Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-22-83

Major comments

1. Page 5, Line 20-24; Please indicate the results in figures, because the change of spleen volume after the chemotherapy has an impact for readers.

Reply: Thank you for your suggestion. This paragraph demonstrated the information of the occurrence and regression of splenomegaly. According to your suggestion, we have added a new figure (Figure 2 in the revised manuscript) to demonstrate the results in this paragraph. We'd appreciate if you provide us with more details of this comment.

2. Figure 4; The title might be wrong because the data indicates minimum value. Differences in the minimum decrease ratio in blood cell counts …….

Reply: Thank you for your comments. As demonstrated in the Methods section (Page 5; Line 19-21), decrease ratio was defined as the minimum blood cell counts during chemotherapy divided by baseline value for each patient. The "median" here refers to the median value of decrease ratios of all patients. However, we also found that this expression would confuse the readers. Therefore, we have deleted the "median" in the figure legends.

3. Page 6, Line 9-11, and Figure 3 and 4; "Splenomegaly patients underwent a more severe decrease in platelet count compared with non-splenomegaly patients (0.36-fold of baseline value (IQR, 0.27-0.43) vs. 0.54-fold (IQR, 0.40-0.66), P<0.001) (Figure 3, Figure 4)." Refer to the figure 3, minimum platelet count divided by baseline value were less than 0.5 both with splenomegaly and non-splenomegaly patients at 5 months after initiation of chemotherapy.

Reply: Thank you for the question. The 0.36-fold of baseline value and the 0.54-fold here were consistent with the first column of Figure 4, which represents the decrease ratio (minimum platelet count divided by baseline). The original Figure 3 was designed to present the changes of decrease ratios of platelet counts over time since the initiation of chemotherapy in both groups respectively. We realized it offered limited information and might confuse readers. Therefore, we have deleted the original Figure 3 in the revised manuscript.

4. Page 6, Line 17-19; "Moreover, the interruptions or terminations of oxaliplatin-based chemotherapy occurred in 19 patients (18.6%) with splenomegaly and 2 (4.8%) without splenomegaly due to thrombocytopenia (P=0.040)." Page 6, Line 8; "Grade 3 or 4 thrombocytopenia occurred in 13 patients (12.7%) with splenomegaly while none in the non-splenomegaly group (P=0.011)." Why the interruptions or terminations due to thrombocytopenia occurred in 19 (18.6%) with splenomegaly and 2 (4.8%) without splenomegaly although the grade 3 or 4 thrombocytopenia occurred in 13 (12.7%) with splenomegaly and none in the non-splenomegaly group.

Reply: Thank you for the question. We have reviewed the medical record of these patients and confirmed that the data are accurate. There were 6 patients in the splenomegaly group and 2 in the non-splenomegaly group undergoing postponement of chemotherapy due to continuous

grade 2 thrombocytopenia which persisted over 2 weeks. We have complemented the relevant information as *"Moreover, the interruptions or terminations of oxaliplatin-based chemotherapy occurred in 19 patients (18.6%) with splenomegaly and 2 (4.8%) without splenomegaly due to thrombocytopenia (P=0.040), including 6 patients in the splenomegaly group and 2 in the non-splenomegaly group who underwent continuous grade 2 thrombocytopenia persisting over 2 weeks."* in the Results section (Page 10; Line 1-3).

Minor comments

1. **Page 2, Line 4; "sought to explore" changes to "aimed to explore"**

Reply: We have revised it in the Abstract section.

2. **Page 3, Line 23; Exclusion criteria should be shown in detail, e.g. the presence of diffuse liver metastasis, portal vein thrombus, and ascites. (well-diagnosed cirrhosis)**

Reply: Thank you for your suggestion. We have followed your advice and the exclusion criteria is now shown in detail as "*Exclusion criteria included recurrence during chemotherapy, administration of other chemotherapy agents, prior splenectomy, active viral hepatitis, prior diagnosed cirrhosis, prior noncirrhotic portal hypertension (right heart failure, constrictive pericarditis, Budd-Chiari syndrome, portal or splenic vein thrombus, etc) and prior hematological disease*." in the Methods section (Page 5; Line 7-10)

3. **Reference 12 might be changed.**

Reply: We have changed the reference to be "*NIoH-NC, I. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017 [cited 2022 03.05]; Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf*"

4. **Page 4, Line 23-25; "Increase ratio of spleen volume was calculated as maximum spleen volume divided by baseline value and an increase ratio over 1.3 was defined as splenomegaly.[8]" The cutoff ratio of increased spleen volume is very important for this study, then the reason of the cutoff ratio defined as splenomegaly would be requested refer to more papers, e.g. Satta Y et al, JGH Open. 2021;5(11):1289-1297.**

Reply: Thank you for your insightful comments. We endorse that the rationale of the choice of cut-off value ought to be explained. We tested the predictive efficacies of different cut-off values for thrombocytopenia. The sensitivities for 1.2, 1.3, 1.4, 1.5 and 1.6 were 0.892, 0.789, 0.736, 0.625 and 0.530 respectively, and the specificities for 1.2, 1.3, 1.4, 1.5 and 1.6 were 0.311, 0.508, 0.558, 0.683 and 0.752 respectively. The Youden indices for 1.2, 1.3, 1.4, 1.5 and 1.6 were 0.203, 0.297, 0.294, 0.308, 0.282 respectively. The Youden indices of 1.3, 1.4 and 1.5 were close. Considering that the aim of our study was to better identify potential thrombocytopenia due to splenomegaly in oxaliplatin-treated patients, we ultimately chose 1.3 as the cut-off value due to its high sensitivity. Therefore, we have added relevant explanations in the Methods section (Page 6, Line 19-22) as *"The predictive efficacy for thrombocytopenia by different increase ratios of spleen volume was assessed. Among all potential cut-off values (1.2 to 1.6), the increase ratio of 1.3 had both satisfactory Youden index (0.297) and sensitivity (0.789)."*

5. Page 7, Line 4-7; “Third, patients with splenomegaly experienced a more severe decrease in blood cell counts, especially in platelet count, which further resulting in more frequent dose reductions and interruptions of oxaliplatin-based chemotherapy.” Please show the frequency of dose reductions.
Reply: Thank you for the question. The results have already been shown in the Methods section (Page 9; Line 19-20) in the original manuscript.

6. Page 8, Line 19-21; “Furthermore, the decrease in lymphocyte counts might potentially affect the efficacy of combination therapy of oxaliplatin and checkpoint inhibitors.” This sentence was irrelevant of this study, so please delete it in conclusion paragraph.
Reply: We have deleted this sentence in the conclusion paragraph.

7. There is no description about Fig. 2 in the text.
Reply: Thank you for your reminder. The original Figure 2 is numbered as Figure 3 in the revised manuscript. We have added the description as” *For splenomegaly patients, the spleen volume increased rapidly after the initiation of chemotherapy and reached 1.74 (IQR, 1.46-2.11) times of the baseline at 6 months, and gradually declined to 1.08 (1.01, 1.34) times of the baseline value at the end of the surveillance. While in the non-splenomegaly group, the spleen volume increased modestly to 1.16 (IQR, 1.03-1.25) times of the baseline at 4.5 months, and rapidly recovered to 1.03 (0.98, 1.11) times of the baseline value at 9 months. (Figure 3)*” in the Result section (Page 8; Line 8-14).

8. Table 1; What mean the “Abnormal liver function No. (%)”? How much? What were the levels of serum bilirubin and albumin? How about prothrombin time?
Reply: Thank you for your comments. In the original manuscript, we defined abnormal liver function as any liver enzymes above the upper limit of normal. However, we do agree with you that such definition is not rigorous. We have changed “abnormal liver function” to “Elevated AST and ALT levels” in Table 1 and corrected the relevant definition the Method section (Page 6; Line 1-2).

9. Table 2: The p value of Past in Drinking habit was 0.281, more than 0.10, in univariate analysis. Please delete in multivariate analysis, if wrong.
Reply: Thank you for your reminder. We have deleted it in the Table 2.

10. Does Capecitabine have any effect on splenomegaly or platelet counts? Please mention in the discussion session.
Reply: Three high quality clinical trials revealed that capecitabine had a minor effect on the platelet counts, with an incidence of 0% to 1.8% of grade 3 or 4 thrombocytopenia. We have added relevant information in the Discussion section (Page 11; Line 18-20) as” *Thrombocytopenia was frequently observed in our patients. Given that capecitabine had a minor effect on thrombocytopenia [17, 18], oxaliplatin might make the major contribution to thrombocytopenia in our patients.*”

1. Cartwright, T.H., et al., *Phase II study of oral capecitabine in patients with advanced or*

metastatic pancreatic cancer. J Clin Oncol, 2002. **20**(1): p. 160-4.
2. Scheithauer, W., et al., *Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial.* Ann Oncol, 2003. **14**(12): p. 1735-43.
3. Twelves, C., et al., *Capecitabine as adjuvant treatment for stage III colon cancer.* N Engl J Med, 2005. **352**(26): p. 2696-704.

11. The references of oxaliplatin-induced toxicity might be a little out of data. Please refer the following manuscript.

Vigano L, De Rosa G, Toso C et al. Reversibility of chemotherapy-related liver injury. J. Hepatol. 2017; 67: 84–91.

Iwai T, Yamada T, Koizumi M et al. Oxaliplatin-induced increase in splenic volume; irreversible change after adjuvant FOLFOX. J. Surg. Oncol. 2017; 116: 947–53. (已经纳入)

Gioia S, Di Martino M, Minozzi M, Nardelli S, Cortesi E, Riggio O. Incidence of portal hypertension in patients exposed to oxaliplatin. Dig. Liver Dis. 2019; 51: 1348–50

Satta Y et al, Prediction of esophagogastric varices associated with oxaliplatin administration. JGH Open. 2021;5:1289-1297.

De Gottardi A, Rautou PE, Schouten J et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol. Hepatol. 2019; 4: 399–411.

Reply: Thank you for the kind suggestion and helps. We have replaced the original reference 9 to the *Vigano L et al* reference and original reference 10 to the *De Gottardi A et al* in the revised manuscript. The *Satta Y et al* reference has also been cited in the Discussion section. The *Iwai T et al* reference has already been cited in the original manuscript.