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Title: Sequential chemotherapy and icotinib as first-line treatment for advanced EGFR-mutated non-small cell lung cancer: a multicenter pilot trial

Journal: World Journal of Clinical Cases

Response to Reviewers' comments

Dear Editor,

We thank you for your careful consideration of our manuscript. We appreciate your response and overall positive initial feedback and made modifications to improve the manuscript. After carefully reviewing the comments made by the Reviewers, we have modified the manuscript to improve the presentation of our results and their discussion, therefore providing a complete context for the research that may be of interest to your readers.

We hope that you will find the revised paper suitable for publication, and we look forward to contributing to your journal. Please do not hesitate to contact us with other questions or concerns regarding the manuscript.

Best regards,

Reviewer #1

Originality is the priority in consideration of a paper publication. During the plagiarism check, I found the similarity rate is 25%, which is the leading cause of MAJOR REVISION.

Response: We thank the Reviewer for the comment. We revised the manuscript to decrease the apparent similarity. We entirely agree that plagiarism is a plague in academia. Automated detection tools greatly improved the fight against this plague, but such tools must be taken with caution. We have to highlight that the Journal considered the CrossCheck score appropriate and that many duplications identified by CroccCheck are short strings of words or factual statements that cannot be considered plagiarism. Numbers, measurement units, P-values, the mandatory Helsinki Declaration statement, and the ethics statement were also identified as “plagiarism”, artificially increasing the similarity score. “Advanced epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC)” is the factual name of the disease and is not plagiarism. We also have to note that considering the wealth of literature available, changing a few words in the short strings of words or factual statements incur the risk of being flagged as duplication of other articles.

Reviewer #2

1) There is a wide range of therapeutic options in lung cancer. The authors should add them and clarify why they selected this type of treatment using the relevant articles such as Alfredo Tartarone, et al - 2019 - Monireh Mohsenzadegan, et al - 2020 - Fausto Petrelli, et al - 2021.

Response: We thank the Reviewer for the comment. Indeed, there are many therapeutic options in lung cancer, including chemotherapy, targeted therapy, and immunotherapy.^[1-6] Icotinib is a promising targeted therapy for *EGFR*-mutated NSCLC.^[7-10] The present study selected the combination of icotinib (or other *EGFR*-TKIs) and chemotherapy since it is the most studied combination in NSCLC, with apparent benefits in response and survival.^[7, 10-15] Still, the combination of *EGFR*-TKIs and immunotherapy could be a promising option for NSCLC,^[16-18] but some evidence suggests that immunotherapy is not effective in patients with *EGFR*-mutated NSCLC, probably because of the specific tumor microenvironment^[18, 19]. Indeed, early trials showed that immunotherapy monotherapy was inferior to *EGFR*-TKIs in *EGFR*-mutated NSCLC^[20, 21]. Subsequent studies showed that the combination of immunotherapy with *EGFR*-TKIs in *EGFR*-mutated NSCLC resulted in high rates of serious AEs (33.3%-71.4% of grade 3-4 AEs)^[22-24]. Therefore, additional studies are necessary before being able to use immunotherapy with *EGFR*-TKIs in patients with *EGFR*-mutated NSCLC.

2) The role of age in this type of treatment should be discussed and the authors should compared their findings with similar data such as Giandomenico Roviello, et al -

2018.

Response: We thank the Reviewer for the comment. Indeed, Roviello et al.^[25] reported that EGFR-TKIs led to good outcomes in older adults with *EGFR*-mutated NSCLC. We agree that EGFR-TKIs could be a valuable and less toxic treatment option for older adults who often have difficulties facing chemotherapy. Unfortunately, in the present study, the sample size was too small to be able to examine the influence of age on the treatment outcomes. Furthermore, as per the inclusion criteria, no patients >72 years old were enrolled. Nevertheless, examining treatment options specifically in older adults is indeed a future direction for research. It was added to the Discussion.

3) *Other important factor is genetic background of population study. I found there is no data regarding the response to immunotherapies in lung cancer cases. The authors should add this point using the relevant articles such as Zahra Fathi, et al - 2018.*

Response: We thank the Reviewer. All patients in this study received first-line treatment for newly diagnosed stage IIIB-IV NSCLC. Therefore, no participants had a history of prior immunotherapy.

Reviewer #3

The authors have done a great job conducting this clinical trial and writing the manuscript. Given Icotinib is only approved for use in China, and the study was conducted on all Chinese patient population, that too a very small population, the study is limited in its generalizability. Also, only PFS was statistically significant in the study, and no statistically significant difference was observed in overall survival, further limiting its potential for future use in trials. Overall, a well written study with need for minor language and grammar polishing. But the overall utility of the study is questionable.

Response: We thank the Reviewer for the comments. We add the points you mentions in the limitations of this article and the manuscript was proofread.

Editorial comments

In general, do not use non-standard abbreviations, unless they appear at least two times in the text preceding the first usage/definition. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, and mAb, do not need to be defined and can be used directly.

The basic rules on abbreviations are provided here:

(1) Title: Abbreviations are not permitted. Please spell out any abbreviation in the title.

(2) Running title: Abbreviations are permitted. Also, please shorten the running title

to no more than 6 words.

(3) *Abstract: Abbreviations must be defined upon first appearance in the Abstract. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori).*

(4) *Key Words: Abbreviations must be defined upon first appearance in the Key Words.*

(5) *Core Tip: Abbreviations must be defined upon first appearance in the Core Tip. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)*

(6) *Main Text: Abbreviations must be defined upon first appearance in the Main Text. Example 1: Hepatocellular carcinoma (HCC). Example 2: Helicobacter pylori (H. pylori)*

(7) *Article Highlights: Abbreviations must be defined upon first appearance in the Article Highlights. Example 1: Hepatocellular carcinoma (HCC).*

Example 2: Helicobacter pylori (H. pylori)

(8) *Figures: Abbreviations are not allowed in the Figure title. For the Figure Legend text, abbreviations are allowed but must be defined upon first appearance in the text. Example 1: A: Hepatocellular carcinoma (HCC) biopsy sample; B: HCC-adjacent tissue sample. For any abbreviation that appears in the Figure itself but is not included in the Figure Legend textual description, it will be defined (separated by semicolons) at the end of the figure legend. Example 2: BMI: Body mass index; US: Ultrasound.*

(9) *Tables: Abbreviations are not allowed in the Table title. For the Table itself, please verify all abbreviations used in tables are defined (separated by semicolons) directly underneath the table. Example 1: BMI: Body mass index; US: Ultrasound.*

Response: The abbreviations were verified.

Science Editor

The authors report a multicenter randomized controlled trial of sequential chemotherapy and icotinib as first-line treatment for advanced EGFR mutant non-small cell lung cancer. The author's manuscript is well written and standardized. However, only PFS has significant difference, and other indicators do not. At the same time, icotinib is only approved for first-line use in China, and the recommendation of this article is limited. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.

Response: We thank the Scientific Editor. We agree that the generalizability of the results is limited, but we also believe that this study provides important data for the use of EGFR-TKIs in NSCLC. We revised the reference list.

Company Editor-in-Chief

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). 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. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: We thank the Editor-in-Chief for the comments. The title was shortened. We are providing the original figures in PowerPoint. We confirm that all figures are original.

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