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Brückenpflege
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Editors-in-Chief:

Rosa M Jimenez Rodriguez, Monjur Ahmed, Pashtoon Kasi

World Journal of Gastrointestinal Oncology

Manuscript ID 58086

"Cancer-related microangiopathic hemolytic anemia (CR-MAHA) in patients with advanced gastric cancer: a retrospective cohort study".

Dear Professor Jimenez-Rodriguez, dear Professor Ahmed, dear Professor Kasi, dear Editorial Board,

thank you very much for your answer concerning the submission of our manuscript and the reviewers` interesting and helpful comments. Please find enclosed our answers to all reviewers` points. All new changes are also highlighted in the revised manuscript (marked version). Since we feel that we could adequately address all aspects and findings, we hope that the manuscript is now acceptable for publication in the *World Journal of Gastrointestinal Oncology.*

Reviewer 1:

This is a good case series about GC related MAHA. Generally well written and presented paper but some points need to correct

1-The MSI status should be assessed whenever possible, since immunotherapy can lead to long-time tumor control even in CR-MAHA patients: authors can not make a comment with only one case

- ⇨ The sentence was adapted (Abstract, p 3 lines 3/4)

2-A large retrospective literature review covering the time period between 1979 and 2012 included 168 CR-MAHA patients and identified another 40 patients with gastric cancer, reported mainly as single case reports: what is the reason for 1979-2012

- ⇨ The paper by Lechner (Lechner K and Obermeier HL. Cancer-related microangiopathic hemolytic anemia: Clinical and laboratory features in 168 reported cases. Medicine (Baltimore). Jul 2012) covered the time period 1979-2012. To avoid misunderstanding, we adapted the sentence more clearly (Introduction, p 4, line 22).

3-Residual survival (RS): what is this, I do not know this terminology as an oncologist and hematologist

- ⇨ The term Residual survival (RS) is now defined in the Patients and Methods section (Patients and methods, p 5, lines 13 ff):

4-Results section: some senteneces could not be understood: ***a-*** *Sex distribution was even.* ***b****-the tumor was found. 5 patients (62.5%) were tested as HER2 negative, for 3 patients (37.5%), the HER2 status is unknown* ***c****-3 patients (37.5%) presented with secondary metastatic disease occurring 0.5, 2 and 10 years* ***d****-and the patient relapsing after 0.5 years presented in our emergency department* ***e****-pulmonary symptoms (dyspnea) and 5 patients (62.5%) complained about severe*

- ⇨ 4a : gender presentation was clarified (Results, line 4)
- ⇨ 4b: We changed the wording (Results, lines 7/8)
- ⇨ 4c: We clarified the date of metastases`diagnosis (Results, lines 12/13)
- ⇨ 4d: We aimed to clarify the presentation of patients` symptoms. (Results, lines 24-26)
- ⇨ 4e: We aimed to clarify the presentation of patients` symptoms. (Results, lines, 38/39)

5- In 5 patients (62.5%), bone marrow biopsy was performed, of which 3 showed infiltration by adenocarcinoma: what about the bone marrow findings in 3 cases?

- ⇨ In three cases, bone marrow biopsy was not performed. We stated this more clearly now (Results, p 7, line 40)

6- CR-MAHA: This is a very high rate for MAHA. Authors must discuss this high rate of MAHA in their clinic.

- ⇨ A new paragraph was added (Discussion, p 9, lines 1-5)

Reviewer 2

-Major Comments: Patients and methods: Based on the definition of CR-MAHA: hemolytic anemia with schistocytes with or without thrombocytopenia. This definition can include disseminated intravascular coagulopathy (DIC) due to solid malignant tumors. DIC in patients with advanced gastric cancer is common. I think it is critical to explain it to differentiated CR-MAHA from cancer-related DIC.

- ⇨ Distinguishing CR-MAHA from CR-DIC can be challenging. However, the vast majority (7/8) of our patients had no signs of

consumption coagulopathy with normal parameters for activated partial thromboplastin time and fibrinogen when the MAHA was diagnosed. In patients with a prolonged clinical history of MAHA-suspect symptoms, coagulation parameters might be altered since CR-MAHA itself can cause a secondary DIC due to organ damage. In addition, more severe microangiopathic changes on the blood smear can be observed in patients with CR-MAHA in comparison to DIC patients. In one patient with slight signs of coagulopathy and fibrinolysis, prolonged CR-MAHA was considered as the more appropriate diagnosis in line with his significantly increases schistocytes and the severely decreased hemoglobin levels. We added a new paragraph to discuss this relevant aspect (Discussion p 9, lines 22 ff)

-Patients and methods: The authors should show the judgment for choice for chemotherapy or best supportive care. Does it depend on the physician's or patient's choice or general condition?

⇨ We clarified the process of decision-making (Patients and methods, p 9, lines 10 ff)

-Results: I recommend that the authors should include more clinical data in Table 1, including initial symptom, and so on.

⇨ We integrated the required information in table 1

-Results. This paper showed 8 cases of CR-MAHA with various backgrounds. There are four years of different ages between the diagnosis of gastric cancer and CR-MAHA. I was wondering if three patients with

secondary were recurrent after definitive surgery. The authors should explain the detail of them or add information in Table 1.

⇨ We added this information (Results, p 6, lines 13/14)

-Results. Antitumor treatment. The authors showed the specific definition of the rapid initial response to chemotherapy. Results. Antitumor treatment. Four patients (50%) showed a rapid initial response. "50%" was incorrect. The authors should revise four patients (67%). I think the authors should analyze except for two patients with best supportive care.

⇨ We adapted the results accordingly (Results, p 7, line 29)

-Discussion. Please discuss or comment on predictive factors for the initial response for chemotherapy (responder N=4, and non-responder N=2) in patients with CR-MAHA. If there was a deferent background, please provide a table for the clinical background between the two groups.

⇨ Unfortunately, the small number of patients does not allow for reliable testing of specific predictive factors that would allow for identification of responders versus non-responders.

-Minor Comments Abstract. Please add "weeks" after 10.3 On Page 3, line 1. Results. Page 8, schistocyts → mistype Table 2. Table 2 included "." or "," in the number. Please unify ".".

⇨ Corrected

Reviewer 3:

-The author reported 8 cases with CR-MAHA which were originated from gastric cancer. The clinical features, treatment and prognosis were described in great detail. the paper was well written and showed a clear conclusion. However due to insufficient patients included, I think title named "case report" much better than "a retrospective cohort study".

⇨ We agree that the number of patients is rather low. However, this is the largest series of CR-MAHA patients with gastric cancer reported so far, registered via a prospectively maintained institutional database. In our opinion, this scientific approach exceeds the characteristics of a mere “case report”. However, we adapted the title to avoid misunderstanding to: “…..a retrospective single-center analysis”.

-Secondly, Whether the different plans of first-chemotherapy having different effects on the prognosis of patients was not mentioned, could immunotherapy be an option for such patients with H-MSI generally considering its adverse reactions to clotting? Please add the above to the discussion

⇨ Unfortunately, the case number is too low to draw firm conclusions concerning efficacy of different chemotherapeutic regimen in this setting. Whether primary immunotherapy in MSI-high CR-MAHA patients would be more beneficial remains unclear, but the required prompt clinical response assumably demands for combined chemotherapy to rapidly reduce tumor burden. We added this aspect in the discussion (Discussion, p 10, lines 5 ff).

Science editor:

1 Scientific quality: The manuscript describes a retrospective cohort study of the cancer-related microangiopathic hemolytic anemia in patients with advanced gastric cancer. The topic is within the scope of the WJGO. (1) Classification: Grade B, Grade C, and Grade C; (2) Summary of the Peer-Review Report: The authors reported 8 cases with CR-MAHA which were

originated from gastric cancer. The clinical features, treatment and prognosis were described in great detail. The paper is well-written, and the conclusion is clear. However, the title named "case report" will be much better than "a retrospective cohort study".

- ⇨ We agree that the number of patients is rather low, due to the rarity of the disease. However, this is the largest series of CR-MAHA patients with gastric cancer reported so far, registered for scientific purposes via a prospectively maintained institutional database. We consider this scientific approach exceeding by far the characteristics of a “case report”, meeting the criteria of an original article. However, we adapted the title to avoid misunderstanding to: “…..a retrospective single-center analysis”.

The questions raised by the reviewers should be answered carefully; and (3) Format: There are 2 tables and 1 figure. A total of 14 references are cited, including 1 reference published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade B, Grade B, and Grade B. 3 Academic norms and rules: The authors provided the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. Please provide the written informed consent and CARE Checklist – 2016. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJGO. 5 Issues raised: (1) The “Author Contributions” section is missing. Please provide the author contributions;

- ⇨ We added this information

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

(3) Please revise the abstract and the text according to the "Guidelines for manuscript preparation, submission, and manuscript format: Case report", in details see https://www.wjgnet.com/bpg/GerInfo/187; and (4) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

⇨ Not applicable, see above

6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Editorial office director:

I have checked the comments written by the science editor. The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, and the Institutional Review Board Approval Form. Written informed consent was waived. The authors need to fill out the STROBE checklist with page numbers.

=> STROBE checklist adapted

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript and the relevant ethics documents, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major

revisions. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements.

Yours sincerely,

Anne Katrin Berger, MD (corresponding author)