

This study is simple, was well conducted. This study was aimed to conduct a study of thalidomide in treating refractory GI bleeding from GIVM in patients with significant comorbidities. Authors are focusing on patients with significant comorbidities and this is interesting concern. However, some aspects may be needed to clarify.

Major comments

1. As author mentioned, in previous many studies, patients with significant comorbidities were excluded. Including patients with comorbidities may be a differentiation from other studies, but it may also be a limitation in evaluating the effectiveness of thalidomide.

-> Comorbidities can be an important confounding variable in assessing treatment effectiveness. If we assess treatment effectiveness in patients with significant comorbidity, it would be better to target patients with one specific disease, like previous study (Garrido Serrano et al (2012)¹⁷).

Response: we agree with the reviewer that ideally it would be best to assess the effectiveness of thalidomide in patients with a specific comorbidity such as cirrhosis. However, given the difficulty in recruiting patients and the small sample size of all studies involving thalidomide and GI bleeding, we included patients with different conditions in this study. For our next study in the future, we will collect more patients in a longer duration to allow us to evaluate the effects of thalidomide in patients with a specific condition.

2. Severity or status of comorbidities before and during thalidomide treatment

Bleeding tendency is often closely related to the condition of underlying disease, especially liver cirrhosis, ESRD, and hematologic disorder. The changes in the status of underlying disease can also be a confounding variable.

-> How was the status or severity of underlying disease before and during treatment?

-> At initial inclusion, how was the severity of disease? For example, child class of liver cirrhosis, stage of CKD

-> It would be better to mention the details above.

Response: we have added the severity and status of CKD and cirrhosis to results.

3. Antiplatelet or anticoagulation

1) In section of Results, 5 patients remained on antiplatelet or anticoagulation such as aspirin, coumadin, clopidogrel, or cilostazol. All 4 patients who remained on anticoagulation or

antiplatelet therapy, including 2 with an LVAD, had a significant decrease in GIB.

-> In table 3, only 1 patient (number 3) in 4 patients (number 2,3,5,6) had no recurrence of bleeding after 6 months (primary endpoint). Does the sentence “significant decrease in GIB” mean the secondary outcomes (number of hospitalization, unit RBC transfused, number of endoscopic treatments)?

Response: yes, “significant decrease in GIB” means decreased transfusion requirements and hospitalizations as the secondary outcomes. We have clarified this on page 10.

2) Anticoagulation or antiplatelet agents

In discussion, only 1 patient with severe GAVE and platelet count < 30,000/mL due to MDS received 99 units of PRBC in the one year before thalidomide treatment, and required no transfusion after treatment.

-> Based on the result of only 1 patient, it is difficult to agree that patients with hematologic disorder and thrombocytopenia may not be necessary to aggressively correct thrombocytopenia.

-> Further large-scale studies are needed to clarify this issue.

Response: we agree with the reviewer that we need more patients with thrombocytopenia to see if it is necessary to correct thrombocytopenia while on thalidomide. We have modified this on page 13.

Minor comments

1. Type of previous endoscopic therapy

Various methods are used for endoscopic hemostasis in GI bleeding from GIVM, but APC is effective and widely used in clinical practice. It is helpful to mention which endoscopic method was used prior to thalidomide treatment.

Response: we mentioned APC in the second paragraph of result section but we have clarified this further in the section of study population to mention APC as our endoscopic therapy as suggested by the reviewer.

2. Inclusion criteria

Documented vascular malformation (either GIAD or GAVE) on upper endoscopy (EGD), colonoscopy, balloon enteroscopy, or capsule endoscopy

-> Was all of the tests (EGDS, CFS, Enteroscopy, or capsule endoscopy) done in included

patients? Enteroscopy or capsule endoscopy was performed in patients with no bleeding focus found in EGDS and CFS?

Response: enteroscopy or capsule endoscopy was performed only if the source of bleeding was not identified on EGD or colonoscopy. We have clarified this in the inclusion criteria.

-> It would be better that other causes of bleeding (peptic ulcer, diverticular bleeding) were excluded (exclusion criteria).

Response: we excluded patients with other causes of bleeding in our study. We have clarified this in our exclusion criteria.

-> It is necessary to mention about the location of vascular malformation (stomach or colon or small bowel) of 15 patients (in Results section or Table 2 patient characteristics).

Response: multiple patients had GIAD through several locations, including gastric fundus (n=1), duodenum (n=3), jejunum (n=5), ileum (n=1), and hepatic flexure of colon (n=1). We have added this information in the result section on page 10.

3. Iron supplementation

8 patients continued with iron supplementation after initiation of thalidomide treatment. (2nd paragraph of Results section).

-> How was the patients' hemoglobin level before starting thalidomide treatment? Was anemia (especially iron deficiency anemia) assessed or excluded?

Response: all patients prior to the initiation of thalidomide were found to be anemic with average hemoglobin level of 7-8g/dL. Five patients were on iron supplement when referred to our care and 3 patients with iron deficiency were not on iron supplement. This has been added to the result section on page 9. We also added a column on Table 2 with the type of iron used by patients.

-> The presence of anemia (especially IDA) before starting thalidomide tx and iron supply during tx are thought to be variables in assessing treatment effectiveness (especially secondary outcomes including "Units RBC transfused")

Response: we agree with the reviewer that the presence of iron deficiency anemia or treatment with iron supplement may affect the assessment of treatment effectiveness. However, given that this is a retrospective study we were not able to control for these variables. We have added an acknowledgement of this limitation in our discussion on page 15.

4. Coumadin is the brand name of warfarin. It would be better to use a term "warfarin" or Coumadin®.

Response: we agree with the reviewer and have replaced Coumadin with warfarin.

5. As author mentioned in discussion, the major limitations of this study are the limitations inherent with a retrospective study and small sample size.

-> I agree that recruiting patients is very difficult in aspects of cost and safety. In this regard, it is thought that this study is meaningful.

We appreciate reviewer's understanding and positive comment.