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Title: Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: result from a retrospective study on 38 Chinese patients
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Response to Reviewers' comments

Dear Editor,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,

Reviewer #00505321

The authors conduct a review of 38 pts treated with Ruxilitinib for SR a or c GVHD. The doses were bid or qd and low. They report an encouraging very high response rate, except for Scleroderma changes. The report is irb approved, well organized, well written and contributes more information on this agent in this setting.
It is not novel as the agent is approved in many countries for this use already. Further, there is concern on how dosing was chosen because the PK of the agent means it should be given BID and not QD unless you are about to discontinue use. Be that as it may, the results are encouraging.

Response: We thank the Reviewer for the comments and for taking time to review our work. According to the drug insert (Chinese), when ruxilitinib is taken in combination with strong CYP3A4 inhibitors, the total daily dose should be reduced by ~50%. If this cannot be achieved using a bid regimen, the frequency of administration can be reduced from bid to qd. In our study, all patients were given azole antifungal drugs to prevent fungal infections after transplantation. Azole antifungal agents are known inhibitors of two key drug-metabolizing enzymes, CYP2C9 and CYP3A4 [1] and therefore the starting dose used in the present study (5mg qd or 5mg bid) was half of the effective dose (5mg-10mg bid) reported previously [2-4]. This theoretically working dose turned out to be effective in the treatment of SR GVHD. Future blood concentration monitoring for ruxilitinib combination therapies might help individualized treatment.

Reviewer #03290441

1. Why were patients receiving other concomitant treatments for GVHD excluded? Ruxolitinib indication is not only as monotherapy. These patients could be included and sub-group analysis would indicate if concomitant treatment affected survival.
2. The authors report that ruxolitinib was administered as "add-on" treatment. This contra-indicates inclusion criteria.

Response: We thank the Reviewer for the comment. In the present study, ruxolitinib was used as an add-on treatment to patients who were refractory to regular immunosuppressive agents. During ruxolitinib treatment, the patients were still on steroids. In the exclusion criteria, we were referring to agents that patients were not refractory to. This was clarified in the manuscript. The standard practice at our hospital is that ruxolitinib is added to the refractory treatment before any other new agents are introduced and this practice is inspired by Caucasian patients [2-4]. Of course, combination therapies should be explored in the future.

3. Survival and cumulative incidence analysis should also be performed

Response: We thank the Reviewer for the comment. Survival analysis was not performed due to the short follow-up (the follow-up time for cGVHD was longer, but the median was only about 5 months), and we wanted to communicate this good early

response as soon as possible. Long-term outcomes, including overall survival, cumulative recurrence, and patient-reported outcomes will be investigated in future studies.

4. Why was the follow-up so short?

Response: As the Reviewer pointed out, this indeed is a major limitation of the study. This practice was implemented about 2 years ago. In addition, some patients are referred to our center for second opinions and consultation and go back to their local center. We will try to conduct a multicenter study that will include those patients, but this an important administrative burden and we wanted to communicate this good early response as soon as possible.

5. Was ruxolitinib offered as second-line treatment after steroids in all patients? Which was the dose of steroids administered?

Response: We thank the Reviewer for the comment. In the present study, ruxolitinib was used as an add-on treatment to patients who were refractory to steroids. We included patients who developed steroid-refractory aGVHD after transplantation (defined as any grade progression within 3 days of the start of 40 mg/day corticosteroid therapy or failure to improve by at least 1 grade within 7 days of corticosteroid therapy) or cGVHD that was refractory to corticosteroids (defined as active cGVHD despite ≥4 weeks of treatment with ≥0.25 mg/kg/day (15-20 mg/day) prednisone or equivalent during the past 12 months, and up to 2 previous lines of cGVHD treatment with stable concurrent immunosuppression during the previous 4 weeks). It has been clarified in the manuscript.

6. The discussion needs to be shorter and to-the-point

Response: We thank the Reviewer. We shortened the Discussion.

References

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