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SAFETY AND EFFICACY OF RUXOLITINIB IN STEROID REFRACTORY ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

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Introduction

Corticosteroid is the standard first-line treatment for Graft Versus Host Disease (GVHD) post allogeneic Hematopoietic Stem Cell Transplantation (HCT). However, patients often become steroid-refractory or steroid-dependent. Ruxolitinib, a selective JAK inhibitor with its broad immune modulatory effect has been approved by FDA as the 2nd line treatment in both acute and chronic GVHD.

Objective

We aim to explore the efficacy and safety of Ruxolitinib in patients with steroid refractory GVHD.

Method

A retrospective study was conducted on patients receiving Ruxolitinib for GVHD after allogeneic HCT from 23th April 2019 till 19th March 2024 in Hospital Pulau Pinang. Acute GVHD cases were graded as per Mount Sinai Acute GVHD International Consortium (MAGIC) criteria, whereas patients with chronic GVHD were evaluated as per National Institutes of Health consensus guidelines.

Results

A total of 10 patients with a median age of 36 years old (range 17-62) were studied. The median duration of follow up was 13.5 months (range 2-59). 4 patients were started on Ruxolitinib for acute GVHD (n=3, grade III; n=1, grade IV) and another 6 for chronic GVHD (n=4, moderate; n=2, severe). 6 were given as 2nd line therapy and 4 of them as 3rd line therapy. Median duration on Ruxolitinib were 57 days for acute GVHD and 130 days for chronic GVHD. Till the end of the study, 8 patients' Ruxolitinib were stopped (n= 4, CR; n=1, PR; n= 3, disease progression), while 2 patients were still on Ruxolitinib. Acute skin GVHD is the commonest presentation (n=4), followed by liver (n=3) and gut (n=3). The most common organs involved in chronic GVHD were oral (n=5), liver (n=4), lung (n=4), followed by skin (n=2) , ocular (n=2) and genitalia (n=1). The overall response rate (ORR) for Ruxolitinib in acute GVHD was 75% on day 28 and 50% on day 56. The ORR for chronic GVHD was 100% at 3 months and 83% at 6 months. 2 patients achieved complete response, each for acute and chronic GVHD. Median time to response was 13.5 days. Most of them had grade I-II cytopenia related to ruxolitinib (n=3, grade I neutropenia; n=5, grade I-II anaemia; n=4, grade I-II thrombocytopenia). Only 2 patients experience grade III cytopenia (n=1, grade III neutropenia; n=1, grade III anaemia). 4 mortality cases were seen; 2 were related to progression of GVHD and 2 had severe infection probably related to grade III-IV cytopenia.

Acute GVHD response to Ruxolitinib

Age/gender	Disease	Status	Organs involvement (stage)	Response			
				Initial	Day 28	Day 56	≥ 3 months
35/female£	AML	Alive	Skin, liver, gut (III)	Skin(PR), liver(CR), gut(PR)	Skin(CR), liver(CR), gut (CR)		
36/male¥	CML	Dead	Skin, liver, gut (IV)	Skin(PR), liver(PR), gut(PD)			
45/male£	CLL	Dead	Skin, liver (III)	Skin(PR), liver(PR)	Skin(CR), liver(PR)	Skin(CR), liver(PR)	Skin(CR), liver(CR)
47/male¥	MM	Dead	Skin, gut (III)	Skin(PR), gut(SD)	Skin(PR), gut(PR)	Skin(PR), gut(PD)	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; AML: acute myeloid leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia; MM: multiple myeloma; £Ruxolitinib was stopped due to CR; ¥Ruxolitinib was stopped due to PD

Chronic GVHD response to Ruxolitinib

Age/gender	Disease	Status	Organs involvement (overall severity)	Response			
				Initial	≥ 3 months	≥ 6 months	≥ 1 year
22/maleα	ALL	Alive	Skin, oral, liver (moderate)	Skin(PR), oral(PR), liver(CR)	Skin(CR), oral(PR), liver(CR)		
24/maleΦ	ALL	Alive	Lung (moderate)	Lung(PR)	Lung(CR)		
17/male₼	ALL	Alive	Oral, liver, lung (moderate)	Liver(PR)	Oral(PR), liver(PR), lung(CR)		
62/femaleΦ	AML	Alive	Oral, liver (severe)	Oral(CR), liver(CR)			
25/male₼	AML	Alive	Oral, lung, ocular (moderate)	Oral(PR), lung(PR), ocular (CR)	Oral(CR), lung(PR), ocular (CR)	Oral(CR), lung(PR), ocular (CR)	Oral(CR), lung(PR), ocular (CR)
37/femaleΨ	AML	Dead	Skin, oral, liver, lung, ocular, genitalia (severe)	Skin(PR), oral(PR), liver(PR), lung(PR), ocular(PR), genitalia(CR)	Skin(PR), oral(PR), liver(CR), lung(PR), ocular(PR), genitalia(PR)	Skin(PR), oral(PD), liver(CR), lung(PD), ocular(PR), genitalia(PD)	

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; αRuxolitinib was stopped due to good PR; ΦRuxolitinib was stopped due to CR; ₼Patient still taking Ruxolitinib; ΨRuxolitinib was stopped due to PD

Discussion

The benefit of Ruxolitinib in treating GVHD was first described in a survey analysis conducted by Zeiser et al[1], with 80% global control rate of GVHD. Several retrospective studies then showed similar response rate of approximately 80%. Subsequent REACH studies[2,3] were conducted prospectively to evaluate Ruxolitinib in patients with steroid resistant GVHD. REACH 1 studies showed 54.9% ORR for acute GVHD with 28.8% of patients able to achieved CR. REACH 3 studies which evaluate response of Ruxolitinib in chronic GVHD reported 50% ORR with higher CR rate compared to BAT. Our data also showed similar encouraging results with 75% ORR at day 28 for acute GVHD and 100% ORR for chronic GVHD at 3 months. 1 patient with acute gut GVHD and another 1 patient with chronic GVHD lost response with GVHD progression although both of them had initial response to Ruxolitinib. Ruxolitinib has acceptable tolerance. Most of the patients had grade I-II cytopenia. We acknowledge that there are inherent limitations due to the retrospective assessments of response and small sample size in this study.

Conclusion

Ruxolitinib is well tolerated and exhibits satisfactory response in patients with acute and chronic GVHD.

References

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