Author's response to reviews

Title: A Long-term follow-up of the imatinib mesylate treatment for the patients with recurrent gastrointestinal stromal tumor: the liver metastasis and the outcome

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Author's response to reviews:

Dear editor

The authors want to thank the reviewers for their reviewing and important suggestions on our manuscript. We discussed the comments carefully. The manuscript had been carefully revised according to the reviewers’ advice. Now, we are prepared to response to the reviewers’ comments point to point.

Referee 1:
1. The question posed by the authors is well defined
2. The manuscript adhere to the relevant standards for reporting and data deposition
3. the methods are appropriate and well describe
4. The data are sound
5. The discussion and conclusions are well balanced and adequately supported by the data
6. limitations of the work are clearly stated
7. The title and abstract accurately convey what has been found
8. The writing is acceptable

Answer: The authors would like to thank referee 1 for his/her positive evaluation on our study.

Minor revision

discussion: line 17 to correct the words after and combained
Answer: The wrong words had been corrected in red color.
Referee 2:
Major Compulsory Revisions
1) The major concern of the reviewer is about the study population that eventually includes three different patterns of patients with recurrent GIST: those with no liver metastases, those with only liver metastases, and those with either liver and extra-hepatic metastases. Authors merged the two latter in a single group but this may result inappropriate. It is far to be proved that the behaviour of recurrent GISTs involving the liver and other abdominal viscera would be the same of GISTs recurred in the liver only. Thus, it is suggested that comparisons should be made only between the group of patients with no liver metastases and the group of patients with both hepatic and extra-hepatic metastases. By this way one can assure that the only, as expressed by the study title, would be the presence or not of liver metastases. Alternatively comparisons might be made including three groups: recurrent abdominal GISTs, recurrent abdominal and liver GISTs, recurrent liver GISTs.

Answer: The authors agree with reviewer’s opinion totally. We had re-arranged the population groups as the suggestions. Thus the comparisons were made including the following 3 groups: LG (recurrent liver GISTs) group, AG (recurrent abdominal GISTs) group and ALG (recurrent abdominal and liver GISTs) group. The corresponding parts in the manuscript had been carefully revised in red color. Figure 1 and Figure 2 had been corrected. New statistical analysis had been performed. The conclusions are supported by the new results.

2) The aggressive behavior of GISTs may be predicted by several items: site of origin (foregut, midgut, hindgut), type of histological pattern (spindle, epithelioid or mixed cells) and, outmost important, by applying the risk criteria assessment as proposed by Fletcher and al. (Human Pathology 2002; 33; 459-467). These include the size of the primitive tumor and the number of mitosis for HPF. In the study there is no data referring to these items. Thus, conclusions may be biased by a different distribution in the two groups of GISTs with low- or high-risk of aggressive behaviour.

Answer: Data of the aggressive behavior of GIST had been added in Table 1 in red color. There are 3 categories: low-risk, intermediate-risk and high-risk presented in the pathology diagnostic reports. The pathologist in our hospital that we consulted confirmed that the low-risk GIST presented in the reports included the very low risk and low risk GISTs according to the Fletcher criteria. Statistical analysis showed no significant difference among groups.
3) Response to imatinib treatment achieves best results for GIST caused by mutations in the KIT or PDGFRalfa receptor tyrosine kinase genes. Conversely, response is very low for GIST that have a wild-type genes pattern. Again, to avoid bias, a mutational analysis should have been performed.

Answer: The authors agree with the above opinions totally. The importance of mutation in the KIT or PDGFRalfa receptor genes is significant for the evaluation of imatinib treatment. Please considering the current study was conducted from a charity program. The team was not supported by any extra research funds to perform the mutational analysis now. Fortunately, the specimens are available. It will be helpful for our further research works.

Minor Essential Revisions

1) The minimum interval from radical resection and recurrence was 2 months: can you surely state that resections were R0 in all patients, including those in which GIST recurred within few weeks?

Answer: Among the 42 patients, 3 (7.1%) of them had a recurrent GIST within 6 months from the radical resection (2 months, 3 months and 4 months, respectively). Here we state radical means R0 resection. The authors checked their clinical data very carefully: the operation records, pathological reports and CT scan after operation, but could not find any clear evidence to indicate that the resection was not done radically.

2) Page 4 of the main text (Discussion), line 23: “Oral imatinib mesylate, instead of another surgery, was the reasonable choice for the patients who had recurrent GIST after a radical resection”. This sentence may be misleading. One can agree with the message coming from the sentence, but only when re-resection appears not radical. In other terms, if recurrence seems to be amenable by radical resection, thus surgery should be warranted. If radicality seems to be out of reach, then patients should be posed on medical treatment. Sentence should be re-arrange accordingly.

Answer: We agree with the opinion above. The sentence was re-arranged in red color.

3) Same page, line 29 and following. The sentences...“Obviously, the liver metastasis did not influence the patients’ survival so seriously if ...So the liver metastasis should not be regarded as an important...” may be re-arranged as follows. Survival was not significantly affected by liver metastases when imatinib mesylate treatment was warranted.

Answer: The sentence was re-arranged in red color as suggestions. We also use it in the conclusion part. Thanks for giving us such a proper expression.

4) The following sentences: ..However it should be noted that adverse effects of the long-term imatinib mesylate treatment were frequently observed. The most common adverse effects were edema and anemia: Fortunately, the toxicities were mild and well tolerated. No grade 4 toxicity was observed. No
treatment-related death was reported. Our data presented a good tolerance of long-term imatinib mesylate treatment. May be re-arranged as follows: Edema and anemia, although mild and well tolerated, were the commonest adverse effects observed during long-term imatinib mesylate treatment.

Answer: The sentence was re-arranged in red color as suggestions.

5) The following period (discussion chapter) starting at line 38, page 4 (...An adjuvant use of imatinib mesylate was reported to be a promising......) and ending on page 5,line 8 (...after a radical resection of the primary tumor is still worth further considering.) deals with the object of whether to give imatinib to patients after primary resection of a GIST. This is beyond the main aim of the study and the period should be deleted.

Answer: We agree with reviewer’s opinion. The above period was deleted.

6) The following sentence may be re-arranged as: Tumor’s resistance to imatinib mesylate is still a major problem.

Answer: The sentence was re-arranged in red color as suggestions.

EDITORIAL REQUESTS:

Ethics and consent

Ethics - Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Answer: The current study was about a wide received treatment for advanced GIST. it was not an experimental research. The authors declare that the study is in compliance with the Helsinki Declaration.

Informed consent must also be documented. Manuscripts may be rejected if the editorial office considers that the research has not been carried out within an ethical framework, e.g. if the severity of the experimental procedure is not justified by the value of the knowledge gained.

Answer: Each patient signed an ICF before the imatinib treatment. We added this information in Methods/Patients part in red color.

At last, we would like to thank the reviewers again for their help in improving our manuscript. All changes had been highlighted with red color. We hope the current revision will meet the requests.

Yours sincerely,
Dr. Jaing Zhu