Manuscript No: 77717
Response to Editors and Reviewers

Dear Ms. Li Ma:

Thank you for inviting us to submit a revised version of our manuscript entitled, "Disseminated carcinomatosis of the bone marrow from early gastric cancer caused by granulocyte colony-stimulating factor: A case report" to *World Journal of Gastrointestinal Oncology*. We also appreciate the time and effort that you and each of the reviewers have dedicated for providing insightful feedback on ways to strengthen our paper. Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated the changes as per the detailed suggestions. We hope that our revisions and responses satisfactorily address all the issues and concerns.

To facilitate your review of our revisions, the point-by-point responses to the questions and comments delivered in your email dated 24/6/2022 have been included below.

Company editor-in-chief: "Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A:...; B:...; C:...; D:...; E:...; F:...; G:...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file."

Response: We have revised the legend of Figure 3 for uniform presentation as "A:...; B:...; C:...; and D:...." (Lines 429–435). We will also upload the PowerPoint file in the online system with decomposable figures.

Moreover, we have revised the abbreviations in the Core Tip (Lines 73, 75) and figure legends (Lines 420, 433) according to the rules provided in the email, and we have revised the running title to six words (Line 8).

Reviewer #1:"This case report described a patient who suffered from disseminated bone marrow carcinomatosis that originated from a cured early gastric adenocarcinoma 8 years ago after a recent multiple G-CSF administrations for netropenia induced by postoperative radiotherapy and chemotherapy for a second primary Ewing sarcoma diagnosed six years after gastrectomy. The case per se is very meaningful and a good reminder for clinical doctors. Leukopenia and neutropenia is very common during chemotherapy, so when doctors prescribe this drug in the future, should be more cautious, especially in gastric

cancer. Additionally, G-CSF/ G-CSFR may need to be stained for risk predicting. Besides, the narrative is clear and smooth, and the discussion is reasonable. the narrative is clear and smooth, and the discussion is reasonable"

Response: Thank you very much for your kind evaluation.

Reviewer #2:"This case report describes A 55-year-old Japanese woman diagnosed as disseminated carcinomatosis of the bone marrow (DCBM) who cured from early gastric cancer caused by granulocyte colony-stimulating factor. In this case report G-CSFR staining was negative in the primary lesion but was diffusely positive in the relapsed lesion. G-CSF can promote the growth of solid tumors not only through G-CSFR on tumor cells but also by modulating immune cell activities or bone remodeling. So that G-CSF administration should be performed carefully in patients who have a preceding cancer. This case report state a rare case about G-CSF could induce cancer recurrence even after curative treatment. It should be watchful for clinicians. It should be watchful for clinicians."

Response: Thank you for evaluating the clinical importance of this case.

Reviewer #3:

In this study the authors introduced a case report with disseminated carcinomatosis of the bone marrow from early gastric cancer, which appeared to be interesting. However, there are some specific points needed to be carefully considered.

Response: We appreciate your insightful feedback. Here we respond to your two points about the strength of causal relation and first-line chemotherapy for DCBM from gastric cancer.

1. "The authors suggested that recurrence presenting as DCBM was caused by the potential of G-CSF administration, while the only envidence was a diffuse positive staining for the G-CSF receptor (G-CSFR) in the relapsed gastric cancer cell cytoplasm of the autopsied bone marrow and negative staining for G-CSFR of primary lesion cancer cells. The causal relation is too weak and more envidences need to be added."

Response: We agree that changes in the immunohistochemical findings are not sufficient to fully explain the causal relationship between G-CSF and relapse. However, as previously discussed in the manuscript (Lines 205–224), other studies reported that G-CSF can promote recurrence or proliferation by stimulating G-CSFR present on tumor cells and by modulating immune cell activities or bone remodeling around the tumor, which also strengthens the causal relationship between G-CSF and relapse. Furthermore, the clinical time course supports the causal relation. Gastric cancer, which seemed to resolve and maintain resolution for as long as 8 years, suddenly relapsed as DCBM just a few months

after the completion of G-CSF administrations.

2. "Methotrexate, fluorouracil and calcium folinate were performed as first-line palliative chemotherapy regimen after diagnosis, however methotrexate was not the standard treatment as first-line therapy. The authors need to explain that."

Response: We considered that methotrexate, fluorouracil, and calcium folinate regimen was effective as first-line palliative chemotherapy for DCBM with DIC caused by gastric cancer. Some studies, including randomized control studies, reported that this regimen could be effective to improve DIC or to prolong survival in patients with advanced gastric cancer with tolerable toxicity. We have added the references [15-18] (Lines 187, 307–329) for supporting the use of this chemotherapy regimen in the manuscript.

We thank you again for giving us the opportunity to strengthen our manuscript with your valuable comments and queries. We have worked hard to incorporate your feedback, and we hope that the revised manuscript is accepted for publication.

Sincerely,

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