Brief report

Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma

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Brentuximab vedotin induces an overall response rate of 75% in patients with relapsed/refractory Hodgkin lymphoma, but its impact on future allogeneic transplantation (allo-HCT) is not known. We retrospectively examined the records of 18 patients with relapsed/refractory Hodgkin lymphoma who were treated on brentuximab vedotin clinical trials to evaluate the efficacy and safety of subsequent reduced-intensity allo-HCT. Seventeen patients had previous autologous transplant; 6 were in complete remission, and 8 were in partial remission before allo-HCT with 12 grafts from unrelated or mismatched donors. The 1-year overall survival was 100%, progression-free survival was 92.3%, and nonrelapse mortality was 0% (median follow-up, 14 months). The incidence of acute GVHD was 27.8% and chronic GVHD was 56.3%. Brentuximab vedotin before reduced-intensity allo-HCT does not appear to adversely affect engraftment, GVHD, or survival and may provide sufficient disease control to enable reduced-intensity allo-HCT. (*Blood*. 2012;119(26):6379-6381)

Introduction

Patients with Hodgkin lymphoma (HL) who relapse after autologous hematopoietic cell transplantation (auto-HCT) have a poor prognosis and very limited options, with a median overall survival (OS) of 2.4 years.[1] Reduced-intensity (RIC) allogeneic hematopoietic cell transplantation (allo-HCT) is a curative option for some patients, with a 1-year progression-free survival (PFS) of 48%,[2] but a high relapse rate, most notably in patients with poor pretransplantation disease control.[3-8] Thus, a safe and effective means of pretransplantation disease control could improve allo-HCT outcomes.

Brentuximab vedotin is an antibody-drug conjugate composed of an anti-CD30 antibody conjugated to the microtubule-disrupting agent, monomethyl auristatin E.[9] Cell surface expression of CD30, a member of the TNF superfamily,[10,11] is characteristic of the malignant Hodgkin Reed-Sternberg cells. A multicenter phase 2 trial of brentuximab vedotin in patients with HL recurring after autologous transplantation demonstrated an overall response rate of 75%, a complete response (CR) rate of 34%, and median duration of response 6.7 months for all patients and 20.5 months for those achieving CR.[12]

Based on the safety and effectiveness of brentuximab vedotin in the after auto-HCT relapse setting and the importance of pretransplantation disease control, we hypothesized that this agent could successfully provide cytoreduction in HL patients before RIC allo-HCT, improving posttransplantation disease-free survival.

Methods

The City of Hope and Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center Institutional Review Boards approved the retrospective analysis of data from this consecutive case series. Patients 18 years of age or older with histologically confirmed HL expressing CD30 were included in the study if they received brentuximab vedotin at City of Hope or Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center and were subsequently treated with a reduced-intensity allo-HCT. All patients were relapsed after prior auto-HCT or were not auto-HCT candidates because of insufficient stem cell collection or chemorefractory disease. Patients were excluded if they had received a previous allo-HCT. Between October 2008 and October 2011, 54 patients with relapsed/refractory HL and no prior allo-HCT received brentuximab vedotin at City of Hope (n = 36) and Seattle Cancer Care Alliance/Fred Hutchinson Cancer Research Center (n = 18). A total of 36 of 54 patients (66.7%) would have been eligible to undergo reduced-intensity allo-HCT based on performance status, donor availability, and disease status after brentuximab vedotin. Eighteen patients (33.3%) eventually received reduced-intensity allo-HCT and are included in this analysis. Reasons for not proceeding to transplantation included: persistent residual disease (n = 7), no donor (n = 4), patient preference (n = 18), comorbidities or advanced age (n = 7). Baseline pretransplantation patient, disease, and treatment characteristics for the 18 patients who proceeded to allo-HCT are summarized in Table 1.

Posttransplantation evaluation of disease status with imaging studies, bone marrow biopsies, and engraftment analysis occurred at 30 days, 100 days, 1 year after transplantation, and yearly thereafter, or as clinically indicated. Response was scored using standard criteria.[13] OS and PFS survival probabilities were calculated by the Kaplan-Meier method,[14] and cumulative incidence of relapse/progression and nonrelapse mortality were calculated as competing risks by the method of Gooley et al.[15]

Results and discussion

As seen in Table 1, the patients in this study represent a heavily pretreated population in which 55.6% had received prior radiation

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Table 1. Patient, disease, and treatment characteristics

Characteristics	N (%) or median (range)
No. of patients	18
Age, y	30.5 (range 23-55)
No. of prior regimens	4.5 (range 3-8)
Prior auto-HCT	17 (94.4)
Previous XRT	10 (55.6)
Best response to brentuximab vedotin	
CR	7 (39)
PR	8 (44)
SD	2 (11)
PD	1 (6)
No. of cycles of brentuximab vedotin	7 (range 2-16)
Baseline neuropathy before allo-HCT	68 (44)
Grade 1	6 (33)
Grade 2	2 (11)
Disease status after brentuximab vedotin	
CR	6 (33)
PR	6 (33)
SD	1 (6)
PD	5 (28)
Disease status at allo-HCT	
CR	6 (33)
PR	8 (44)
SD	1 (6)
PD	3 (17)
Time from brentuximab vedotin to allo-HCT	62 d (range 24-276)
Type of transplantation	
MRD	7 (39)
MUD	8 (44)
Haplo	3 (17)
Conditioning regimen	
Flu/Mel	14 (77)
Flu/Cy/TBI	3 (17)
2 Gy TBI	1 (6)
GVHD prophylaxis	
Tacro/Siro	10 (55)
Tacro/Siro/MTX	2 (11)
Cy/Tac/MMF	3 (17)
CSA/MMF	1 (6)
CSA/MTX	2 (11)

XRT indicates irradiation; SD, stable disease; PD, progressive disease; MRD, matched related donor; MUD, matched unrelated donor; Haplo, haploidentical; Flu, fludarabine; Mel, melphalan; TBI, total body irradiation; Tacro, tacrolimus; Siro, sirolimus; Cy, cyclophosphamide; Tac, tacrolimus; MMF, mycophenolate mofetil; CSA, cyclosporine A; ATG, antithymocyte globulin; and MTX, methotrexate.

therapy, 94% had undergone high-dose chemotherapy and auto-HCT, and the median number of prior regimens was 4.5. The majority of patients (11 of 18; 61.1%) did not have a matched related sibling and required a matched unrelated donor or haploidentical transplant.

All patients achieved engraftment. The median time to neutrophil recovery was 14 days (range, 0-21 days) as defined by absolute neutrophil count ≥ 500 cells/μL. The median time to platelet recovery was 12.5 days (range, 0-21 days) as defined by platelet count $> 20\,000$ cells/μL without transfusion support. Chimerism studies were performed in patients from day 30 to day 209. All patients achieved more than 99% donor chimerism. Brentuximab vedotin treatment seemed to have no adverse impact on engraftment. No differences in engraftment were noted between patients who proceeded directly to allo-HCT after brentuximab vedotin compared with those that received intervening therapy ($P = 6$).

Acute GVHD occurred in 6 of 18 patients (33.3%). The incidence of acute GVHD grades 1 and 2 was 5.5% and 27.8%, respectively. The incidence of chronic GVHD was 56.3% (9 of 16 patients): limited in 5 patients and extensive in 4. No differences in acute or chronic GVHD were noted between patients with recent (< 60 days before allo-HCT) versus distant (> 60 days) exposure to brentuximab vedotin. The rates of acute and chronic GVHD were not noticeably affected by pretreatment with brentuximab vedotin.

We evaluated the toxicities of reduced-intensity allo-HCT after brentuximab vedotin using the Bearman toxicity scale. There were no grade 3 or 4 events. The most common toxicities ($> 20\%$) were grade 1 gastrointestinal toxicity (36%), grade 1 hepatotoxicity (36%), grade 1 renal toxicity (43%), and grade 2 stomatitis (43%). Two (11.1%) patients had EBV PCR reactivation and 3 (16.7%) had CMV PCR reactivation, all without clinical manifestation of infection. There were no incidents of sinusoidal obstructive syndrome. Eight patients had peripheral neuropathy before allo-HCT; 7 patients improved or stabilized after transplantation, whereas one patient progressed from grade 1 to 2, attributed to tacrolimus and prior brentuximab vedotin. With a median follow-up of 14.0 months (range, 1.7-22.9 months) for surviving patients, 18 patients were alive at the analytic date: 16 were progression-free and 2 patients were in relapse. The CR rate was 100% at first imaging after reduced-intensity allo-HCT (15 of 18 by CT/PET and 3 of 18 by CT). The estimated OS at 1 year after transplantation was 100%, and PFS was 92.3% (95% confidence interval [CI], 61.3-98.7; Figure 1A). The day 100 and 1-year nonrelapse mortality rates were 0% (Figure 1B). The cumulative incidence of relapse/progression at 1 year was 7.7% (95% CI, 1.3-38.7; Figure 1B).

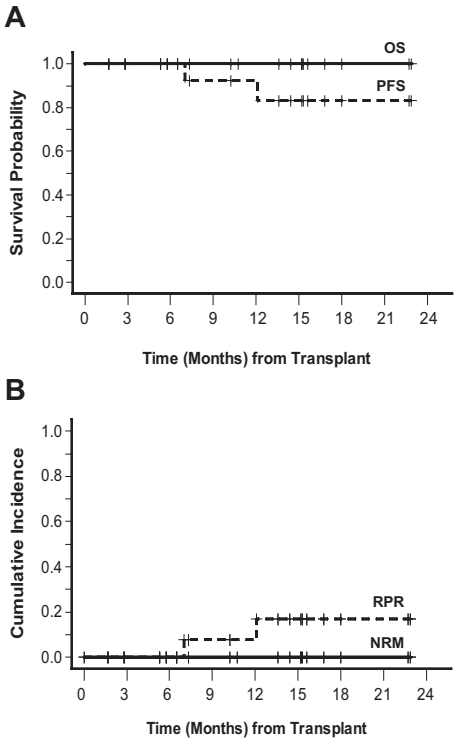

Figure 1. Outcomes. N = 18 patients with median follow-up of 14.0 months. (A) Kaplan-Meier survival probabilities overall survival (solid line) and progression-free survival (PFS; dashed line). OS was measured from stem cell infusion to death from any cause. PFS was defined as time from stem cell infusion to recurrence, progression, or death from any cause, whichever occurred first. (B) Cumulative incidence of relapse/progression (RPR; dashed line) and nonrelapse mortality (NRM; solid line), calculated as competing risks. The cumulative incidence of relapse/progression (RP) was defined as time from stem cell infusion to recurrence or progression. Nonrelapse mortality (NRM) was measured from transplant to death from any cause other than disease relapse or progression.

The only patient who relapsed within 1 year of allo-HCT was transplanted with chemoresistant progressive disease, having relapsed and then progressed on 2 different salvage therapies after an initial CR to brentuximab vedotin; 276 days had elapsed between the last dose of brentuximab vedotin and allo-HCT. The range of time intervals between brentuximab vedotin and allo-HCT was the result of varied times to best response, donor availability, disease relapse, or patient choice.

The optimal timing of reduced-intensity allo-HCT after brentuximab vedotin response in this setting remains a question. For example, who would benefit more from immediate allo-HCT versus sustained treatment with brentuximab vedotin? To address this issue, we plan a separate analysis of patients whowere eligible for allo-HCT but elected against it. We do know that the median duration of CR is at least 20.5 months and the median duration of partial response (PR) after brentuximab vedotin is only 6.7 months. Perhaps patients with a best response of PR would benefit from earlier allo-HCT.

In conclusion, we have shown that allo-HCT with reduced-intensity conditioning after brentuximab vedotin was safe in our cohort of heavily pretreated relapsed HL patients. We did not observe increases in engraftment time, transplant toxicity, or incidence of acute and chronic GVHD. Another antibody-drug conjugate, gemtuzumab ozogomycin, increases the incidence of sinusoidal obstructive syndrome after allo-HCT[16]; but thus far, this does not appear to be the case with brentuximab vedotin. After objective responses to brentuximab vedotin in a heavily pretreated population, 36 of 54 patients were eligible for reduced-intensity allo-HCT, with 18 of 36 electing to undergo transplantation. Although our follow-up is short, the 1-year PFS of 92.3% and 1-year OS of 100% inspire optimism, and in time we hope to validate the role of brentuximab vedotin before reduced-intensity allo-HCT.

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Authorship

Contribution: R.C., S.J.F., J.M.P., and A.K.G. designed the study; R.C., N.-C.T., J.M.P., and A.K.G. collected data and performed data analysis; and R.C., A.K.G., S.H.T., L.F., and A.N. interpreted data and wrote the manuscript.

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References

1. Horning SJ, Fanale M, de Vos S, et al. International Conference on Malignant Lymphoma. Lugano, Switzerland; 2008:iv120-iv121.
2. Sureda A, Canals C, Arranz R, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study: a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica.* 2012;97(2):310-317.
3. Anderson JE, Appelbaum FR, Fisher LD, et al. Allogeneic bone marrow transplantation for 93 patients with myelodysplastic syndrome. *Blood.* 1993;82(2):677-681.
4. Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol.* 2008;26(3):455-462.
5. Armand P, Kim HT, Ho VT, et al. Allogeneic transplantation with reduced-intensity conditioning for Hodgkin and non-Hodgkin lymphoma: importance of histology for outcome. *Biol Blood Marrow Transplant.* 2008;14(4):418-425.
6. Anderlini P, Saliba R, Acholonu S, et al. Fludarabine-melphalan as a preparative regimen for reduced-intensity conditioning allogeneic stem cell transplantation in relapsed and refractory Hodgkin's lymphoma: the updated MD Anderson Cancer Center experience. *Haematologica.* 2008; 93(2):257-264.
7. Chen R, Palmer JM, Popplewell L, et al. Reduced intensity allogeneic hematopoietic cell transplantation can induce durable remission in heavily pretreated relapsed Hodgkin lymphoma. *Ann Hematol.* 2011;90(7):803-808.
8. Robinson SP, Sureda A, Canals C, et al. Reduced intensity conditioning allogeneic stem cell transplantation for Hodgkin's lymphoma: identification of prognostic factors predicting outcome. *Haematologica.* 2009;94(2):230-238.
9. ADCETRIS. *Package Insert.* Bothell, WA: Seattle Genetics; 2011.
10. Dürkop H, Latza U, Hummel M, Eitelbach F, Seed B, Stein H. Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. *Cell.* 1992;68(3):421-427.
11. Falini B, Pileri S, Pizzolo G, et al. CD30 (Ki-1) molecule: a new cytokine receptor of the tumor necrosis factor receptor superfamily as a tool for diagnosis and immunotherapy. *Blood.* 1995; 85(1):1-14.
12. Chen RW, Gopal AK, Smith SE, et al. Results from a pivotal phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma (HL) [abstract]. *ASCO Meeting Abstracts.* 2011;29(15 Suppl):8031.
13. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-586.
14. Kaplan G, Meier P. Non-parametric estimations from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
15. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med.* 1999;18(6):695-706.
16. Wadleigh M, Richardson PG, Zahrieh D, et al. Prior gemtuzumab ozogamicin exposure significantly increases the risk of veno-occlusive disease in patients who undergo myeloablative allogeneic stem cell transplantation. *Blood.* 2003; 102(5):1578-1582.