Biol Blood Marrow Transplant 25 (2019) 265–269

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Ruxolitinib as Salvage Therapy for Chronic Graft-versus-Host Disease

Badri Modi[1,*], Michael Hernandez-Henderson[2], Dongyun Yang[3], Jeremy Klein[4], Sanjeet Dadwal[5], Erin Kopp[6], Karen Huelsman[6], Sally Mokhtari[6], Haris Ali[6], Monzr M. Al Malki[6], Ricardo Spielberger[6], Amandeep Salhotra[6], Pablo Parker[6], Stephen Forman[6], Ryotaro Nakamura[6]

[1] *Department of Surgery, Division of Dermatology, City of Hope, Duarte, California*
[2] *Meharry Medical College, Nashville, Tennessee*
[3] *Department of Information Sciences, Division of Biostatistics, City of Hope, Duarte, California*
[4] *Department of Developmental and Stem Cell Biology, City of Hope, California*
[5] *Department of Infectious Disease, City of Hope, Duarte, California*
[6] *Department of Hematology and Hematopoietic Cell Transplantation, City of Hope, Duarte, California*

Article history:
Received 11 June 2018
Accepted 4 September 2018

Key Words:
Ruxolitinib
Chronic GVHD
Salvage therapy

A B S T R A C T

Chronic graft-versus-host disease (cGVHD) continues to be a major complication after allogeneic hematopoietic cell transplantation, significantly affecting patients' quality of life. A regimen of systemic corticosteroids is considered first-line therapy but is often associated with inadequate responses and multiple side effects. In patients with refractory disease, an evidenced-based consensus is lacking as to the single best approach to managing symptoms. Ruxolitinib, a selective JAK1/2 inhibitor, has recently gained favor as a second-line approach in patients with steroid-refractory cGVHD. In this retrospective study, we evaluated the outcomes of 46 patients who received ruxolitinib for cGVHD between March 2016 and December 2017 at our institution, and evaluated ruxolitinib's impact at 6 and 12 months, based on the National Institutes of Health Severity Scale, including organ-specific responses, and mean prednisone dose. Furthermore, we present the first reported probability of ruxolitinib's treatment failure-free survival (FFS) in patients with cGVHD. After 12 months of ruxolitinib therapy, complete response, partial response, and stable disease was observed in 13% (n = 6), 30.4% (n = 14), and 10.9% (n = 5) of patients, respectively. The 1-year probability of FFS was 54.2% (95% confidence interval, .388 to .673), and ruxolitinib use was associated with a reduction in prednisone dose. In conclusion, our data, which represent the largest cohort of patients with cGVHD reported to date, support the use of ruxolitinib for cGVHD refractory to steroids and currently available salvage therapies, discontinued due to lack of response and high cost.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) remains a major barrier to a successful hematopoietic stem cell transplantation (HSCT), associated with lower quality of life and significant morbidity and mortality [1]. Corticosteroids are widely accepted as first-line therapy and are most often recommended by expert consensus groups [2]. Unfortunately, a significant percentage of patients with cGVHD do not improve with steroids, and there is no widely agreed-upon second-line agent to treat these patients [3].

The pleomorphic presentation of cGVHD contributes to challenges inherent to this unmet therapeutic need. The National Institutes of Health (NIH) consensus group produced a cGVHD scale to allow for consistent symptom evaluation and to measure the response to therapy [4,5]. Furthermore, Martin et al [6] proposed that a combination of the NIH overall response and failure-free survival (FFS), defined as absence of additional systemic therapy or relapsed malignancy, can serve as a meaningful outcome measure for response to second-line therapy in cGVHD. Finally, the ability to taper corticosteroids is often reported as a secondary outcome for measuring response to second-line therapy in cGVHD.

In cGVHD, alloreactive T-cell trafficking into target organs is facilitated by interferon γ (IFNγ) and the chemokine receptor CXCR3 [7]. Knockout mice lacking the IFNγ-receptor (IFNγR) or its downstream target CXCR3 have less severe GVHD and reduced T cell infiltration into the spleen and gastrointestinal tract, while maintaining robust engraftment and a graft-versus-leukemia (GVL) effect [8]. The JAK/STAT pathway is central to IFNγ-IFNγR signaling and thus is an attractive target for abrogating GVHD while maintaining GVL.

Ruxolitinib (Jakafi; Incyte, Wilmington, DE) is a selective JAK 1/2 inhibitor approved by the Food and Drug

Financial disclosure: See Acknowledgments on page 269.

* Correspondence and reprint requests: Badri Modi, MD, Department of Surgery, Division of Dermatology, City of Hope, 1500 E Duarte Rd, Duarte, CA 91010.
E-mail address: bamodi@coh.org (B. Modi).

https://doi.org/10.1016/j.bbmt.2018.09.003
1083-8791/

Administration for management of myelofibrosis. In 2015, a multicenter international retrospective review of ruxolitinib use as salvage therapy for cGVHD reported an overall response rate of 85% (complete response [CR], 7%; partial response [PR], 78%) in 41 corticosteroid-refractory patients with moderate-to-severe cGVHD and persistent symptoms despite 3 previous rounds of therapy. Based on the results of that single retrospective analysis, ruxolitinib has emerged as a popular, off-label treatment option for cGVHD [9]. Prospective phase II and III trials using ruxolitinib have been initiated [10]. More recently, Khoury et al [11] reported their experience in 19 patients, of whom 18 achieved PR and 1 achieved CR, according to NIH consensus criteria. Responses occurred early and were sustained, which enabled discontinuation of treatment in 68% of patients or reduction of steroids to physiological doses in 21% of patients. Another report retrospectively evaluating off-label use of ruxolitinib in 20 patients with cGVHD reported a slightly lower overall response rate of 75% [12].

In the present study, we conducted a retrospective analysis of the largest cohort of patients to date treated at a single institution with ruxolitinib as salvage therapy for cGVHD and evaluated its impact at 6 and 12 months, based on NIH disease severity score, including organ-specific responses, and mean prednisone dose. In addition, we evaluated the probability of FFS, defined as the absence of initiating additional systemic therapy, medication intolerance, relapsed malignancy, or death, associated with ruxolitinib treatment in patients with cGVHD.

METHODS

Study Subjects and Data Collection

In this single-center Institutional Review Board-approved retrospective analysis, we reviewed the charts of 46 patients who received ruxolitinib as salvage therapy for cGVHD at City of Hope between March 2016 and December 2016. Follow-up was continued up through February 2018, until the last follow-up visit or the patient's death, whichever occurred first. Basic transplantation-related data, including sex, age, reason for transplantation, date of transplantation, conditioning regimen, degree of host-donor match/mismatch, and post-transplantation GVHD prophylaxis regimen, were collected. The intervals from transplantation to the onset of cGVHD and to ruxolitinib initiation were also identified.

Clinical data were collected at the start of ruxolitinib treatment and for 12 months post-treatment to identify changes in NIH disease severity score for cGVHD [4] and prednisone dose. Treatment FFS after the initiation of ruxolitinib was noted based on the earliest date of developing any of the following events: initiation of new cGVHD therapy, relapsed disease, patient death, or discontinuation of ruxolitinib for any reason other than complete response of cGVHD symptoms. In addition, infectious disease and cytology data were collected throughout the duration of ruxolitinib treatment.

Statistical Analysis

Descriptive statistics were used for patient characteristics. A Kaplan-Meier curve was generated for FFS. Prednisone doses by treatment period were summarized as median and interquartile range. Changes in prednisone doses by time were evaluated using the signed-rank test.

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The tests were 2-sided at a significance level of $P < .05$.

RESULTS

Patient Characteristics

Our cohort comprised 46 patients (26 males and 20 females) who received ruxolitinib as salvage therapy between April 4, 2016, and December 20, 2016. The median patient age was 49 years (range, 21 to 77 years). The patients underwent HSCT between July 1994 and April 2015, most commonly for an underlying diagnosis of acute myelogenous leukemia (n = 15) or acute lymphoblastic leukemia (n = 10). The conditioning regimen was myeloablative in 22 patients, reduced intensity in 15 patients, and unknown in 9 patients. For some patients, available transplantation data were limited because the procedure either predated creation of the transplantation database or was performed in an outside institution. Grafts were provided by an HLA-identical sibling in 15 patients, an HLA-matched unrelated donor in 10, an HLA-mismatched unrelated donor in 16, and an unknown donor in the remainder (Table 1). In patients with transplantation data available, the onset of cGVHD occurred approximately 7 months post-HSCT on average (range, 3 to 42 months), and the median time to ruxolitinib initiation after HSCT was 40 months (range, 8 to 108 months).

Baseline Characteristics of cGVHD

The baseline NIH disease severity score before initiation of ruxolitinib was extracted from clinical charts (Table 2). Almost all (93.5%) of the cohort had severe (n = 35) or moderate (n = 8) disease based on the NIH global severity scale for staging cGVHD. Skin was the most commonly involved organ, with 63% of patients (n = 29) having severe skin disease based on either body surface area score or skin feature score. The mouth was involved in 32.6% of patients (n = 15), eyes in 47.8% (n = 22), lungs in 21.7% (n = 10), and joints/fascia in 47.8% (n = 22) (Table 2). Owing to varying degrees of reporting, data on the gastrointestinal tract and genitals were not collected.

On average, more than 3 previous therapies (range, 1 to 8) per patient were attempted before initiating ruxolitinib. Among previous therapies, prednisone (n = 40), tacrolimus (n = 33), sirolimus (n = 27), and photopheresis (n = 21) were the most frequently used and azathioprine, colchicine, narrow-band ultraviolet-B therapy, tocilizumab, and bortezomib were the least frequently used (n = 1 each; Figure 1). Six patients did not receive corticosteroids after onset of cGVHD symptoms owing to patient preference or comorbidities. Ruxolitinib was started as add-on therapy in all patients.

Response to Ruxolitinib

Table 3 presents the response rates in our cohort at 6 and 12 months. After 6 months of ruxolitinib therapy, we observed CR in 10% (n = 5), PR in 37% (n = 17), and stable disease in 15%

Table 1
Patient Characteristics

Characteristic	Value
Number of patients	46
Date of ruxolitinib initiation	4/4/16-12/20/16
Age, yr, median (range)	49 (21-77)
Sex, n	
Male	26
Female	20
Date of transplantation	July 1994-April 2015
Reason for transplantation, n	
Acute erythroid leukemia	1
Acute lymphoblastic leukemia	10
Acute myelogenous leukemia	15
Chronic lymphocytic leukemia	2
Diffuse large B cell lymphoma	2
Hodgkin lymphoma	2
Myelodysplastic syndrome	6
Myelofibrosis	2
Peripheral T cell lymphoma	4
Conditioning regimen, n	
Myeloablative	22
Reduced intensity	15
Unknown	9
Donor type, n	15
HLA-identical sibling	10
HLA matched unrelated	16
HLA mismatched unrelated	5
Unknown	

Table 2
Baseline Disease Severity

Parameter	Score, % (n)			
	3 (Severe)	2 (Moderate)	1 (Mild)	0
Skin	63 (29)	11 (5)	N/A	26 (12)
Mouth	4 (2)	13 (6)	15 (7)	67 (31)
Eyes	9 (4)	13 (6)	26 (12)	52 (24)
Lungs	4 (2)	7 (3)	11 (5)	78 (36)
Joints/fascia	9 (4)	24 (11)	15 (7)	52 (24)
Global severity score	76 (35)	15 (7)	9 (4)	0 (0)

N/A indicates not applicable.
Severity scores based on the 2014 NIH Consensus Project Report on Diagnosis and Staging of cGVHD [4].

(n = 7). After 12 months of ruxolitinib therapy, these results differed only slightly, with CR in 13% (n = 6), PR in 30% (n = 14), and stable disease in 15% (n = 5). Organ-specific responses are reported in Table 4. After 12 months of ruxolitinib therapy, we observed an organ response in 25% of patients with skin involvement (n = 10), in 60% with mouth involvement (n = 15), in 26% with eye involvement (n = 23), in 10% with lung involvement (n = 1), and in 41% with joint/fascia involvement (n = 23). In univariate analysis, we found no significant associations between 12-month response and clinical variables including number of previous therapies, sex, age, steroid dose at baseline, and donor type. Global response at 12 months was analyzed by baseline disease severity. Among the 6 patients who experienced CR, baseline disease severity was mild in 3,

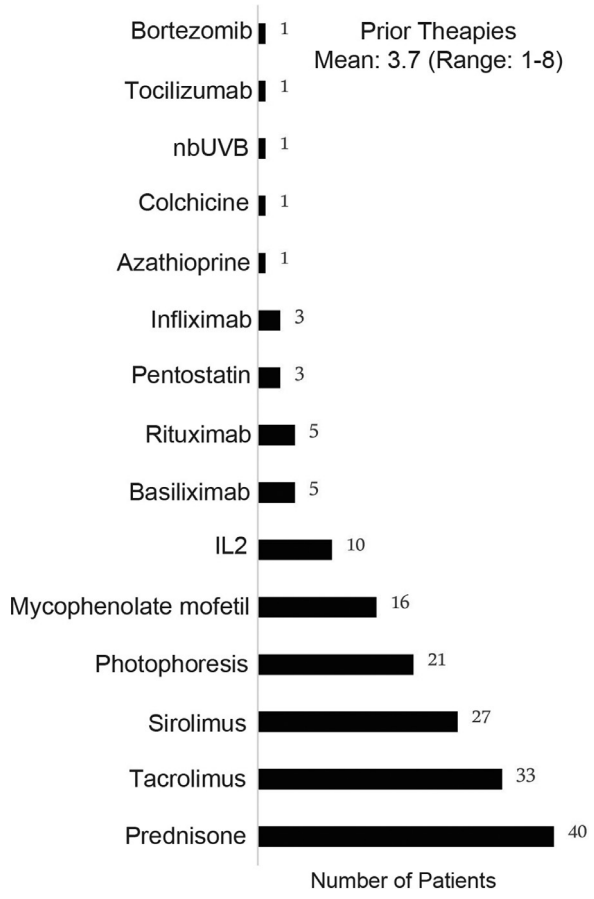

Figure 1. Previous therapies for cGVHD.

Table 3
Global Response

Response	6 months, % (n)	12 months
CR	10 (5)	13.0 (6)
PR	37 (17)	30.4 (14)
Stable disease	15.2 (7)	15 (5)
Overall response rate	47.8 (22)	43.4 (20)

moderate in 2, and severe in 1. Among the 14 patients who experienced PR at 12 months, 1 patient had moderate disease and 13 patients had severe disease at baseline (Table 5).

FFS

At 1 year, treatment failure was observed in 45.7% of patients (n = 21). Causes of failure included relapsed malignancy (2.2%; n = 1), death (17.4%; n = 8), initiation of a new second-line agent for cGVHD (10.9%; n = 5), and discontinuation of ruxolitinib for any reason other than complete resolution of cGVHD (15.2%; n = 7). Two of 21 patients discontinued ruxolitinib due to medication intolerance including pruritus and recurrent infections. Five of these 21 patients discontinued ruxolitinib due to the high cost of medication and a lack of observed response. The 1-year probability of FFS was 54.2% (95% confidence interval, .388-.673) (Figure 2A). In the patients who did not experience treatment failure, there was a statistically significant decrease in mean prednisone dose at 1 year compared with the baseline dose (Figure 2B).

Adverse Effects

During the 12-month follow-up period, 52% of the patients (n = 24) developed a total of 42 infectious complications. Cytomegalovirus (CMV) viremia occurred in 4 patients, of whom 3 developed the disease, 1 had retinitis, and 2 had pneumonia. Invasive fungal infection was observed in 4 patients, including 3 with pulmonary aspergillosis and 1 with cutaneous *Scedosporium apiospermum* infection. A total of 13 episodes of bacteremia were observed in 11 patients, and 2 of these patients developed septic shock. *Pneumocystis jiroveci* pneumonia was seen in 2 patients. Thirteen patients had a total of 15 episodes of upper respiratory infection with a community respiratory virus, of whom only 2 developed related pneumonia (1 with respiratory syncytial virus and 1 with rhinovirus). There were 4 deaths attributable to infection. (More detailed descriptions of infectious complications are provided in the Supplementary Materials). Severe cytopenia was uncommon. Of the 42 patients evaluable at 6 months, 3 had new-onset grade I leukopenia, 2 had new-onset grade II leukopenia, 1 patient had grade I thrombocytopenia, and 1 patient had grade II thrombocytopenia (data not shown).

DISCUSSION

The potential benefit of ruxolitinib in refractory cGVHD was first demonstrated in a 2015 retrospective analysis of 41 patient that found a high overall response rate of 85% [9]. Since then, reports of ruxolitinib impact have been limited to small case series and a retrospective analysis [4,11,12].

Compared with previous reports, our data suggest a more modest benefit of ruxolitinib when used in patients with cGVHD. We observed an overall response rate of 47.8% at 6 months that was slightly reduced to 43.4% at 12 months. Furthermore, we provide a representative treatment FFS curve to better reflect the benefit of ruxolitinib as salvage therapy for cGVHD. Our treatment FFS analysis applies a rigorous definition of treatment FFS, including

Table 4
Organ-Specific Response at 1 Year

Response	Organ-Specific Response at 6 and 12 mo (n of Patients with Organ Involved at Baseline), %									
	Skin (n = 39)		Mouth (n = 15)		Eyes (n = 23)		Lungs (n = 10)		Joints (n = 23)	
	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo	6 mo	12 mo
CR	12.5	15	40	60	0	4.3	10	10	9.1	9.1
PR	15	10	6.7	0	21.7	21.7	0	0	36.4	31.8
No response/ failed	72.5	75	53.3	40	78.2	73.9	90	90	54.5	59.1

Table 5
Reasons for Treatment Failure

Reason	% (n)
Initiation of new second-line agent	10.9 (5)
Relapsed malignancy	2.2 (1)
Death	17.4 (8)
Discontinuation of ruxolitinib*	15.2 (7)

* For any reason other than resolution of cGVHD (eg, intolerance, cost).

cost as a reason for treatment failure. Cost proved to be the major contributing factor for treatment discontinuation in 5 of 21 patients. Analyzed by organ, we observed higher response rates in the mouth and the joints/fascia compared with the eyes, skin, and lungs. A phase 3 randomized controlled study comparing ruxolitinib with the best available therapy for steroid-refractory cGVHD is currently underway

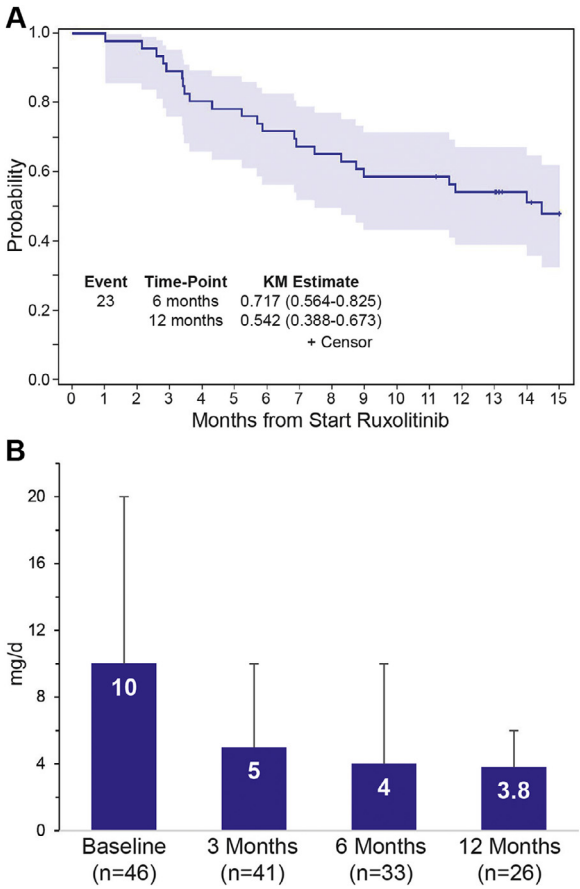

Figure 2. Outcomes of ruxolitinib treatment. (A) FFS. (B) Impact of ruxolitinib therapy on prednisone dose.

(ClinicalTrials.gov: NCT03112603) and should provide evidence regarding the true impact of ruxolitinib.

Unlike acute GVHD, the biological underpinnings of cGVHD are poorly understood. Current prevailing mechanistic theories suggest an initial phase of acute inflammation and tissue injury mediated primarily by the innate immune system, followed by a second phase of chronic, alloreactive inflammation carried out by dysregulated T and B cells. These autoimmune injuries occur in any organ of the body and may culminate in a third phase of aberrant tissue repair and tissue fibrosis [13,14].

Because ruxolitinib inhibits JAK-STAT signaling and thereby abrogates T cell activation, differentiation, and survival [15], this drug may be more effective in the second phase of disease development and less effective in the third phase during which fibrosis predominates, suggesting that appropriate selection of patients with active inflammatory cGVHD may lead to greater disease responses. At baseline, the majority of our cohort had moderate to severe disease that failed to improve with multiple previous therapies. In particular, the majority of patient with skin involvement had severe skin disease and fibrosis, which may explain why our overall response rate was lower than previously reported by Khoury et al [11], Ferreira et al [12], and Zeiser et al [14].

In our cohort, 52% of the patients developed infectious complications. Whereas previous studies have highlighted a risk of CMV reactivation in patients with cGVHD treated with ruxolitinib [9], the major limitation in defining the true estimate of CMV reactivation in our cohort (and those of others) is the absence of a universal CMV surveillance system. In this study, we observed fewer CMV infections (8.6%) compared with the rate reported by Zeiser et al [14] in their multicenter cohort of 41 patients with cGVHD (14.6%). However, our rate of CMV reactivation was higher than that reported by Ferreira et al [12], who found refractory CMV infection in only 1 of 20 patients (5%). We observed a high incidence of CMV-related disease (75%; 3 of 4). In both our cohort and the cohort of Zeiser et al, 1 patient developed CMV retinitis (2.1% and 2.4%, respectively). These rates of CMV retinitis are much higher than the .17% reported by Crippa et al [16] in a population of 5721 HCT recipients. Patients with CMV disease had extensive GVHD and were severely immunosuppressed, making it difficult to attribute the development of CMV disease to ruxolitinib alone; nonetheless, the high rate of CMV retinitis is concerning, and this entity should be considered in the differential diagnosis in patients with new onset of visual impairment. In our cohort, 24% of the patients developed a bacterial infection, including bloodstream infections and pneumonia, with many patients having polymicrobial infections and 3 deaths related to these infections. High rates of bacterial infection have been observed by others in the setting of ruxolitinib use in cGVHD [17] and myelofibrosis [18], postulated to result from ruxolitinib interference with the innate immunity, especially neutrophil activation. Infectious complications were high in our cohort and included viral, bacterial, and fungal infections (see

Supplementary Materials). These infections need to be approached aggressively given their apparent contributions to morbidity and overall mortality.

Our study is limited by its retrospective design and interobserver variability at baseline and at the 1-year time point. Our study did not control for site-directed therapies, which might have contributed to the improved NIH disease severity scores at 1 year. For instance, patients with fascial/joint involvement are often referred to physical therapy and encouraged to participate in stretching and yoga, which might have contributed to the higher rates of improvement seen in these patients. Similarly, the use of topical corticosteroids might have impacted skin scores. Finally, the severity of cGVHD at baseline may serve as a confounder. In our cohort, only 3 patients had mild disease severity at baseline, and all 3 of these patients experienced CR, representing one-half of the 6 patients who experienced a CR.

In summary, our analysis of the largest reported cohort of patients with cGVHD receiving ruxolitinib as salvage therapy in a real-world practice setting demonstrated an FFS rate of 54.2% and an overall response rate of 43.4% at 12 months. Although the sustained response rate appears to be modest, ruxolitinib represents a new and promising option for cGVHD refractory to steroids and currently available salvage therapies.

ACKNOWLEDGMENTS

Financial disclosure: None reported.

Conflict of interest statement: There are no conflicts of interest to report.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.09.003.

REFERENCES

1. Inamoto Y, Storer BE, Petersdorf EW, et al. Incidence, risk factors, and outcomes of sclerosis in patients with chronic graft-versus-host disease. *Blood*. 2013;121:5098–5103.
2. Wolff D, Gerbitz A, Ayuk F, et al. Consensus conference on clinical practice in chronic graft-versus-host disease (GVHD): first-line and topical treatment of chronic GVHD. *Biol Blood Marrow Transplant*. 2010;16:1611–1628.
3. Wolff D, Schleuning M, von Harsdorf S, et al. Consensus Conference on Clinical Practice in Chronic GVHD: second-line treatment of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2011;17:1–17.
4. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389–401. e1.
5. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015;21:984–999.
6. Martin PJ, Storer BE, Inamoto Y, et al. An endpoint associated with clinical benefit after initial treatment of chronic graft-versus-host disease. *Blood*. 2017;130:360–367.
7. Choi J, Ziga ED, Ritchey J, et al. IFNγR signaling mediates alloreactive T-cell trafficking and GVHD. *Blood*. 2012;120:4093–4103.
8. Yang YG, Wang H, Asavaroengchai W, Dey BR. Role of interferon-gamma in GVHD and GVL. *Cell Mol Immunol*. 2005;2:323–329.
9. Zeiser R, Burchert A, Lengerke C, et al. Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. *Leukemia*. 2015;29:2062–2068.
10. Jagasia M, Zeiser R, Arbushites M, Delaite P, Gadbaw B, Bubnoff NV. Ruxolitinib for the treatment of patients with steroid-refractory GVHD: an introduction to the REACH trials. *Immunotherapy*. 2018;10:391–402.
11. Khoury HJ, Langston AA, Kota VK, et al. Ruxolitinib: a steroid-sparing agent in chronic graft-versus-host disease. *Bone Marrow Transplant*. 2018;53:826–831.
12. Ferreira AM, Pontes da Silva CA, Pereira AD, et al. Ruxolitinib in steroid-refractory chronic graft-versus-host disease: experience of a single center. *Bone Marrow Transplant*. 2018;53:503–506.
13. Cooke KR, Luznik L, Sarantopoulos S, et al. The biology of chronic graft-versus-host disease: a task force report from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2017;23:211–234.
14. Zeiser R, Blazar BR. Pathophysiology of chronic graft-versus-host disease and therapeutic targets. *N Engl J Med*. 2017;377:2565–2579.
15. Pérez-Simón JA. Anti-common γ-chain antibody: one for all in GVHD. *Blood*. 2015;125:424–426.
16. Crippa F, Corey L, Chuang EL, Sale G, Boeckh M. Virological, clinical, and ophthalmologic features of cytomegalovirus retinitis after hematopoietic stem cell transplantation. *Clin Infect Dis*. 2001;32:214–219.
17. Khandelwal P, Millard HR, Thiel E, et al. Hematopoietic stem cell transplantation activity in pediatric cancer between 2008 and 2014 in the United States: a Center for International Blood and Marrow Transplant Research Report. *Biol Blood Marrow Transplant*. 2017;23:1342–1349.
18. Polverelli N, Palumbo GA, Binotto G, et al. Epidemiology, outcome, and risk factors for infectious complications in myelofibrosis patients receiving ruxolitinib: a multicenter study on 446 patients [e-pub ahead of print]. Hematol Oncol. http://dx.doi.org/10.1002/hon.2509, Accessed 15 July, 2018.