4 (4)	3 (4)	
Secondary malignancy	2 (2)	0 (0)	
Unknown	1 (1)	0 (0)	

Abbreviation: GVHD= graft versus host disease; NRM= non-relapse mortality; CIR= cumulative incidence of relapse; PFS= progression free survival; OS= overall survival; SCT= allogeneic stem cell transplant.

Table 4: Multivariate analysis

Variables	cGVHD HR [95%CI] P	NRM HR [95%CI] P	CIR HR [95%CI] P	PFS HR [95%CI] P	OS HR [95%CI] P
BV salvage vs no BV salvage	**0.67 [0.47-0.96] P=0.0298**	0.94 [0.54-1.63] P=0.8310	1.26 [0.90-1.79] P=0.1823	1.16 [0.86-1.55] P=0.3283	0.94 [0.66-1.35] P=0.7477
Age at SCT above or equal to 40 y.o. vs under 40 y.o.	1.15 [0.78-1.68] P=0.4877	**2.17 [1.27-3.70] P=0.0046**	1.19 [0.81-1.75] P=0.3709	**1.45 [1.07-1.98] P=0.0181**	**2.08 [1.45-2.97] P<0.001**
Male vs female	1.30 [0.93-1.82] P=0.1253	1.12 [0.67-1.89] P=0.6598	1.27 [0.91-1.77] P=0.1641	1.22 [0.92-1.61] P=0.17	1.38 [0.98-1.95] P=0.0644
Karnofsky 90,100 vs under 80	0.95 [0.64-1.40] P=0.7938	0.66 [0.38-1.14] P=0.1379	0.72 [0.50-1.05] P=0.089	**0.70 [0.52-0.95] P=0.0242**	**0.58 [0.41-0.82] P=0.0021**
Four or more treatment lines vs three or less	**1.60 [1.11-2.31] P=0.0111**	1.07 [0.62-1.86] P=0.8027	1.13 [0.80-1.60] P=0.4983	1.12 [0.83-1.50] P=0.4623	1.22 [0.85-1.75] P=0.2708
Active disease vs sensitive or stable disease	**1.48 [1.06-2.07] P=0.0226**	**2.86 [1.69-4.84] P<0.001**	**2.43 [1.75-3.39] P<0.001**	**2.56 [1.93-3.39] P<0.001**	**2.62 [1.87-3.69] P<0.001**
Time from diagnosis to SCT above or equal to 24 months vs under 24 months	1.01 [0.68-1.48] P=0.9731	1.45 [0.73-2.85] P=0.2875	0.84 [0.58-1.22] P=0.3597	0.96 [0.70-1.33] P=0.8123	1.01 [0.68-1.49] P=0.9622
Radiotherapy before SCT vs no radiotherapy	**1.43 [1.03-2.00] P=0.0347**	1.44 [0.85-2.43] P=0.1756	0.94 [0.68-1.32] P=0.7375	1.07 [0.81-1.41] P=0.6365	**1.43 [1.02-2.00] P=0.0391**

Abbreviations: BV= brentuximab-vedotin; SCT= allogeneic stem cell transplant; cGVHD= chronic graft versus host disease; NRM= non relapse mortality; CIR= cumulative incidence of relapse; PFS= progression free survival; OS= overall survival.