Peer Review File

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Reviewer A

Comment 1: You describe three cases of a venous thrombo-embolic event in patients who had been treated with osimertinib. You note in your introduction that "whether osimertinib is a risk factor for VTE remains unclear." Yet your abstract mentions "three…patients who developed osimertinib-induced VTE," and in the discussion you note that "Thus, the patient was diagnosed with osimertinib-induced VTE." While a cause-and-effect relationship could exist, the conclusion that osimertinib induced these events may be overstated, and that a diagnosis recorded does not offer convincing and undisputable evidence of cause and effect. While the incidence may suggest that the drug could be a risk- or etiologic factor, as you mention elsewhere, it's causational role is not yet established beyond dispute. Interestingly, the fact that osimertinib could be continued without further VTE problems might provide some speculation that the VTE was coincidental.

The logic of your statement in the discussion, "it was difficult to explain VTE as Trousseau syndrome caused by lung cancer because all patients developed VTE during the osimertinib treatment..." is not apparent. If you selected the three osimertinib patients because they were on the drug and had VTE, why is it difficult to explain Trousseau? How many lung cancer patients were treated over a time when osimertinib was available, how many received the drug, and if in a large group of non-osimertinib patients none had VTE, this would be important.

Reply 1: We would like to thank the reviewer for this comment. We diagnosed VTE caused by osimertinib based on the clinical course. I have added the rationale for this. In addition, Wells score was not a risk assessment, but a score used for diagnosis. The risk assessment for VTE was Khorana score, so the text has been revised.

It is difficult to determine the incidence of VTE in lung cancer patients treated with other than osimertinib because there is no comprehensive database of patients who develop VTE.

Changes in the text: We have added the following sentence in the discussion section (page 10, line 3): It was difficult to explain VTE as Trousseau syndrome caused by lung cancer because all

patients developed VTE during disease control with osimertinib treatment. The risk of developing VTE when the disease is controlled is low (7). Additionally, the Khorana score, a risk factor for VTE, was one in all patients, indicative of a low-risk group (8). The cumulative probability of VTE after 6 months was low (3.8%) in the low-risk group.

Comment 2: Consider if formal statistics should be reported when only three data points are available. The individual data is presented, and the statistical information does not contribute.

Reply 2: We agree with this reviewer's comment. We have revised the manuscript to include the PFS and the OS of the individual data.

Changes in the text: We have added the following sentence in the discussion section (page 9, line 24): The PFS from VTE onset in each of the three cases was 11.4+ months, 7.7 months, and 6.1 months, respectively. The OS from VTE onset was 11.4+ months, 26.0 months, and 25.9+ months, respectively.

We have added the following sentence in the abstract section (page 5, line 13): The PFS from VTE onset in each of the three cases was 11.4+ months, 7.7 months, and 6.1 months, respectively. The OS from VTE onset was 11.4+ months, 26.0 months, and 25.9+ months, respectively.

Comment 3: You might emphasize and strengthen what you have stated, and to this reviewer seems most relevant, i.e., that regardless of whether or not osimertinib was a major contributing factor, continuation of the drug in the face of the adverse event is feasible and should be a consideration. Continuation may allow meaningful efficacious intervention in the face of a tumor with limited other treatment options, and where abandonment of a meaning treatment in the face of an adverse event must be balanced with the advantages of meaningful ongoing oncologic efficacy as we determine the optimal path for our patients.

Reply 3: We would like to thank you for the comment. Understanding the risk–benefit ratio of continuation of osimertinib with concomitant anticoagulation therapy is necessary for choosing the best treatment option. Although our three patients were successfully treated with osimertinib continuation and DOAC after the onset of VTE, understanding the risks and benefits of

osimertinib continuation with concomitant anticoagulation therapy is necessary to select the best treatment option.

Changes in the text: We have added the following sentence in the introduction section (page 11, line 13): There is only one report of successful retreatment with osimertinib after the development of osimertinib induced VTE (9). In addition, there are no reports of switching to other EGFR-TKIs after the onset of VTE. VTE is a serious complication that can be fatal, and we should be cautious about continuing treatment after the appearance of VTE. On the other hand, EGFR-TKI is a key drug in lung cancer treatment, and successful continuation leads to significant benefits. Understanding the risks and benefits of osimertinib continuation with concomitant anticoagulation therapy is necessary to select the best treatment option.

Reviewer B

Comment 1: What is the pathogenesis of VTE complications in patients treated with EGFR TKIs?

Reply 1: We would like to thank the reviewer for this comment. I have described the pathogenesis of VTE complications in patients treated with EGFR TKIs.

Changes in the text: We have added the following sentence in the introduction section (page 6, line 15): EGFR-TKIs are known to trigger platelet activation. This platelet activation may promote thrombus formation via platelet adhesion, aggregation, and release reaction (6).

Comment 2: What is the place of prophylaxis in patients with VTE risk factors who are eligible for EGFR TKI treatment?

Reply 2: We would like to thank the reviewer for this comment. There are ASCO guidelines for the prevention of VTE. I have described about the place of prophylaxis in patients with VTE risk factors.

Changes in the text: We have added the following sentence in the discussion section (page 11, line 3): There is an ASCO Clinical Practice Guideline for VTE prophylaxis (12). The guideline does not recommend routine anticoagulation for VTE prophylaxis in all cancer patients. However, pharmacologic thromboprophylaxis may be offered in high-risk cases such as hospitalized patients who have active malignancy and acute medical illness or reduced mobility, and high-risk

outpatients with cancer (Khorana score of 2 or higher). For example, apixaban therapy resulted in a significantly lower rate of venous thromboembolism than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy in the AVERT study (13).

Comment 3: What is the optimal treatment of VTE in patients treated with EGFR TKIs, taking into account other drugs in this group-is it recommended to temporarily stop EGFR TKIs?

Reply 3: We would like to thank the reviewer for this comment. I have described the optimal treatment of VTE in patients treated with EGFR TKIs.

Changes in the text: We have added the following sentence in the discussion section (page 11, line 13): There is only one report of successful retreatment with osimertinib after the development of osimertinib induced VTE (9). In addition, there are no reports of switching to other EGFR-TKIs after the onset of VTE. VTE is a serious complication that can be fatal, and we should be cautious about continuing treatment after the appearance of VTE. On the other hand, EGFR-TKI is a key drug in lung cancer treatment, and successful continuation leads to significant benefits. Understanding the risks and benefits of osimertinib continuation with concomitant anticoagulation therapy is necessary to select the best treatment option.

Also, we have added the following sentence in the discussion section (page 11, line 24):

This report supports the hypothesis that continuation of osimertinib with concomitant anticoagulation therapy may be a treatment option for patients with osimertinib-induced VTE.

Post-revision Review

Reviewer A

Comment 1: In the last sentence of the abstract, you note that "[i]n such cases, osimertinib treatment can be continued with direct oral anticoagulation therapy." Is this not over-stated? Consider noting that osimertinib was continued in these three cases, and continuing osimertinib should be a viable consideration when this adverse event is encountered. Is three cases really sufficient to state that osimertinib can be continued as you recommend?

Reply 1: We agree with this reviewer's comment. With only three cases, it is not possible to be certain that treatment can be safely continued. We have revised the text as follows.
Changes in the text: We have revised the following sentence in the abstract section (page 5, line 18): osimertinib treatment may be continued with direct oral anticoagulation therapy.

Line 22: cases rather than "case" ?

Reply 1: We agree with this reviewer's comment. We have revised the text as follows.
Changes in the text: We have revised the following sentence in the introduction section (page 6, line 22): We present the following three cases in accordance with the CARE reporting checklist.

Page 9, line23: consider "…were able to safely continue using osimertinib while undergoing concomitant anticoagulation therapy."

Reply 1: We agree with this reviewer's comment.
Changes in the text: We have revised the following sentence in the discussion section (page 9, line 15): …were able to safely continue using osimertinib while undergoing concomitant anticoagulation therapy.

Page 10, line 8: consider. "Thus, these patient were considered to have a VTE event that was attributable to osimertinib."

Reply 1: We agree with this reviewer's comment. The original sentence determined that osimertinib is the cause of VTE, which is inappropriate.
Changes in the text: We have revised the following sentence in the discussion section (page 10, line 1): Thus, these patients were considered to have a VTE event that was attributable to osimertinib.

At line 13 you note that "[t]hese findings indicate that osimertinib-induced VTE can occur…. This may overstate the causality of osimertinib. While this reviewer understands the possibility, or even the likelihood of causality, I again suggest that you not state that osimertinib-induced VTE is a certain entity. This is also implied at line 12 at page 11 and page 12, line 3-4, and line 5.

Reply 1: We agree with this reviewer's comment. It is not possible to determine that osimertinib is the cause of VTE. The phrase "osimertinib-induced VTE" is not appropriate.
Changes in the text: We have changed all the phrases "osimertinib-induced VTE" to "VTE during osimertinib" in the manuscript. The changes are on (page 5, line 5), (page 5, line 8), (page 6, line 19), (page 10, line 6), (page 11, line 5), (page 11, line 7), (page 11, line 20), and (page 11, line 22). We also checked for other places where osimertinib is definitively stated to be the cause of VTE. Nothing was found that needed to be changed.

Comment 2: The paper still needs a bit of cleaning up of language. There are a few small things that would improve the objectivity of the paper that have been noted for the authors. Some material might be moved, as, for example the paragraph at lines 12-20 of page 9.

Reply 2: We agree with this reviewer's comment. We asked an English editing service to improve our English usage again.
Changes in the text: Because "The authors are accountable ……office of this journal." was already listed in the FOOTNOTE, the sentence on page 12, lines 11-19 has been deleted.

Notwithstanding these facts, the paper has a message that is important, and therefore additional revision should be a consideration:

1) Patients with lung cancer being treated with osimertinib may be at higher risk for VTE, and VTE certainly does occur in this group of patients.

Reply 2: Thank you for your suggestion. We agree with this reviewer's comment.
I am afraid that the information is already on (page 10, line 16-19) and (page 11, line 24 – page 12, line 1). The contents are as shown in " At our hospital, three of 95 patients (3.2%) developed VTE …. higher risk of developing VTE in the real world and this should be considered in clinical practice." and " Osimertinib may cause VTE and should be used with caution." , respectively. These sentences are highlighted in blue.

2) Patients who are responding to osimertinib may not need to have the drug discontinued, as treatment has been continued in a small group of patients (3) while on anticoagulation, despite the occurrence of VTE.

Reply 2: Thank you for your suggestion. We agree with this reviewer's comment.
I am afraid that the information is already on (page 11, line 18-21), and (page 12, line 1-2). The contents are shown as " This report supports the hypothesis that continuation of osimertinib with concomitant anticoagulation therapy may be a treatment option for patients with VTE during osimertinib." and " In such cases, the patient may continue treatment using concomitant anticoagulation therapy.", respectively. These sentences are highlighted in blue.

3) This finding allows the oncologist to better weigh risks and benefits in a new light in view of this observation.

Reply 2: Thank you for your suggestion. This is very important content.
Changes in the text: We have added the following sentence in the discussion section (page 12, line 2-3): This finding allows the oncologist to better weigh risks and benefits in a new light in view of this observation.