Peer Review File

Article Information: https://dx.doi.org/10.21037/jgo-21-202

Reviewer A

I greatly appreciate the effort involved in conducting a study of this type and the scientific value on such an important issue as the efficacy and safety of the first-line treatment regimens in patients with mPC.

In this retrospective and a single-institution study, a total of 363 patients were included for over an 8-year period. Seventy-four percent were treated with FFX and 26%-with GN.

The efficacy data show a median OS of 11.3 months (95% CI 10.7 - 12.9) in the FFX group vs 7.0 months (95% CI 6.0 - 8.7) in the GN group ($p < 0.001$). Treatment was discontinued due to chemotherapy toxicity in 26 (10%) and in 14 (15%) between the FFX and the GN cohorts, respectively ($p = 0.275$).

Comments:

1. The functional situation of the patients, measured by the ECOG-PS, is one of the determining parameters in the selection of patients for chemotherapy treatments. In your document there is no reference to the ECOG of the patients. Can you provide this information? Do you consider that only this parameter can explain that 67 patients in the group <76 years old have been treated with GN and not with FFX? Do you have institutionally defined selection criteria for the first-line treatment in mPC?

Reply 1: Thank you for this comment. We performed a manual review of documentation within the electronic medical records at Yale New Haven Hospital and it affiliated care centers. We discovered inconsistent or absent documentation of the initial visit or pretreatment ECOG performance status, thus we cannot provide this information. We cannot conclude that the ECOG performance status is the only parameter to explain why 67 patients younger than 76 were treated with GN and not FFX; rather it is likely a multifactorial decision made by the individual oncologist. We do not have an institution selection criterion for the first line treatment of mPC to choose between FFX or GN; each of these regimens is permitted to be used and it is up to the individual treating oncologist.

Changes in the text: None

2. The efficacy data are similar to those, presented in previous series; however, they correspond to a scheme that has already been modified from the beginning in all patients, who received FFX and in a significant number of patients, treated with GN. Could you make any reference to this, bearing in mind that large retrospective series based their studies on the original schemes even though they later specified the subsequent reductions? Do you think this may be a limitation in the interpretation of the results?

Reply 2: We did find that both FFX and GN had initial and subsequent dose modifications, with a greater initial dose modification with FFX. We cited in reference 18 (line 385) a phase II study showing similar efficacy of dose reduced (modified) FFX compared to standard dose FFX, so we do not think there was a great limitation in survival outcomes with patients treated with modified FFX.

Changes in the text: None

3. Were there any fatal adverse events, associated with the treatments? What were the causes of death of the patients?

Reply 3: We did not discover any fatal adverse event linked to FFX or GN in our manual review of the literature.

Changes in the text: None

Changes in the text: None

4. Bibliographic reference No. 12 (line 369) is not complete.

Reply 4: Thank you for catching this. We have made this edit on line 367.

Thank you again for the effort you have made to enrich the information related to this topic.

Reviewer B

It was a pleasure to read the paper entitled " Clinical Outcomes of First Line FOLFIRINOX versus Gemcitabine plus Nab – Paclitaxel in Metastatic Pancreatic Cancer at the Yale Smilow Hospital System". Timil Patel and colleagues report the results of their retrospective study investigating the comparison between FOLFIRINOX and Gemcitabine + nab-paclitaxel in metastatic pancreatic cancer.

Comment 1. The large difference in the number of patients in the two groups is considered to be one of the limitations. Is there any strategy to overcome this?

Reply 1: Despite the difference in the number of patients between the two groups, we still had large numbers in both groups to detect a statistical difference in survival between the two groups. Given the retrospective nature of this study, we cannot overcome the difference in how many were treated in either arm, we reported what we found in our manual review.

Change in the text: None

Comment 2. The difference in age distribution would be a important factors on survival outcome. Is there any strategy to adjust this imblance? Although the authors showed OS outcomes stratified by 76, youger patients could still be included in FFX group. And perfomance status of patients (eg. ECOG-PS or Karnofsky PS) can be a factor that affects survival, has this been investigated?

Reply 2: We acknowledged in our paper that one limitation of study was the age difference between the two treatment arms. In a retrospective study, finding case controls for each arm is not feasible. We performed a manual review of documentation within the electronic medical records at Yale New Haven Hospital and it affiliated care centers. We discovered inconsistent or absent documentation of the initial visit or pretreatment ECOG performance status, thus we cannot provide this information.

Change in the text: None

Comment 3. As the authors metioned in discussion (line 269-271), the difference in hospitalization rate is likely to be due to differences in comorbidities and age. Could this have affected the difference in rates of receiving secondary treatment and survival outcomes?

Reply 3: It is possible that secondary treatment was affected by the difference in hospitalization rates being increased with GN than FFX. However, in line 210-211 we did find from our manual review, “The rates of treatment discontinuation due a hospitalization was similar between both FFX and GN cohorts (21% vs 23%)”. This tells us that after being hospitalized, both groups had similar treatment discontinuation rates.

Change in the text: None

Comment 4. Recommend citing the following article: BMC Cancer. 2021 May 11;21(1):537. This article showed the diffence in treatment-related toxicities that led to discontinuation between two groups.

Reply 4: Thank you for the recommendation. We added this reference in our discussion.

Change in the text: Line 264-266, (This was also shown in another retrospective study by Chun et al, where they found interruptions of chemotherapy due to toxicity was more frequent in the GN group compared to FFX (29.3% vs 6.8%, P<0.001) (22)).

Reviewer C

First, I want to congratulate the authors for the effort of putting together all these data in a setting in which the optimal chemotherapy regimen remais unknown. I believe this manuscript can certainly give big contributions to the current knowledge on the field. Overall, the manuscript is very well-written. Headings and subheadings are organized in a logical manner

However, there are major issues that should be addressed before the publishing process can proceed.

1) It is not common practice to start GEM + NAB with reduced doses (despite the fact that some retrospective evidence suggest that there might be no detrimental effect with such adjustment). Is that standard in your institution?

Reply 1: Dose reduction for Gem+Nab is up to the individual oncologist at our institution. We would not define that that initial dose reduction is "standard", but it is commonly practiced to give dose reduced paclitaxel compared to the original studies. Of note, most of the dose reductions were in the paclitaxel.

Change in text: None

2) In North America, GEM + NAB is the most commonly used chemotherapy regimen (Abrams TA, et al. Oncologist 2017;22:1-9). Is there any particular reason why in your institution mFFX is the preferred regimen? Also, do you believe this could be associated with a decreased experience in dealing with the toxicity profile of GEM + NAB?

Comment 2: In North America, GEM + NAB is the most commonly used chemotherapy regimen (Abrams TA, et al. Oncologist 2017;22:1-9). Is there any particular reason why in your institution mFFX is the preferred regimen? Also, do you believe this could be associated with a decreased experience in dealing with the toxicity profile of GEM + NAB?

Reply 2: At our institution, we believe FFX is more commonly used as many oncologists believe it offers superior survival compared to gem+nab. We do not think there is a decreased experience in dealing with the toxicity profile with Gem+Nab at our institution, as this regimen is often given in the second line anyway.

Change in text: None

3) When the study population was characterized, many important features were not presented (ECOG, comorbidity, CA 19-9). These data are very importante and should be available. If ECOG is not readily available, a proxy of this variable should given or an inference of the ECOG could be withdrawn from the EMR.

Comment 3: When the study population was characterized, many important features were not presented (ECOG, comorbidity, CA 19-9). These data are very importante and should be available. If ECOG is not readily available, a proxy of this variable should given or an inference of the ECOG could be withdrawn from the EMR.

Reply 3: We did not include ECOG, comorbidity or CA-19-9 as we did a manual review of each individual chart, and this was not standardly documented in all patients we collected data on.

Change in text: None

4) Many patients who underwent first-line treatment with mFFX underwent second-line treatment, in opposition to what was found for patients treated with GEM + NAB. That seems to be another indicator that patients in the GEM + NAB were sicker or that they had more aggressive disease rather than that mFFX increased their chances of receiving further treatment. That could also explain the toxicity profile of GEM + NAB being worse than expected. That should be pointed out (and corrected) in the discussion.

Reply 4: This is a good point. We had added this suggestion to our discussion.

Changes in the text: We added line 284-286 ("On the other hand, it is possible that patients treated with GN were sicker given their advanced age compared to the average FFX treated patient, thus the chances of receiving second line treatment was lower in this cohort").

5) The greater limitation of this study is that despite significant imbalances in the frequency of some of the characteristics between the two groups, only a crude unadjusted analysis was presented. In my opinion that might be misleading and perhaps dangerous. Proper statistical methods to deal with such imbalances are strongly advised. At least a Cox Proportional Hazards model should be implemented, bearing in mind that important prognostic variables such as ECOG and CA 19-9 should be present in the model as they are widely known to be associated with the prognosis in advanced PDAC. More advanced statistical techniques, such as Propensity Score Matching (PSM) with population matching or Inverse Propability Weightning (IPW) could also be used and would probably fit well in this analysis (unless there is a clear bias toward one of the chemotherapy regimens).

Reply 5: Thank you so much for this input. We acknowledge the lack of ECOG or CA-19-9; however, we explain that this was a manual chart review of each patient treated with FFX or GN and not all charts had a consistent ECOG status documented at the start of treatment. Our objective for this study was to retrospective review the consecutive patients treated with FFX or GN at the Yale New Haven Hospital system. Thus we applied the statisticial methods we did on our paper. We acknowledge such a retrospective analysis brings with it both observed and hidden bias, which we detail in our discussion. Applying a statistical method such as propensity score matching one can argue that hidden bias may actually increase because matching on observed variables may unleash bias due to dormant unobserved confounders
Change in text: none