

Format for ANSWERING REVIEWERS

25th of October 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name wjge-2012-002429-review .doc).

Title: Prognostic value of chemotherapy-induced hematological toxicities in metastatic colorectal cancer patients.

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Manuscript No: 5609

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated
2. Revision has been made according to the suggestions of the reviewer

(1) - According to reviewer 1 request we change the figure 2 and present the Kaplan-Meier curves for overall survival stratified according to the hematological toxicity severity for anemia, neutropenia, and trombopenia. Such data underline that we could observed the same prognostic role for each hematological toxicity. We add these data in a new figure 2.

2- According to reviewer 1 requesting we mansion in the description of that:" Two hundred and four patients received FOLFOX alone or with target therapies, 113 patients received FOLFIRI alone or with target therapies and 82 patients received monotherapy by fluoropyrimidine alone or with target therapies as a first line treatment. We observed that neutropenia is a factor of better outcome in patients that received

FOLFOX alone or with target therapies (mean OS of 27 months in patients without neutropenia versus 47 months in patients with neutropenia $P=0.004$) or in patients that received FOLFIRI alone or with target therapies as a first line (mean OS of 28 months in patients without neutropenia versus 41 months in patients with neutropenia $P=0.04$). Same results were observed in patients treated with fluoropyrimidine alone or with target therapies as a first line (mean OS of 22 months in patients without neutropenia versus 34 months in patients with neutropenia $P=0.0005$)". These data were added in the revised manuscript.

(3) Accordingly to the reviewer 2 request we moderate our conclusion as proposed.

(4) The reviewer 3 raises an important question of the possible bias of an association of hematological toxicity with longer treatment. If such bias explains our result anemia would be also associated with poor outcome, like neutropenia and thrombopenia. In contrast anemia is associated with poorer outcome thus suggesting that our observation is not a consequence to a methodological bias.

In addition to avoid the bias of longer survival in patients with hematological toxicities, a landmark analysis using a time point of 6 months from the diagnosis was performed because more than 90% of patients developed hematological toxicities during the first 6 months of follow-up. (reference in : Di Maio M, Gridelli C, Gallo C, Shepherd F, Piantedosi FV, Cigolari S, et al. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. *Lancet Oncol* 2005;6(9):669-77.) Patients who died before the landmark time were excluded from the analysis regardless the presence or absence of hematological toxicities. Thirty-five patients were excluded from the analysis because they died before the landmark time. Using such analysis, univariate and multivariate analyses confirm that neutropenia and thrombopenia during chemotherapy for mCRC are associated with increased survival. In addition we also test in the occurrence of neutropenia during the first 3 months of chemotherapy is associated with better outcome. Similar results were observed than with our initial analysis (mean OS 28 months without

neutropenia versus 34 months with neutropenia $P=0.01$)

Minor editing comments were performed as requested (Abstract line 4: use the term patient characteristics instead of biological data; Introduction line 7: 5-year OS is closer to 10%; Introduction line 8: OS is closer to 50%. Methods: The variables (cut-offs) for neutropenia, thrombopenia (should be 400) and anemia (should be 10) need to be specified. Methods line 10: use targeted therapy instead of molecules.

(3) According to the reviewer 3 requests with mention that 38% of patients have metachronous and 62% have synchronous disease. 83% of patients have liver metastases, 35% have lung metastases, 12% have peritoneal carcinomatosis. We also mention that while 60% of patients had only one tumor most of these patients have diffuse liver or lung involvement and less than half of these patients were treated by surgery. These data were added in the revised manuscript.

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,