developing aGVHD may be started on treatment preemptively. Among biomarkers identified in current study, only ST2 was prognostic of aGVHD risk before day +14 after hematopoietic cell transplantation; this is not surprising given the relatively late (median, 36 days) onset of aGVHD after NMAT. Clinically relevant prognostic tools proposed in prior studies consisted of a panel rather than a single biomarker; therefore, combinations of biomarkers need to be explored further [1,2,9].

In conclusion, the current study identified ST2, REG3α, and elafin as prognostic biomarkers to stratify for risk of developing aGVHD after Cy/Flu-based NMAT. These results need to be confirmed in a large independent validation cohort, ideally among a number of institutions, to establish clinically useful cut-offs for their future use in clinical trials.

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Conflict of interest statement: S.P. holds a patent on "methods of detection of graft-versus-host disease" (US Patent 13/573,766).

REFERENCES

1. Paczesny S, Krijanovski OI, Braun TM, et al. A biomarker panel for acute graft-versus-host disease. *Blood*. 2009;113:273-278.
2. Levine JE, Logan BR, Wu J, et al. Acute graft-versus-host disease biomarkers measured during therapy can predict treatment outcomes: a Blood and Marrow Transplant Clinical Trials Network study. *Blood*. 2012;119:3854-3860.
3. Vander Lugt MT, Braun TM, Hanash S, et al. ST2 as a marker for risk of therapy-resistant graft-versus-host disease and death. *N Engl J Med*. 2013;369:529-539.
4. Nelson RP Jr, Yu M, Schwartz JE, et al. Long-term disease-free survival after nonmyeloablative cyclophosphamide/fludarabine conditioning and related/unrelated allotransplantation for acute myeloid leukemia/myelodysplasia. *Bone Marrow Transplant*. 2010;45:1300-1308.
5. Childs R, Clave E, Contentin N, et al. Engraftment kinetics after nonmyeloablative allogeneic peripheral blood stem cell transplantation: full donor t-cell chimerism precedes alloimmune responses. *Blood*. 1999;94:3234-3241.
6. American Society of Blood and Marrow Transplantation. Disease Classifications Corresponding to CIBMTR Classifications 2014.
7. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825-828.
8. Paczesny S, Braun TM, Levine JE, et al. Elafin is a biomarker of graft-versus-host disease of the skin. *Sci Transl Med*. 2010;2:13RA2.
9. Paczesny S, Braun T, Lugt MV, et al. Three biomarker panel at day 7 and 14 can predict development of grade II-IV acute graft-versus-host disease abstract. *Blood*. 2010;116:675.
10. Elphick DA, Mahida YR. Paneth cells: their role in innate immunity and inflammatory disease. *Gut*. 2005;54:1802-1809.
11. Ferrara JLM, Harris AC, Greenson JK, et al. Regenerating islet-derived 3-alpha is a biomarker of gastrointestinal graft-versus-host disease. *Blood*. 2011;118:6702-6708.
12. Hayakawa H, Hayakawa M, Kume A, Tominaga S-I. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem*. 2007;282:26369-26380.

Brentuximab Vedotin Is Associated with Improved Progression-Free Survival after Allogeneic Transplantation for Hodgkin Lymphoma

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We previously reported that brentuximab vedotin (BV) enabled successful reduced-intensity allogeneic hematopoietic cell transplantation (RIC-alloHCT) in patients with relapsed Hodgkin lymphoma, after a median follow-up of 14.4 months. We now provide an updated report on 21 patients who were treated from 2009 to 2012 with BV before RIC-alloHCT with a uniform fludarabine/melphalan conditioning regimen and donor source after a median follow-up of 29.9 months. We have also retrospectively compared the patient characteristics and outcomes of these BV-pretreated patients to 23 patients who received fludarabine/melphalan RIC-alloHCT without prior BV, in the time period before the drug was available (2003 to 2009). Patients who were treated with BV before RIC-alloHCT had a lower median hematopoietic cell transplantation–specific comorbidity index and a reduced number of peri-transplantation toxicities. There were also improvements in 2-year progression-free survival (59.3% versus 26.1%) and cumulative incidence of relapse/progression (23.8% versus 56.5%).

INTRODUCTION

Brentuximab vedotin (BV) is an antibody-drug conjugate of anti-CD30 antibody and the microtubule-disrupting agent, monomethyl auristatin E [1]. BV is approved for use in Hodgkin lymphoma (HL) patients who have failed autologous hematopoietic cell transplantation (autoHCT). Phase II studies report

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an overall response rate of ~75% with an acceptable safety profile [2,3]. We previously published our findings on the use of reduced-intensity (RIC) allogeneic hematopoietic cell transplantation (alloHCT) in 24 relapsed/refractory patients with HL [4], yielding a 2-year progression-free survival (PFS) of 27% (95% confidence interval [CI], 22% to 32%). We have also reported early data showing that BV salvage before RIC-alloHCT results in a 1-year overall survival (OS) of 100% and PFS of 92.3% (95% CI, 61.3% to 98.8%) in patients with relapsed HL [5]. We now report on a more homogenous Hodgkin patient population, with extended follow-up for outcomes of RIC-alloHCT after BV salvage. Additionally we have retrospectively compared the outcomes of these patients to a consecutive case series of BV-naïve patients who underwent RIC alloHCT in the pre-BV era. Our hypothesis is that BV salvage therapy could deliver patients who are better candidates for transplantation, via higher response rates and lower toxicity, thus contributing to improved outcomes after RIC-alloHCT.

PATIENTS AND METHODS

The City of Hope Institutional Review Board approved the retrospective analysis of data from a consecutive case series of 23 HL patients who underwent RIC-alloHCT with no prior BV exposure (no-BV group) between January 2003 and July 2009 (pre-BV era) and a consecutive case series of 21 HL patients who received BV before RIC-alloHCT (BV group) from July 2009 to December 2012. Sixteen of the 21 HL patients who received BV were enrolled on prospective clinical trials (4 separate trials). None of the 23 HL patients without prior BV exposure received BV at relapse after RIC-alloHCT. Eligible patients were $\geq$ 18 years old with histologically confirmed HL expressing CD30, who had relapsed after previous autoHCT or were not autoHCT candidates. Patients were excluded if they had received a previous alloHCT. All patients received fludarabine/melphalan (fludarabine 25 mg/m^2 $\times$ 5 days followed by melphalan 140 mg/m^2 $\times$ 1 day) as their transplantation conditioning regimen. Only matched related sibling donor and matched unrelated donor transplantations were included; haploidentical and cord blood transplantations were excluded. Comorbid conditions at the time of alloHCT were scored using the hematopoietic cell transplantation–specific comorbidity index (HCT-CI) [6]. The Bearman scale [7] was used to capture toxicities associated with RIC-alloHCT. Baseline patient characteristics for the 44 patients are summarized in Table 1.

Post-transplantation evaluation of disease status with imaging studies, bone marrow biopsies, and engraftment analysis occurred at 30 days, 100 days, and 1 year after transplantation and yearly thereafter, or as clinically indicated. HL disease response was scored using standard criteria [8]. OS and PFS probabilities were calculated using Kaplan-Meier [9] (differences assessed by log-rank test) and cumulative incidence of relapse/progression and nonrelapse mortality (NRM) were calculated as competing risks [10] (differences assessed using the Gray method).

RESULTS

There were no significant baseline differences between the 2 groups in terms of age, disease stage at diagnosis, response to induction, number of prior therapies, donor type, stem cell source, and time from diagnosis to RIC-alloHCT. The patients in this study represent a heavily pretreated population in which the majority of patients had undergone high-dose chemotherapy and autoHCT; the median number of prior regimens was 4. The ratio of matched related donors to matched unrelated donors in each group was roughly one half. Graft-versus-host disease (GVHD) prophylaxis differed slightly between the 2 groups because of an institutional shift to tacrolimus/sirolimus in 2005. Although the median number of prior regimens was the same, the no-BV group received more combination chemotherapy and radiotherapy (Table 1). The 2 groups also differed in terms of disease status at the time of RIC-alloHCT and HCT-CI score. The median HCT-CI score was significantly better in the BV group (0 versus 2, $P < .01$) and patients in this group were also more likely to be in complete remission before RIC-alloHCT (28.6% versus 4.3%, $P = .04$).

Table 1
Patient, Disease, and Treatment Characteristics

Characteristics	BV N = 21	No-BV n = 23
Age, median (range), yr	31 (22-55)	37 (16-63)
Disease stage at diagnosis		
I-II	9 (43)	11 (48)
III-IV	11 (52)	11 (48)
Unknown	1 (5)	1 (4)
Response to induction		
Refractory	5 (24)	7 (30)
Relapsed	16 (76)	16 (70)
No. previous regimens, median (range)	4 (3-6)	4 (3-6)
Previous regimens		
Induction-ABVD	19 (90)	19 (83)
Salvage chemo before autoHCT		
ICE	17	16
ESHAP	2	10
Others	1	2
AutoHCT	19	19
Salvage chemo after autoHCT		
ICE	4	3
ESHAP	0	5
Gemcitabine based	14	17
Bendamustine	3	0
Others	4	9
Radiotherapy	10	17
Consolidation	9	12
Treatment for relapse/refractory	1	5
Time from diagnosis to HCT, median (range), mo	60.6 (13.8-258.3)	36.4 (13.6-214.7)
Intermittent therapy between BV and alloHCT	7	N/A
Gemcitabine based	5	
ICE	1	
Bendamustine	3	
XRT	1	
No. cycles of BV, median (range)	7 (2-16)	0
Best response to BV		NA
CR	6 (29)	
PR	14 (67)	
SD/PD	1 (5)	
Disease status at end of BV		NA
CR	4 (19)	
PR	7 (33)	
SD/PD	10 (48)	
Disease status at HCT		
CR	6 (29)	1 (4)
PR	9 (42)	9 (39)
SD/PD	6 (29)	13 (57)
Stem cell source		
Bone marrow	1 (5)	3 (13)
Peripheral blood	20 (95)	20 (87)
HCT-CI score, median (range)	0 (0-3)	2 (0-4)
Type of donor		
MRD	10 (48)	12 (52)
MUD	11 (52)	11 (48)
GVHD prophylaxis		
Tacrolimus/sirolimus	19 (90)	16 (70)
Cyclosporine A/MMF	2 (10)	6 (26)
Tacrolimus/methotrexate	0 (0)	1 (4)

ABVD indicates adriamycin, bleomycin, vinblastine, dacarbazine; ICE, ifosfamide, carboplatin, etoposide; ESHAP, etoposide, cisplatin, Ara-C, methylprednisolone; XRT, radiation therapy; PR, partial response; SD, stable disease; PD, progressive disease; MRD, matched related donor; MUD, matched unrelated donor; MMF, mycophenolate mofetil.
Data presented are n (%), unless otherwise indicated.

There were no significant differences between groups in terms of engraftment or acute/chronic GVHD incidence. All patients engrafted, with median time to absolute neutrophil count $\geq$ 500 cells/μL of 14 days (range, 11 to 21) in the BV