January, 2014

Dear Editor,

Title: Cytoprotective effects of amifostine, ascorbic acid and N-acetylcysteine against methotrexate-induced hepatotoxicity in rats

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7984

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

Reviewer comment: This is an interesting study. The results can be placed in a more general perspective if the authors address these issues: 1) the effects of protective treatments are actually minor effects. What is the translational value of this study? What are known differences between the pathophysiology in rodents and humans? 2) what does the paper add to the existing literature? Mtx-induced toxicity has long been known. 3) how were doses of protective agents selected? Was a dose-dependent effect possible? Minor point units: "gr" should be "g"; rpm does not exist as a unit and should be expressed in g (gravity).

Response: Thank you for your evaluation. For many years amifostine is in clinical use for limitation of radiotherapy side-effects. Following submission of our manuscript, an experimental study titled “Protective effect of amifostine on high-dose methotrexate-induced small intestinal mucositis in mice ” was published. However there exists no study about hepatotoxicity. As far as we know, there is not also a study comparing acetyl cystein with ascorbic acid. Although there is a variety of human studies on acetyl cystein and ascorbic acid treatment for benign (extra-malignant) diseases, there is a lack of enough evidence to make a study with amifostine. Our study aims to present the relation between amifostine, hepatotoxicity, methotrexate and similar drugs to the readers.

Reviewer comment: The results of the research are very interesting for both, basic scientist and clinicians. Presentation and readability of the manuscript are good. The title accurately reflects the contents of the study. Readability of the abstract is good. The design of the study and statistical methods are appropriate. Standard materials and methods were used with a detailed description (the study could be easily reproduce or validate by other investigators). The sample size is big enough for experimental study. Tables and figures are relevant. Discussion is well organized but can be improved. I suggest extending the discussion with comments on recently published data about protective effect of Chrysin (2014) and previously published data on thiamine pyrophosphate (2012) and ursodeoxycholic acid(2008)against MTX-induced hepatic oxidative stress and apoptosis in rats (for example comment on resveratrol study was properly carried out; study with ursodeoxycholic acid was only cited without comment). From the clinical point of view it will be very important to find out which one of all possible protective agents has the biggest potential for clinical use in humans. The manuscript can be improved

by inclusion of minor changes and comments. The manuscript is appropriate for publishing – grade C.

Response: Thank you for your evaluation and recommendation. Taking your recommendations into account, I organized the references and added three latest citations. Also, I added a few sentences on the discussion section.

3 References and typesetting were corrected

4 English language of this article re-evaluated by native language editor

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

Sincerely yours,

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