LETTER TO THE EDITORS

Ruxolitinib for steroid-refractory acute graft-versus-host disease

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Dear Editors

Corticosteroids are still the standard initial therapy for acute graft-versus-host-disease (aGVHD), but are effective in only approximately half of cases [1]. Many treatment options have been tested and used as second line, but none have been established yet as the standard of care.

Our institution has been using ruxolitinib for steroid-refractory aGVHD (SR-aGVHD), as well as chronic GVHD, for the past several years. We conducted a retrospective review (approved by IRB) of patients who were treated with ruxolitinib for SR-aGVHD over a 2-year period (2015–2016). SR-aGVHD was defined as no response in any stage of GVHD in any organ after 5 days of steroids initiation or worsening GVHD stage in any organ after 3 days of steroids. Primary aGVHD and aGVHD/chronic GVHD (cGVHD) overlap were both included. We defined high-risk acute GVHD by using acute GVHD risk score refined by Minnesota group [2]. Only patients who received> 14 days of ruxolitinib were considered evaluable for response assessment.

Thirty-six patients were included in the analysis described in Table 1. Methylprednisolone 2 mg/kg/day was used as initial steroid in most patients; however, different doses were used at the physician discretion. Twenty-four patients (67%) received at least 14 days of treatment and were evaluable for response; the overall response rate (ORR) was 58% (95% CI 38%-78%) with 25% obtaining a complete (CR). Of those who were evaluable for response, the median overall survival (OS) was 7.4 months (95% CI UTQ-15.9) for responders compared with 0.9 months (95% CI 0.7–1.1) for nonresponders ($P < 0.001$). The relapse rate of primary disease was 8%; one patient relapsed while on ruxolitinib and two within 6 months following discontinuation. Ruxolitinib was well tolerated; hematologic toxicity was generally mild, and there were no cases of treatment-related mortality reported.

The data presented herein are similar to what was recently reported from the REACH1 trial [3]. However, in our study, SR-aGVHD was defined as worsening disease after 3 days of steroids or no improvement in 5 days versus 3 days or 7 days, respectively, in REACH1. In addition, we included patients who received numerous prior treatments for SR-aGVHD, while REACH1 only allowed patients to receive calcineurin inhibitors. Thus, our patients were more heavily treated which may account for differences in response rates; in our study, the ORR was 58% with 25% CR compared to 73% with 56% CR in REACH1. Our study did not have explicit eligibility criterion and may reflect more real-world use of ruxolitinib for SR-aGVHD. Several patients were given very short durations of ruxolitinib < 14 days before transitioning to comfort care or expiring, and these patients were excluded as response was difficult to assess and likely does not reflect the efficacy of ruxolitinib.

Additionally, in a moderate/severe cGVHD, ruxolitinib induces high response rates, and reduction to physiologic doses/discontinuation of prednisone was possible in 90% of patients at a median of 106 days (range, 31–365) from starting ruxolitinib [4,5]. In conclusion, ruxolitinib appears to be a viable treatment option for SR-aGVHD.

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Table 1. Patient characteristics

Demographics (*N* = 36)		
Median age (range)	55 years (27–72)	
Male	20 (56%)	
Disease for transplant (*N* = 36)		
AML	15 (44%)	
MDS/MPN	12 (31%)	
Others	9 (25%)	
Stem cell sources (*N* = 36)		
Matched sibling	7 (19%)	
Haploidentical related	5 (14%)	
Unrelated	24 (67%)	
Conditioning regimens (*N* = 36)		
Myeloablative	35 (97%)	
Reduced intensity	1 (3%)	
GVHD prophylaxis* (*N* = 36)		
CNI/MTX	23 (64%)	
CNI/MMF/PT CY	7 (19%)	
Others	6 (17%)	
GVHD treatment (*N* = 36)		
Median number of treatments		
Prior to ruxolitinib	2 (0–5)	
With ruxolitinib	1.5 (0–5)	
Median time from steroid start to ruxolitinib	16.5 (2–280)	
Starting dose of RUX (*N* = 36)		
5 mg daily	1 (3%)	
5 mg BID	26 (72%)	
10 mg BID	9 (25%)	
RUX treatment duration (N = 36)		
Median days (range)	21.5 (1–560)	
≥14 days of treatment	67%	
Evaluable for response (*N* = 24)		
Complete response	6 (25%)	
Partial response	8 (33%)	
No response	10 (42%)	
Risk factor (N = 24)	**Responders**	**Non-responders**
Skin aGVHD	7 (50%)	2 (20%)
GI aGVHD	10 (71%)	8 (80%)
Liver aGVHD	2 (15%)	5 (50%)
> 1 organ	5 (35%)	6 (60%)
Low albumin	13 (93%)	8 (80%)
Reason for discontinuation (*N* = 24)		
Treatment failure	15 (64%)	
Relapse of primary disease	1 (3%)	
Cytopenias	3 (14%)	
Issues obtaining ruxolitinib	4 (17%)	
Complete response	1 (3%)	

*GVHD prophylaxis included calcineurin inhibitors (CNI) with either methotrexate (MTX) or mycophenolate mofetil (MMF); post-transplant cyclophosphamide (PT CY)

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