Sep 03, 2019

Prof. Dr. Monjur Ahmed, Rosa M Jimenez Rodriguez, Pashtoon Murtaza Kasi

Editors-in-Chief, *World Journal of Gastrointestinal Oncology*

Thank you for the comprehensive review of the manuscript.

All authors have agreed to accept all the revisions which have been revised by editorial staff. We reviewed carefully again and revised the manuscript. All authors have read and approved the revised manuscript.

We thank you again for the careful review of our paper for publication in *World Journal of Gastrointestinal Oncology*. We look forward hearing from the editorial staff.

Sincerely yours,

Se Jun Park / MyunAh Lee, MD, PhD

Reviewer #1: Reviewer's code: 03706560

Reviewer #1: I read the manuscript "Oral chemotherapy for second-line treatment in patients with gemcitabine-refractory advanced pancreatic cancer with interesting. This is a well-written retrospective analysis and I have made some comments to improve the manuscript.

Comment 1: Introduction: The information is good. However, need some minor English review.

Response 1: Thank you for your very supportive comments. I received an English editing service for this manuscript and submit the certificate of English editing. However, I totally agree with that an English review is required for the introduction section. The article has been edited by a native language English speaker again.

Comment 2: Methods: Well done. Unfortunately, the number of included patients is very small. If it is possible, would be great to include more patients from other institutions and made a multicenter retrospective study.

Response 2: As reviewers have mentioned, the small sample size in our analysis is the major limitation of our study. There are several reasons for small sample size. First of all, capecitabine and S-1 were not used in Korea for patients with pancreatic cancer before 2011, so we enrolled patients who diagnosed after 2011. Second, among patients with pancreatic cancer who received as front line gemcitabine based treatment, patients with good performance status were treated with FOLFINOX or 5-FU/leucovorin+nanoliposomal irinotecan, and many patients received best supportive care due to their poor performance status. Third, many patients were unable to take oral medication due to carcinomatosis peritonei or gastric outlet obstruction.

This study can act as a pilot study to propose multicenter, prospective study to compare capecitabine and S-1 for gemcitabine-refractory pancreatic cancer. We are

planning to carry on follow-up study for confirmation of our study results with larger sample size.

The manuscript is revised as follows;

In conclusion, this is the first retrospective study to compare the efficacy and safety of capecitabine and S-1 as second-line therapy in patients with gemcitabine-refractory pancreatic cancer. Although the retrospective nature of the study and the small number of patients are major limitations, capecitabine and S-1 showed similar efficacy and safety for patients with gemcitabine treatment failure. However, HFS was significantly more common in the capecitabine group. **This study can act as a pilot study for initiation of a large sample, multicenter study.** To confirm our preliminary results, we need a randomized study to compare the efficacy of capecitabine and S-1 for gemcitabine-refractory pancreatic cancer patients with poor PS.

Comment 3: Results: The results showed similar efficacy. However, the capecitabine group had significant more hand-foot syndrome than S-1 group. If the author's need to recommend one treatment. Which one they will recommend? Please include this in the discussion.

Response 3: Thank you for your thoughtful review. Hand-foot syndrome (HFS) is significantly less common with oral 5-FU prodrugs containing dihydropyrimidine dehydrogenase inhibitors, such as uracil/tegafur or S-1 than with capecitabine. HFS is a common dose-limiting toxicity of capecitabine, which can occur in up to 53% of patients. Although, HFS is not life threatening, it can significantly impair a patient's daily activity and decrease their quality of life. Therefore, S-1 could be beneficial for patients with intolerable HFS while on capecitabine treatment.

The manuscript is revised as follows;

In the current study, capecitabine and S-1 showed similar response rates, that were not significantly different from those reported in previous studies. Also, there was

no statistically significant difference in median OS. The safety profile for both regimens was consistent with those reported previously[7,9]. **Prior clinical studies have suggested that 5-FU prodrugs containing dihydropyrimidine dehydrogenase inhibitors such as S-1 or uracil/tegafur can reduce the incidence of HFS[17]. In this study, HFS was significantly less common in the S-1 group than in the capecitabine group, consistent with previous studies[18, 19]. Although HFS is not life-threatening, it can significantly impair a patient's daily activities and decrease their quality of life. Therefore, S-1 could be beneficial for patients who experience intolerable HFS while on capecitabine treatment.**

Comment 4: Discussion: Author's should discuss their limitations in detail, such as retrospective design and small number of patients.

Response 4: I totally agree with your opinion. I wrote the several limitations of this study in the discussion section.
The manuscript is revised as follows;

Our study has some limitations, the first being the non-randomized, retrospective nature of evaluation. The small sample size from a single-center study is another limitation. Third, patients in the capecitabine group generally underwent response evaluation every 9 weeks, while those in the S-1 group were evaluated for response at various intervals (every 6 or 12 weeks). In addition, the proportion of patients in whom response was evaluated earlier than scheduled was higher in the capecitabine group than in the S-1 group; results for PFS may therefore not be comparable due to this different timing.

In conclusion, this is the first retrospective study to compare the efficacy and safety of capecitabine and S-1 as second-line therapy in patients with gemcitabine-refractory pancreatic cancer.

Comment 5: Conclusion: Well done. I think the higher number of hand-foot syndrome in the capecitabine group should be included in the conclusion.

Resopnse 5: Thank you for your thoughtful review. As I mentioned above, I added to the discussion section about the difference in HFS incidence between capecitabine and S-1. In conclusion, the difference in incidence of HFS is briefly described.
The manuscript is revised as follows;

In conclusion, this is the first retrospective study to compare the efficacy and safety of capecitabine and S-1 as second-line therapy in patients with gemcitabine-refractory pancreatic cancer. Although the retrospective nature of the study and the small number of patients are major limitations, capecitabine and S-1 showed similar efficacy and safety for patients with gemcitabine treatment failure. **However, HFS was significantly more common in the capecitabine group. This study can act as a pilot study for initiation of a large sample, multicenter study.** To confirm our preliminary results, we need a randomized study to compare the efficacy of capecitabine and S-1 for gemcitabine-refractory pancreatic cancer patients with poor PS.

Reviewer #2: Reviewer's code: 02445626

Comment 1: In the introduction section, the authors states that "To date, there is no standard guideline for second-line treatment of gemcitabine-refractory pancreatic cancer patients with poor performance status". Can they provide a reference to support this statement since this is a key background for the study?

Response 1: We really appreciate this advice. For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable as second-line options. Clinical trials that have performed as second-line therapy after gemcitabine based chemotherapy in patients with pancreatic cancer were only enrolled patients with good performance status (FOLFIRINOX; ECOG 0-1, 5-FU/leucovorin+nanoliposomal irinotecan;

Karnofsky PS 70 or more). Additionally, 5-FU combination regimens are not recommended for patients with pancreatic cancer with older age or with poor performance status due to frequent hematological toxicity. Therefore, according to the NCCN (National Comprehensive Cancer Network) guidelines, best supportive care or single agent chemotherapy may be considered for patients with pancreatic cancer with poor performance status.
The manuscript is revised as follows;

As a second-line treatment after progressive disease following gemcitabine-based chemotherapy, the 5-FU/leucovorin+nanoliposomal irinotecan treatment showed promising clinical outcomes in the NAPOLI-1 trial; however, it is considered only for patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1, due to treatment-related toxicity[5,6]. **To date, treatment with fluoropyrimidine-based combination regimens in gemcitabine-refractory pancreatic cancer patients with poor PS, is controversial.**

Capecitabine, a prodrug of 5-FU, is one of the options as a second-line agent after gemcitabine failure in patients with pancreatic cancer and poor PS[7].

Comment 2: Also for "Capecitabine, a prodrug of 5-FU, is one of the most commonly used second-line agents after gemcitabine failure."?

Response 2: Thank you for the careful review. For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are recommended as second-line options. According to the NAPOLI-1 phase III trial, 5-FU/leucovorin+nanoliposomal irinotecan showed better median OS than 5-FU/leucovorin in pancreatic cancer with good performance status (Karnofsky PS 70 or more). Another second-line treatment option in patients with good performance status (ECOG 0-1) and locally or metastatic pancreatic cancer is FOLFIRINOX/modified FOLFININOX. Therefore, the sentence "Capecitabine is one of the most commonly used second-line agents after gemcitabine failure" is a

misconception. However, 5-FU/leucovorin+nanoliposomal irinotecan or FOLFIRINOX can be used in patients with good performance status only. Results from the AIO-PK0104 trial, capecitabine showed that relatively good efficacy after progression on gemcitabine/erlortinib in patients with advanced pancreatic cancer. Thus, capecitabine could be an another option after gemcitabine failure in patients with advanced pancreatic cancer and poor performance status.

The manuscript is revised as follows;

As a second-line treatment after progressive disease following gemcitabine-based chemotherapy, the 5-FU/leucovorin+nanoliposomal irinotecan treatment showed promising clinical outcomes in the NAPOLI-1 trial; however, it is considered only for patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1, due to treatment-related toxicity[5,6]. **To date, treatment with fluoropyrimidine-based combination regimens in gemcitabine-refractory pancreatic cancer patients with poor PS, is controversial.**

Capecitabine, a prodrug of 5-FU, is one of the options as a second-line agent after gemcitabine failure in patients with pancreatic cancer and poor PS[7]. Capecitabine has shown a relatively good response as a first-line treatment in patients with metastatic pancreatic cancer, with a response rate of 24%[7,8].

Comment 3: "S-1 is an another oral drug that is a combination of….". Since S-1 is a group of drugs, it cannot be called an…drug.

Response 3: I totally agree with your opinion. Since S-1 is a combination of three drugs, calling it "an drug" is incorrect.
The manuscript is revised as follows;

S-1 is a fourth-generation oral fluoropyrimidine that combines tegafur (5-FU prodrug) with two modulators, 5-chloro-2,4-dihydroxypyridine (gimeracil) and potassium oxonate (oteracil) in a molar ratio of 1:0.4:1. According to some randomized studies, S-1 as second-line chemotherapy in gemcitabine-pretreated

advanced pancreatic cancer showed a relatively high disease control rate, and was well tolerated with acceptable toxicity[9,10].

Comment 4: The characteristic of patients have been summarized in Table 1, the authors do not need to explain the information in context.

Response 4: We really agree with this advice. The information mentioned in the table has been removed from the text. Only those factors that may affect the outcome are briefly mentioned in context.

The manuscript is revised as follows;

Patient baseline characteristics in the two groups were well balanced (Table 1). Median age was 61 years (range 39-77 years) in the capecitabine group and 63 years in the S-1 group (range 41-78 years). **Nearly one-quarter of the patients in both groups exhibited ECOG PS 2. Although not statistically significant, the capecitabine group had more patients with lesions that were initially unresectable compared with the S-1 group. (56% vs 35%, respectively, p=0.057).** As first-line chemotherapy, gemcitabine plus erlotinib was given to most patients in the capecitabine group (76%), and gemcitabine plus nab-paclitaxel was given to most patients in the S-1 group (60%). Overall, 1 (2%) of 41 patients in the capecitabine group and 4 (10%) of 40 patients in the S-1 group had received two or more previous lines of therapy.

Comment 5: The discussion section should be re-written. The discussion of "immune checkpoint inhibitors" and "molecular targeting drugs." appears to be too abrupt without linking contexts. Some discussions are not closely related to the study. The authors should focus on discussing the reasons and mechanisms regarding differences in the efficacy and toxicities of capecitabine and S-1.

Response 5: Thank you for the thoughtful review. I totally agree with your opinion that the comments for the immune checkpoint inhibitors and the molecular targeting drugs has appeared suddenly without linking contexts. I wanted to say that we should consider less toxic treatment in pancreatic cancer patients with poor performance status. There are limited treatment options for patients with poor performance status who previously treated with gemcitabine-based chemotherapy. Immune checkpointinhibitors such as, pembrolizumab, showed clinical benefit in tumors with mismatch repair deficiency. Thus, it might be helpful to identify dMMR status in patients who had limited treatment options.

The manuscript is revised as follows;

Assessment of a patient's symptom burdens, PS, and associated comorbidities are important considerations in selecting the most appropriate chemotherapy. Therefore, for elderly patients or those with a poor PS, chemotherapy regimens with less toxicity should be considered.

Immune checkpoint inhibitors are also known to be less toxic and can be used in such patients. As a single agent, immune checkpoint inhibitors have shown limited response in patients with pancreatic cancer[12-14]. However, immune checkpoint inhibitors such as pembrolizumab may be effective in tumors, including pancreatic cancer, with mismatch repair deficiency (dMMR) or high microsatellite instability (MSI)[15,16]. Hence, there is a need to identify dMMR or MSI status in patients with pancreatic cancer and poor PS after gemcitabine failure, to confirm whether the immune checkpoint inhibitor will be effective. However, immune checkpoint inhibitors are limited because they can be used only in a few selected patients.

Oral fluoropyrimidine treatment, such as capecitabine or S-1, can be a second-line treatment option for patients with poor PS or those who are elderly, due to less severe hematologic or non-hematologic adverse events compared with intravenous cytotoxic agents[7,9].