

## Peer Review File

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### **Reviewer A**

**Comment 1:** As all patients also received carboplatin (which also causes CIPN) in addition to paclitaxel, carboplatin needs to be added to the manuscript title.

**Reply:** We thank the reviewer for the helpful suggestions. We have modified title as advised (see Page 1, line 2).

**Changes in the text:** We have changed the title as “A randomized trial to evaluate the preventive effect of lafutidine on chemotherapy-induced peripheral neuropathy in patients treated with carboplatin and paclitaxel for lung cancer”.

**Comment 2:** The fact that all patients received carboplatin in addition to paclitaxel needs to be stated in the Abstract.

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (see Page 2, line 31).

**Changes in the text:** Patients were randomly assigned (1:1) to carboplatin and paclitaxel chemotherapy with lafutidine 10 mg twice daily (lafutidine group) or without lafutidine (control group).

**Comment 3:** For the key findings statement, suggest adding the words, ‘in this underpowered study’ to the end of the statement.

**Reply:** We appreciate the reviewer’s suggestions. We have modified our text as advised (see Page 3, line 58, Highlight Box)

**Changes in the text:** No significant preventive effect of lafutidine on CIPN was observed in this underpowered study.

**Comment 4:** P3, line 86. Replace ‘systemic’ by ‘systematic’

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (see Page 4, line 84).

**Changes in the text:** The frequency of CIPN has been reported in several publications: a systematic systematic review and meta-analysis of 31 trials and 4,179 patients reported that 68.1% of patients developed CIPN within 1 month after completion of chemotherapy (5).

**Comment 5:** P3, line 98, add the fact that patients also received carboplatin.

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (see Page 4, line 96).

**Changes in the text:** The purpose of this study was to assess the prophylactic effect of lafutidine on CIPN during chemotherapy with carboplatin and tri-weekly PTX.

**Comment 6:** P3, line 111. ....administered to all patients....

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (see Page 5, line 110).

**Changes in the text:** In this study, paclitaxel was administered to **all** patients in a single dose so as to make it easier to evaluate the effect of lafutidine.

**Comment 7:** P5, line 219. Replace 'could be expected to' by 'may'

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (see Page 9, line 218-219).

**Changes in the text:** According to the results of the FACT/GOG-Ntx in our study, administration of lafutidine **may** ~~could be expected~~ have some effect in preventing CIPN, but this effect could not be proven statistically.

**Comment 8:** P5, line 234. ....in the control group but this did not reach statistical significance possibly due to the study being underpowered as only 16 patients of the planned for 40 patients were recruited.

**Reply:** We thank the reviewer for these insightful comments. We have modified our text as advised. Considering the composition of the text and reviewer B's comments, the following text was added and revised (See Page 9, line 236-242).

**Changes in the text:** On the other hand, FACT/GOG-Ntx tended to show less peripheral neuropathy in the lafutidine group than in the control group **but this did not reach statistical significance possibly due to the study being underpowered as only 16 patients of the planned for 40 patients were recruited. Since the FACT/GOG-Ntx questions were more relevant to daily life than the CTCAE and PNQ questions, it is possible that the FACT/GOG-Ntx scores were more likely to reflect severity of peripheral neuropathy.**

**Comment 9:** The number randomized should be 16, not 18.

**Reply:** We thank the reviewer for the careful review. We have modified Figure 1. as advised.

**Changes in the text:** The number of randomized patients was changed from 18 to 16.

**Comment 10:** Add the SD error bars to this figure. Also add a phrase to the legend addressing the point that the study was underpowered with recruitment of only 16 of the planned for 40 patients.

**Reply:** We appreciate these helpful suggestions. We have modified Figure 2. The fact that the target number of eligible patients was not reached is noted several times in the Results and Discussion section of the text. (See Figure 2. and Page 16, line 428).

**Changes in the text:** The lafutidine group is shown by the blue line. The control group had higher median scores of FACT/GOG-Ntx than the lafutidine group after cycle 4. There was no significant difference in the scores between the two groups **during the entire period.**

**Comment 11:** Add information to the legend to state that all patients received

carboplatin in addition to paclitaxel.

**Reply:** We thank the reviewer for the careful review. We have modified our text as advised (See Page 16, line 442-443).

**Changes in the text:** All patients received carboplatin in addition to paclitaxel.

## **Reviewer B**

**Comment 1:** The authors tend to emphasize the data which numerically favored the study drug and thus make the claim that the study drug looked promising. There are a number of items that numerically favored the control arm. This includes the data presented in table 2, whereby 100% of the patients had greater than grade 2 neuropathy in the treatment group versus 71% in the control group.

**Reply:** We thank the reviewer for these insightful comments. We agree that we have overemphasized the positive aspects of this study. We have modified our text as advised (See Page 9, line 233-234 and line 236-242).

**Changes in the text:**

Rather, grade 2 or higher peripheral sensory neuropathy in CTCAE was more common in the lafutidine group than in the control group.

Since the FACT/GOG-Ntx questions were more relevant to daily life than the CTCAE and PNQ questions, it is possible that the FACT/GOG-Ntx scores were more likely to reflect severity of peripheral neuropathy. This may be due to the fact that the questions asked in the FACT/GOG-Ntx are more relevant to daily life than those in the CTCAE or PNQ. It could be implicitly suggested that lafutidine has a potentially positive effect on CIPN.

**Comment 2:** The lack of a placebo is a major confounding issue in this study. This could be stated more forcefully, in the manuscript.

**Reply:** We thank the reviewer for the helpful suggestions. We agree that the lack of placebo was a major limitation. We have modified our text (See Page 9-10, line 246-248).

**Changes in the text:** The study did not use placebo and was not blinded in the assessment of peripheral neuropathy. The lack of placebo may have influenced the assessment of peripheral neuropathy.

**Comment 3:** The following statement is confusing to this reviewer: “Because one of the anti-ulcer drugs, lafutidine, was scheduled to be administered as the study drug, the other anti-ulcer drug was changed to lafutidine.”

**Reply:** We thank the reviewer for the careful review. We modified the text (See Page 5, line 118-121).

**Changes in the text:** If patients assigned to the lafutidine group were taking other anti-ulcer drugs, they were switched to lafutidine.

**Comment 4:** The references provided to support that the study drug was beneficial contain a variety of reports some of which looked at the prevention of neuropathy while others of them looked at treatment of established neuropathy. These are likely to be different things and it is unlikely that one drug would affect both processes.

**Reply:** We appreciate the opportunity to clarify this point. Some of our references describe the potential of lafutidine to relieve CIPN symptoms and the mechanism. But there are no prospective studies concerning the preventive effect of lafutidine on CIPN. Thus, we assess the preventive effect of lafutidine on CIPN.

**Changes in the text:** None.

**Comment 5:** I do not think that the manuscript data support the following statement that the authors made: “A larger, multicenter, prospective, blinded study of CIPN prevention is warranted.”

**Reply:** We thank the reviewer for these insightful comments. We agree that our results do not lead directly to that idea. I hope to see further development of research for the prevention of CIPN. We have changed the text to that emphasize the need for research for the prevention of CIPN (See Page 10, line 262-264 and Page 2, line 51-52).

**Changes in the text:** CIPN has a significant impact on the quality of life and treatment efficacy of patients receiving chemotherapy, and more reliable studies using lafutidine on the prevention of CIPN should be conducted. ~~A large, multicenter, blinded, prospective study of CIPN prevention is warranted.~~

**Comment 6:** The following statement, from the title page, seems hard to believe: “These authors contributed equally to this work.”

**Reply:** Though all members worked together on this study, we agree that we did not divide the workload equally. So, we have deleted the relevant sentence (See Page 1, line 19).

**Changes in the text:** We have deleted the sentence.