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Ruxolitinib - a Steroid Sparing Agent in Chronic Graft-versus-Host Disease

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Summary

Inhibition of the Janus-associated kinases (JAK) with ruxolitinib (RUX) reduces graft-versus-host disease (GVHD) in preclinical and clinical models. Nineteen allograft recipients with moderate/severe steroid-dependent chronic GVHD received RUX as ≥ 2nd line salvage. RUX was well tolerated, and led to complete/partial resolution of oral (92/7%), cutaneous (82/0%), hepatic (71/28%), gastro-intestinal (75/17%), musculoskeletal (33/67%), pulmonary (0/80%), scleroderma (0/75%), vaginal (0/75%), and ocular (0/100%) chronic GVHD. Overall 18 achieved partial response and 1 complete response according to NIH Consensus Criteria. Responses occurred early and were sustained which enabled discontinuation (68%) or reduction of steroids to physiologic doses (21%). We conclude that RUX is an effective steroid-sparing agent in chronic GVHD.

Introduction

Relapse of the underlying hematological disease and graft-versus-host disease (GVHD) are the most significant barriers for successful allogeneic hematopoietic stem cell transplantation (HSCT). Chronic GVHD (cGVHD) is a major contributor to late morbidity and mortality,[1] especially when the manifestations are severe.[2] Corticosteroids are partially effective and remain the backbone of cGVHD treatment,[3] but contribute to an already high morbidity and mortality. While no therapy or intervention is highly effective against steroid-resistant cGVHD, mycophenolate,[4] photopheresis,[5]and rituximab [6] are commonly used with

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HJK and JFD: designed research, performed research, collected data, provided subjects, analyzed and interpreted data, performed statistical analysis, wrote the manuscript; VKK, AAL, IP, AJ, EW, DR, ZAK, IB and MA performed research, collected data, provided subjects, analyzed and interpreted data, reviewed and approved the manuscript; JW, SB, and ASK: collected data, analyzed and interpreted data, reviewed and approved the manuscript.

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mixed responses. There is no consensus or FDA-approved drugs for second-line therapy in cGVHD.

Ruxolitinib (RUX, Jakafi^{R}, Incyte, Wilmington, Delaware, USA) is an oral selective Janus-associated kinase 1 (JAK1) and JAK2 inhibitor that was approved by the FDA in 2014 for the treatment of patients with myelofibrosis. JAKs mediate signaling of multiple cytokine receptor family members (including interferon-γ and interleukin-6), many of which mediate coordinated inflammatory responses. Inhibition of JAK is effective in autoimmune disorders.[7] In MHC-mismatched mouse transplant models, pharmacologic inhibition of IFNγR signaling with RUX prevented GVHD and improved survival;[8,9] and high response rates to RUX in steroid-refractory acute and chronic GVHD were recently reported in humans.[10]

We report outcomes of 19 patients with cGVHD who required salvage RUX therapy. Given the complexity of the licensing of RUX for non-cancer indications in the US, a prospective study was impossible to conduct, we herein report a retrospective analysis of prospectively collected data in patients who were able to receive RUX for cGVHD.

Materials and Methods

Between 09/2014 and 9/2016, 19 recipients of sibling or unrelated donor, blood or marrow stem cell transplant for hematological malignancies and with cGVHD received RUX as ≥ 2nd line salvage. Steroid-dependent (SD) cGVHD was defined by stable disease on ≥ 0.5mg/kg/day of prednisone for 4-8 weeks and inability to taper prednisone below 0.5mg/kg/day.[3] Records were reviewed and epidemiological information, disease and transplant characteristics, acute and chronic GVHD presentation, treatment and GVHD response, and overall outcomes including relapse and survival were extracted. Grading of cGVHD and response (complete (CR) and partial (PR) organ based on clinician assessments) was performed by clinicians with extensive transplant experience, and according to the 2014 NIH Consensus Conference Criteria for cGVHD.[11,12] Complete organ response (CR) was defined as the resolution of clinical manifestations of cGVHD in a specific organ, and partial response (PR) as a 50% improvement. Flare of cGVHD was defined as a progression of clinical or laboratory manifestations of cGVHD after an initial response. Statistics were descriptive. This is a 2 site study (Emory University in Atlanta and Washington University in St. Louis), that was approved by the Institutional Review Boards of both Universities.

Results

Patients, age 53 (range, 28-73), were recipients of unrelated donor (13), matched sibling (6) blood (17) or marrow (2) transplant following myeloablative (8) or reduced intensity conditioning (11) for acute myeloid leukemia (5), acute lymphoblastic leukemia (2), chronic myeloid leukemia (3), chronic lymphocytic leukemia (1), myelodysplastic syndrome (5), myeloproliferative disease (1), cutaneous T-cell lymphoma (1) or Hodgkin's disease (1). Male/female ratio was 11/8. Twelve (63%) experienced grades 1 (6), 2 (8), or 3 (1) steroid sensitive acute GVHD that affected the skin (9) and/or gastrointestinal system (GI, 7). Table 1.

Patients developed severe (15) or moderate (4) quiescent (13) or de novo (6) cGVHD on d +180 (range, 90-302) that affected skin (17) eyes (14), oral mucosa (13), GI track (12), lungs (5), liver (7), vagina (4) and the musculoskeletal system (6). Median duration of previous continuous exposure to steroids for cGVHD was 20 months (range, 3-45), and patients underwent 4 (range, 2-10) attempts of steroid taper. All, but 1 patient, received at least one second-line agent that included: rituximab (3), mycophenolate mofetil (11), photopheresis (5), sirolimus (8), azathioprine (5), weekly methotrexate (1), ibrutinib (1), or infliximab (1). Table 2**.**

RUX was administered as 2nd (1), 3d (3) 4th (11), 5th (3) or 6th (1) line of salvage therapy at the initial dose of 5 mg BID. Median weight was 66 kg (range, 45-158). RUX dose was increased to 20 mg/d (10) due to physician preference (7), patient weight (1), flare of cGVHD following discontinuation of immunosuppression after initial response to RUX (1) or temporary perioperative hold of RUX (1). Median duration of RUX therapy was 18 months (range 2.5-27). RUX was well tolerated. Assessment of relationship between adverse events and RUX outside a prospective trial is complex in SD cGVHD; but overall, no toxicities leading to dose-reductions or interruptions of RUX were observed, and no unusual cytopenias, recurrences of CMV viremia or infections were noted. Dose reduction to 5 mg/d was done in 2 patients due to limited drug supply. All patients were evaluable for response. CR was observed in the following organs: mouth (oral ulcerations, 12), skin (non-scleroderma, 14), liver (5), GI (diarrhea, 8; esophagus, 1), and musculoskeletal (2). PR was observed in mouth (1), lungs (4), liver (2), GI (2), scleroderma (3), vaginal (4), ocular (14) and musculoskeletal (4) cGVHD. UPN6 became oxygen and wheelchair independent 2 weeks after starting RUX. Two patients showed no response to RUX in scleroderma and lungs (UPN7), and GI (UPN18), however they achieved PR1 in GI and eyes (UPN7) and CR in skin, mouth and liver (UPN18). Outcomes are summarized in Table 3, 18 had overall PR and 1 overall CR. Responses were observed early after initiation of RUX (within 2 weeks) in all responding organs, and prednisone was successfully reduced to physiologic doses in 4 or discontinued in 13 at a median of 106 (range, 31-365) days from starting RUX. With a median follow-up of 17 months (range, 3-25) from prednisone discontinuation/reduction to physiologic doses, 2 patients experienced a transient flare of cGVHD symptoms associated with discontinuation of immunosuppression (1), and temporary hold of RUX (1). Prednisone doses were increased for UPN07 from physiological doses to stress doses following an infectious complication. None of the other responding patients required a restart of prednisone or increased immunosuppression. At last follow-up, 2 patients expired from sepsis/respiratory failure, and 16 are still receiving an immunosuppressant in addition to RUX.

Discussion

In the absence of standard therapy and with the disappointing available treatments, newer approaches for resistant or SD cGVHD are desperately needed.[13] RUX's pre-clinical anti-GVHD activity supported its clinical use as a GVHD mitigating agent. Similar to the report by Zeiser et al.,[10] we observed high responses to RUX in moderate/severe cGVHD, but more importantly reduction to physiologic doses/discontinuation of prednisone was possible in 90% of patients. RUX was well tolerated and effective at 25% of the dose used in

myeloproliferative diseases. At these doses no unusual patterns of opportunistic infections or cytopenias were noted (data not shown). The optimal doses and duration of RUX therapy are unknown, all patients are currently still receiving RUX. Of note, cGVHD flares occurred very quickly (within 1 week) in the 2 cases where RUX was held or when immunosuppressive drugs were discontinued, suggesting that prolonged RUX treatment in conjunction with an immunosuppressive agent may be needed. Given the ease of administration (oral) and the apparent safety and efficacy, RUX represents a promising treatment option for cGVHD that deserves further investigations in controlled multicenter prospective trials.

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Table 1.

Patient Characteristics

Characteristics	
Median age (range), years	53 (28-73)
Male/Female	11/8
Blood/Marrow	17/2
Sibling/Unrelated donor	6/13
Myeloablative/Reduced Intensity Conditioning	9/10
Prior acute graft-versus-host disease Skin GI	12 9 7

Table 2.
Chronic Graft-versus-Host Disease Characteristics

Characteristics	
Median time from transplant to cGVHD (range), d	180 (90-302)
NIH score: severe/moderate	15/4
Onset of cGVHD: quiescent/de novo	12/7
cGVHD organ affected Skin Eyes Mouth Gastrointestnal Lungs Liver Vagina Musculoskeletal	17 14 13 12 5 7 4 6
Median number of regimens prior to RUX (range)	2 (0-4)
Median duration of prior prednisone therapy, (range) mo	20 (3-45)

Abbreviations: cGVHD= chronic Graft-versus-Host Disease; RUX = ruxolitinib

Table 3.

Chronic GVHD: characteristics, treatment and outcomes

	cGVHD day† and onset	cGVHD manifestations	† Day Prednisone Started	Second- line	†† Month RUX Started	Response to RUX	Time RUX to prednisone stop (days)	Duration RUX (months)	Status/IS
UPN01	118 quiescent	mouth, skin, eyes, liver, GI, PS	58	MMF	10	CR: mouth, skin, liver, GI, PS PR: eyes	46	27	Alive/MMF
UPN02	184 de novo	GI, eyes, mouth, Skin	210	MMF, azathioprine	41	CR: GI, mouth, skin PR: eyes	110	24	Alive/MMF
UPN03	136 quiescent	scleroderma, eyes, mouth, esophagus	22	Rituximab, MMF	28	CR: mouth, PR: scleroderma, eyes, esophagus	120	22	Alive/MMF-azathioprine
UPN04	90 quiescent	skin, mouth, eyes, joints, GI, PS	21	Rituximab; MMF; azathioprine	44	CR: skin, mouth, joints, GI, PS PR: eyes	106	22	Alive/none
UPN05	128 quiescent	skin, mouth, eyes, GI, vagina, PS	155	Infliximab, sirolimus	4	CR: skin, mouth, GI, PS PR: eyes, vagina	86	21	Alive/FK
UPN06	150 de novo	skin, eyes, mouth, GI, lungs, PS	148	none	13	CR: skin, mouth, GI, PS PR: eyes, lungs	31	21	Alive/FK
UPN07	130 quiescent	lungs, eyes, scleroderma, GI	60	photopheresis, MMF, Tacrolimus	26	PR: GI, eyes NR: scleroderma, lungs	270 *	6	Alive/ MMF, sirolimus, prednisone 20 mg/d **
UPN08	299 de novo	skin, eyes, mouth, edema, muscles	312	azathioprine	42	CR: mouth, edema, PR: skin, eyes, muscles	69	19	Alive/azathioprine
UPN09	130 quiescent	skin, GI, eyes	152	budesonide, sirolimus, MMF, photopheresis	11	CR: skin, GI PR: eyes	240 *	18	Alive/Prednisone 7.5 mg/d
UPN10	130 quiescent	lung, skin, eyes, GI	26	sirolimus, MMF, photopheresis	23	CR: skin, GI PR: eyes, lung,	240 *	17	expired 8/02/16 pneumonia
UPN11	250 de novo	Skin	1,825	Sirolimus, photopheresis	109	CR: skin	52	18	Alive/FK
UPN12	183 quiescent	skin, eyes, mouth, liver	49	MMF, azathioprine	41	CR: mouth, liver PR: skin, eyes	72	17	Alive/CSA-MMF
UPN13	110 quiescent	Skin	34	Sirolimus, photopheresis	15	CR: skin	365	15	Alive/none
UPN14	180 de novo	scleroderma, mouth, joints, esophagus	270	Sirolimus, weekly methotrexate	49	CR: esophagus PR scleroderma, mouth, joints	182 *	15	Alive/sirolimus-FK-prednisone 10 QOD

	cGVHD day† and onset	cGVHD manifestations	† Day Prednisone Started	Second- line	†† Month RUX Started	Response to RUX	Time RUX to prednisone stop (days)	Duration RUX (months)	Status/IS
UPN15	225 quiescent	mouth, scleroderma, eyes, liver, vagina, joints, esophagus	238	sirolimus	34	CR: joints, mouth, esophagus PR: scleroderma, eyes, liver, vagina	83	14	Alive/sirolimus
UPN16	199 quiescent	eyes, mouth, liver, joints, vagina, PS	210	MMF, sirolimus	14	CR: mouth, liver, PS PR: eyes, joints, vagina	300	13	Alive/MMF
UPN17	302 de novo	skin, liver, joints, lungs	375	MMF, rituximab	13	CR: skin PR: liver, joints, lungs	42	10	Alive/FK
UPN18	210 quiescent	skin, esophagus, mouth, liver, GI	209	ibrutinib, budesonide	20	CR: skin, mouth, liver NR: esophagus, GI	-	2.5	expired 3/14/16 pneumonia
UPN19	193 quiescent	eyes, lungs, vagina, mouth, liver	22	MMF, azathioprine	7	CR: mouth, liver PR: eyes, lungs, vagina	-	8	Alive/CSA-MMF-azathioprine, prednisone 12.5 mg/d

Abbreviations: cGVHD= chronic graft-versus-host disease, PS=Performance score, RUX=ruxolitinib, IS=immunosuppressants for cGVHD, GI=gastrointestinal, MMF=mycophenolate mofetil, CSA=cyclosporine, QOD= every other day, CR= complete response, PR=partial response, NR= progression

† day post-transplant,

†† month post-transplant,

* reduction of prednisone to physiologic doses (< 7.5 mg/d),

** steroid stress doses for pneumonia