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Reviewer A

It cannot be said that nab-paclitaxl is less toxic than paclitaxel except for allergies. In addition, there is no data showing superiority in comparison with paclitaxel. A randomized phase II trial of nab-paclitaxel + ramucirumab and paclitaxel + ramucirumab for peritoneal dissemination cases was reported at last year's scientific meeting, but nab-paclitaxel did not show efficacy (P-SELECT study).
Oxaliplatin is neurotoxic. Also, the background should show the S-1+oxaliplatin data, not the S-1 and CDDP data.
Describe how you would consider the next trial given how effective S-1+LBP+nab-paclitaxel regimen was.
Response: Thank you for your comment. Indeed, nab-paclitaxl is less toxic than paclitaxel except for allergies. Albumin-bound paclitaxel which is using human blood albumin as a carrier, it does not require co-solvents such as polyethylene castor oil, so hormone pretreatment is not required during infusion, and to a certain extent, allergies and other problems caused by co-solvents can be avoided (1. Gardner et al. Clin Cancer Res. 2008;14(13):4200-4205; 2. Desai et al. Clin Cancer Res. 2006;12:1317-1324.). Here, given the convenience of such a mode of administration, we used albumin paclitaxel instead of paclitaxel in this study. In addition, in a randomized phase II trial of nab-paclitaxel + ramucirumab and paclitaxel + ramucirumab for cases of peritoneal dissemination, but nab-paclitaxel did not show efficacy (P-SELECT study). However, there are no reports about the efficacy of nab-paclitaxel in neoadjuvant chemotherapy for patients with locally advanced gastric cancer. In the P-SELECT study, researchers focused more on the first-line treatment of unresectable advanced or recurrent gastric cancer peritoneal dissemination refractory. In this study we focused more on the utility of nab-paclitaxel in the neoadjuvant setting for patients with locally advanced gastric cancer.

Indeed, oxaliplatin has some neurotoxicity. The description in line 117 of the manuscript that oxaliplatin has no neurotoxicity is a clerical error, and we have made modifications in the corresponding positions. We modified the background section which describing S-1 and CDDP to show S-1+oxaliplatin data in line 124-137.

It is known that SOX regimen (oxaliplatin + S-1) is mostly used for perioperative or postoperative maintenance treatment of gastric cancer, which can significantly improve prognosis and improve OS（Koizumi W, etl. Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). Ann Oncol. 2010 May;21(5):1001-5）. Paclitaxel can be used for the comprehensive treatment of unresectable locally advanced gastric cancer (Lu Z, etl. A multicenter, randomized trial comparing efficacy and safety of paclitaxel/capecitabine and cisplatin/capecitabine in advanced gastric cancer. Gastric Cancer. 2018 Sep;21(5):782-791). However, there are no reported data on albumin-bound paclitaxel combined with oxaliplatin and Tegafur in combination with neoadjuvant chemotherapy for locally advanced gastric cancer. In this study, we sought to investigate the safety of nab-

paclitaxel combined with SOX regimen in the neoadjuvant therapy for patients with locally advanced gastric cancer. On this basis, further studies will focus on the effectiveness of the present study protocol in the neoadjuvant chemotherapy, thereby allowing this subset of patients to lower their tumor stage, achieve optimal tumor shrinkage, and strive for the opportunity of surgical resection, and then improve their prognosis.

Reviewer B

This is an interesting protocol paper about combined chemotherapy with poor information. This study is well planned about main indicators, research endpoints and statistical analysis program. However, I have some comment on the following issues.

Comments

1. What is setting basis about dosage regimen and sample size? You might be better to describe setting basis in the methods.

Response: Thank you for your comment. It is known that SOX regimen (oxaliplatin + S-1) is mostly used for perioperative or postoperative maintenance treatment of gastric cancer, which can significantly improve prognosis and improve OS（Koizumi W, etl. Phase II study of oxaliplatin plus S-1 as first-line treatment for advanced gastric cancer (G-SOX study). Ann Oncol. 2010 May;21(5):1001-5）. Paclitaxel can be used for the comprehensive treatment of unresectable locally advanced gastric cancer (Lu Z, etl. A multicenter, randomized trial comparing efficacy and safety of paclitaxel/capecitabine and cisplatin/capecitabine in advanced gastric cancer. Gastric Cancer. 2018 Sep;21(5):782-791). However, there are no reported data on albumin-bound paclitaxel combined with oxaliplatin and Tegafur in combination with neoadjuvant chemotherapy for locally advanced gastric cancer. In this study, we sought to investigate the safety of nab-paclitaxel combined with SOX regimen in the neoadjuvant therapy for patients with locally advanced gastric cancer. On this basis, further studies will focus on the effectiveness of the present study protocol in the neoadjuvant chemotherapy, thereby allowing this subset of patients to lower their tumor stage, achieve optimal tumor shrinkage, and strive for the opportunity of surgical resection, and then improve their prognosis.

Considering that albumin-bound paclitaxel uses human blood albumin as a carrier and does not require co-solvents such as polyethylene castor oil, it does not require hormone pretreatment during infusion, and to a certain extent, it can avoid allergies and other problems caused by co-solvents, and the safety is better. Moreover, oxaliplatin in combination with S-1 is a common regimen for perioperative or postoperative maintenance therapy of gastric cancer, so we do not expect that the combination of three drugs will have particularly serious safety problems, so it is not necessary to set a large sample size to observe the safety of this regimen. Therefore, we designed small exploratory studies to first observe the safety of this protocol. Also taking into account financial reasons, we set the sample size to 10.

2. I think that patient background between the study group and the control group will be different. You might be better to match those patient background.

Response: Thank you very much for your suggestions. Indeed, the background of the patients in study and control group in this study were different. We also find that the creation of the

control group is not mandatory based on the research objectives of the present study. Therefore, we modified it in line 227-233 accordingly and no longer set up the control group.

3. Aren't phase I and II trials needed to scientifically assess the safety and efficacy of nab-paclitaxel combined with oxaliplatin and tegafur?
Response: Thank you very much for your comment. We believe that phase I and II trials are needed to scientifically evaluate the safety and efficacy of Nab-paclitaxel in combination with oxaliplatin and tegafur. In this study, we aimed to validate the safety of the albumin paclitaxel combined with Sox regimen in the neoadjuvant setting for patients with locally advanced gastric cancer using a small sample of patients, and lay a foundation for subsequent evaluation of the efficacy of this regimen.

4. There is phase 1 study of combined chemotherapy of nab-paclitaxel, S-1, and oxaliplatin for gastric cancer (References 28). Please refer to this study to determine a superior protocol.
Response: Thank you for being so meticulous in giving meaningful advice on our research. In the NSOX Study (References 28), researchers work to improve the antitumor efficacy for gastric cancer patients with peritoneal metastasis. In our study, we focused more on neoadjuvant chemotherapy for locally advanced gastric cancer. The purpose is to reduce the stage of the tumor, achieve the best tumor shrinkage effect, win the opportunity for surgery for patients, and improve the prognosis. By observing the safety and efficacy of patients using this regimen, we can explore whether there is a greater benefit for patients. Therefore, our research also holds promise to solve clinical problems.

Reviewer C

The authors proposed a prospective clinical trial to test nab-paclitaxel in association with oxaliplatin and tegafur in advanced gastric cancer.

My comments are the following:
- MSI patients should be excluded.
Response: Thank you for very valuable comments. We have revised the manuscript in the corresponding section and exclude MSI patients in line 196.

- There is no sample size calculation.
Response: Thank you very much for your comment. Considering that albumin-bound paclitaxel does not require co-solvents such as polyethylene castor oil, it does not require hormone pretreatment during infusion, and to a certain extent, it can avoid allergies and other problems caused by co-solvents, so the safety is better. Meanwhile, SOX regimen is a common regimen for perioperative or postoperative maintenance therapy of gastric cancer, the combination of three drugs probably has no particularly serious safety concerns, so it is not necessary to set a large sample size to observe the safety of this regimen. Here, we designed small exploratory studies to first observe the safety of this protocol. Taking into account financial reasons, we set the sample size to 10.

- A phase I study could be more appropriate
Response: Thank you very much for your comment. It is appropriate for a phase I study.

- The control group is not mandatory.
Response: Thank you very much for your suggestions. We also think that the creation of the control group is not mandatory based on the research objectives of the present study. Therefore, we modified it in line 227-233 accordingly and no longer set up the control group.

- we found several spelling errors (eg. randomization on line 246.)
Response: Thank you very much for your comment. We have already made corresponding modification of the spelling errors in the corresponding section of the manuscript on line 263.

Reviewer D

The authors describe a clinical trial protocol to study perioperative nab-paclitaxel, oxaliplatin, and tegafur. They describe the therapies and their rationale for this perioperative treatment in patients. The trial has not begun; instead this is a description of the protocol.
My main feedback surrounds the endpoints of the trial. The authors need to define what their primary and secondary endpoints are going to be. What are the historical standards that will be used for comparison to determine that their experimental therapy is worthy of further study or use in the clinical setting? It is an interesting concept, but I wonder how it will be better than current standard of care FLOT, which could be the hypothesis, but it needs to be clarified.
Response: Thank you very much for your comment. The main purpose of this study is to preliminarily investigate the safety of albumin-bound paclitaxel combined with oxaliplatin and Tegafur for neoadjuvant chemotherapy for locally advanced gastric cancer. Therefore, the primary endpoint was the occurrence of adverse events, and if no adverse events occurred, treatment was continued until the end of the course. Since SOX regimen (oxaliplatin + S-1) is mostly used for perioperative or postoperative maintenance treatment of gastric cancer and nab-paclitaxel can avoid allergies and other problems, it is expected that the combination of three drugs will not have particularly serious safety problems. Therefore, the creation of the control group is not mandatory based on the research objectives of the present study. Considering this, we think that it is more appropriate to not set the control group in this study. There after, we made the modifications in the corresponding positions of the manuscript in line 227-233.

Minor comments:
Line 111: Oxaliplatin does have significant neurotoxicity actually.
Response: Thank you very much for your comment. We think that oxaliplatin has neurotoxicity. The description in line 113 of the manuscript that oxaliplatin has no neurotoxicity is a clerical error, and we have made modifications in the corresponding positions in line 117.

Line 204: Preoperative adjuvant chemotherapy is contradictory. I think the authors mean neoadjuvant since they describe 3 cycles of chemotherapy, surgery, and 6 cycles of adjuvant therapy.

Response: Thank you very much for your comment. We mean neoadjuvant treatment of advanced gastric cancer. We made the corresponding modification in the manuscript.

Line 218: Advanced gastric cancer is a different population from what the authors are trying to study, I believe. I think they are studying perioperative therapy in localized gastric cancer.
Response: Thank you very much for your comment. We are studying neoadjuvant therapy in advanced localized gastric cancer in this trial.