

Peer Review File

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Reviewer A

Title and Abstract

- The title is clear and accurately reflects the content of the article. It effectively highlights the novel aspect of the treatment approach described.

- The abstract provides a concise and comprehensive summary of the case report. It effectively outlines the background, case description, and conclusions. However, consider expanding on the specific outcomes and long-term implications in the abstract for more clarity.

Reply 1: Thank you for this comment. we have modified our text as advised (see Page 2, line 40-44).

Changes in the text: For GIST patients with liver metastases, TACE combined with various TKI drugs could effectively control intrahepatic tumor progression and prolong patient survival. During six TACE sessions, the patient experienced liver tumor rupture and massive bleeding. However, the bleeding was completely stopped by embolization, and the lesion shrank.

Introduction

- The introduction is well-written and sets the stage for the case report by providing relevant background information on GIST and the challenges associated with its treatment. It clearly states the rationale for combining TACE with TKI therapy.

- Suggestion: Briefly mention the significance of this case report in the context of existing literature to highlight its contribution.

Reply 2: Thank you for this comment. we have modified our text as advised (see Page 3, line 82-92).

Changes in the text: TACE is the standard treatment method for intermediate-stage liver cancer. A previous study performed by Cao et al founded that TACE was both effective and well-tolerated in GIST patients experiencing liver metastases following TKI failure and could prolong the survival outcomes (median overall time: 68.5 months). Another research showed that the median overall survival of GIST patients with LM could be extended to 74 weeks after receiving Embosphere(®)-TAE treatment. (13-15).

In this case report, the GIST patient with LM successively experienced post-surgical recurrence and resistance to TKI treatment, and by undergoing TACE treatment, the progression of intrahepatic tumors was ultimately controlled, achieving a survival period of 12 years.

Case Presentation

- The case presentation is detailed and well-organized, providing a clear timeline of the patient's treatment history and outcomes.

- Suggestion: Include more information on the patient's quality of life and symptom

management throughout the treatment period. This can provide a more holistic view of the treatment's impact.

Reply 3 : Thank you for this comment. we have modified our text as advised .

Changes in the text: Page 4, line 117-118: the patient was a truck driver and can work normally.

Page 4, line 124-125:The patient was capable of performing light physical labor.

Page 5, line 152-155:Ten months after the rupture and bleeding of the liver lesion, the patient spent most of the time being treated in the hospital. Subsequently, the abdominal distension gradually disappeared and returned to a normal life.

Page 5, line 159-160:The patient was capable of performing housework.

Methods

- The methods section is thorough and describes the procedures used in TACE and the administration of TKIs. It provides sufficient detail for reproducibility.

- Suggestion: Add more information on the decision-making process for selecting specific TKIs and the rationale for dose adjustments. This can help readers understand the clinical considerations involved.

Reply 4: Thank you for this comment. we have modified our text as advised.

Changes in the text: Page 4, line 121:We considered that the patient developed tolerance to imatinib.

Page 5, line 149-151:Based on genetic testing, second-line and third-line drugs were used, but the therapeutic effects of Sunitinib and Regorafenib were relatively minor or intolerable.

Results

- The results section effectively describes the outcomes of the TACE sessions and TKI therapy. The use of figures to illustrate the treatment timeline and changes in tumor size is commendable.

- Suggestion: Provide quantitative data on tumor shrinkage and other measurable outcomes where possible. This can enhance the robustness of the findings.

Reply 5: Thank you for this comment. We have showed the data on tumor shrinkage and other measurable outcomes in Case Presentation and figure legend. We have modified our text as advised (see Page 5, line 158).

Changes in the text: the largest lesion in the hepatogastric gap sized only 4 cm × 3 cm.

Discussion

- The discussion is comprehensive and effectively integrates the case findings with existing literature. It provides a balanced view of the strengths and limitations of the treatment approach.

- Suggestion: Discuss potential alternative therapies and their comparative effectiveness. Additionally, consider elaborating on future research directions and the potential for clinical trials based on this case.

Reply 6: Thank you for this comment. we have modified our text as advised (see Page 7, line

215-220).

Changes in the text: TACE plays a significant role in the treatment of intermediate and advanced liver cancer as well as hepatic hemangiomas. Moreover, TACE for colorectal cancer liver metastases is also listed as an option in the Japanese colorectal cancer treatment guidelines. TACE and percutaneous ablation are mature and effective interventional radiology therapies for primary hepatocellular carcinoma, metastatic liver cancer and hepatic hemangioma.

- Additional Suggestion: In the discussion, consider adding a paragraph about the safety and feasibility of transarterial embolization for other hepatic tumours as HCC/hemangiomas/metastases. Highlight the importance of assessing new interventional techniques and their potential applicability to similar cases of hepatic metastases from GIST. Discussing the use of advanced embolization techniques and their outcomes can provide a broader context and reinforce the novelty of your case report.

Reply 7: Thank you for this comment. we have modified our text as advised (see Page 7, line 228-232).

Changes in the text: In the situation where the patient's vital signs are unstable, how to both embolize the bleeding blood vessels and take into account the liver reserve function of the patient's large liver tumor to avoid serious complications such as liver failure after hemostasis, is a test of the technical skills of the interventional radiologist.

Conclusion

- The conclusion succinctly summarizes the key takeaways from the case report. It highlights the potential of combining TACE with TKI therapy for long-term management of GIST with liver metastases.

- Suggestion: Emphasize the implications for clinical practice and the potential benefits for similar cases in more detail.

Reply 8: Thank you for this comment. we have modified our text as advised (see Page 8, line 254-262).

Changes in the text: As a relatively rare and specific tumor, GIST has highly diverse biological behaviors and significant differences in disease conditions. Each treatment has its limitations. Domestic and foreign guidelines have clearly clarified the tiered structure of drug treatment for GIST: first-line imatinib, second-line sunitinib, third-line regorafenib, fourth-line ripretinib and avapritinib. However, with the gradual popularization of the clinical application of targeted drugs, the problem of drug resistance has gradually emerged and become the main reason restricting the efficacy of advanced GIST. In particular, after multiple lines of drug therapy have progressed, the choice of posterior line therapy remains limited and the efficacy is unsatisfactory.

References

- The references are appropriate and relevant to the content of the case report. They provide a solid foundation for the discussion and support the conclusions drawn.

Reply 9: Thank you for this comment.

Reviewer B

Dear Authors, I would like to congratulate both the interventional radiologists and oncologists for their exceptional skill in successfully managing such a complicated patient case.

Reply 1: Thank you for this comment.

Reviewer C

This is an interesting clinical case report of TACE plus TKIs for GIST-LM. First, the abstract is not standardized. I suggest the authors to indicate the uniqueness and potential clinical contribution of this case in the background. In the case presentation, please provide data on the adverse events of the current treatment. The authors need to tone down the current conclusion and avoid vague comments such as “new perspective and treatment strategy”. Please have more detailed comments for the clinical implications of the findings.

Reply 1: Thank you for this comment. we have modified our text as advised (see Page 3, line 92-98).

Changes in the text: TACE plays an important role in the treatment of liver tumors and emergency bleeding. However, there were few reports on its use in the treatment of hepatic metastatic GIST. Here, we report the application of TACE combined with TKI in a GIST-LM patient. Facing sequential resistance to targeted drugs, waiting for new drugs due to economic factors, and experiencing two instances of liver tumor rupture with massive bleeding, the treatment has bought time and turned a critical situation into a safer one.

Second, in the introduction of the main text, the authors need to review the challenges and strategies in treating GIST-LM and analyze why TACE plus TKIs are the most suitable strategy. It is also necessary to describe the uniqueness and potential clinical contribution of this case.

Reply 2: Thank you for this comment. we have modified our text as advised (see Page 9, line 268-273).

Changes in the text: GIST-LM faces the challenges of successive drug resistance, economic factors, waiting for available new drugs, and massive hemorrhage from giant stromal tumor rupture. TACE has won valuable treatment time and turned to safety for patients. TACE can treat tumors that have already appeared, but for mesenchymal tumors that have not yet appeared, it is necessary to combine with TKIs.

Third, in the case presentation of the main text, more data on the adverse events during the treatment are needed.

Reply 3: Thank you for this comment. we have modified our text as advised.

Changes in the text: Page 4, line 116-117: the main side effect of Imatinib was mild facial edema.

Page 4-5, line 129-131:the main discomfort after TACE was manifested as post-embolization syndrome: mild to moderate pain in the liver area and nausea within 1-2 days, fever of 38-39°C from 2 to 5 days post- TACE, which gradually disappeared at 6-7 days.

Fourth, please consider to cite several related papers: 1. Teke ME, Choi A, Sarvestani AL, Blakely AM, Carr SR. An unusual paraesophageal and diaphragmatic SDHA-deficient gastrointestinal stromal tumor (GIST) metastases case report. *J Gastrointest Oncol* 2023;14(1):429-434. doi: 10.21037/jgo-22-714. 2. Cananzi FCM. Minimally invasive approach in gastrointestinal stromal tumors. *Laparosc Surg* 2022;6:32. 3. Kalinowska I, Zdzienicki M, Skoczylas J, Rutkowski P. A narrative review of surgical management of gastrointestinal stromal tumors. *Gastrointest Stromal Tumor* 2021;4:5. 4. Hu Y, Pan T, Cai X, He QS, Zheng YB, Huang MS, Jiang ZB, Chen JW, Wu C. Addition of transarterial chemoembolization improves outcome of tyrosine kinase and immune checkpoint inhibitors regime in patients with unresectable hepatocellular carcinoma. *J Gastrointest Oncol* 2023;14(4):1837-1848. doi: 10.21037/jgo-23-486.

Reply 4: Thank you for this comment. we have modified our text as advised (see Page 3, line 65).

Changes in the text: Surgical resection has been a cornerstone in the treatment of GISTs, especially for localized tumors(3-5).