

## Format for ANSWERING REVIEWERS



January 9, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6205-review.doc).

**Title:** hENT1 is predictive of gemcitabine outcome in pancreatic cancer; a systematic review

**Author:** Stina Nordh, Daniel Ansari, Roland Andersson

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 6205

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) Reviewer No. 00182439**

The authors presented a good review regarding an association between hENT1 and response to gemcitabine in patients with pancreatic cancer. The manuscript is very good and needs only minor changes before being accepted for publication. The authors should include information about the costs of hENT1 testing and limitations, if any, that may preclude this test to be used widespread. any specific patient group?

**Answer:** We appreciate the positive comments of reviewer 1. In a previous study, we estimated the costs of hENT1 testing (50-200 Euros) and concluded that such testing would be cost saving and also reduce unnecessary treatment toxicity related to gemcitabine overtreatment by selecting only those patients that would most likely derive benefit from treatment (*Acta Oncologica* 2013; 52:1146-51). The hENT1 test may be used for pancreatic cancer patient being considered for gemcitabine-based chemotherapy, be it adjuvant or palliative. Patients that are elderly and have poor performance status traditionally undergo best supportive care and therefore need not be tested for hENT1. This reference is included in the discussion (page 11, second paragraph).

**(2) Reviewer No. 02860797**

Dr. Nordh and colleagues systematically review the topic that hENT1 expression and outcomes in pancreatic cancer patients with gemcitabine treatment. Particularly they evaluated the role of hENT1 as a predictive rather than prognostic factor. The included studies showed significant heterogeneity regarding treatment regimes that patients received. However, the authors implied that this heterogeneity would hardly influence the reliability of their conclusions. The better outcome in high/positive hENT1 group thus might mix with influence from other treatments such as surgery and radiation, which could alter the efficacy

of gemcitabine in pancreatic cancer. Given this shortcomings, the manuscript showed a good review in the topic and was still valuable to understand the role of hENT1 as well as possible benefits for clinical use. Minor comments: 1. I suggest focused discussion on the underlying influence of different regimens patients had. 2. In Response rate section, is the number of patients underwent PR, SD and PD was totally 24, however 34 patients were evaluated RR. What was the outcome of the left 10 patients?

**Answer:** We thank the reviewer for the valuable comments. 1) It is true that the treatment regimens differed between the included studies but they all contained gemcitabine as the base for chemotherapy, as shown in Table 2. This has been clarified (page 9, last paragraph). 2) 5 patients had PR, 13 had SD and 16 had PD, this has been changed (page 8, last paragraph).

**(3) Reviewer No. 02441494**

The authors have obtained most of relevant published papers, and summarized the critical points. The review is the first report, which indicated hENT1 gene over expression in pancreatic carcinoma being a potential predictive value for gemcitabine treatment.

**Answer:** We appreciate the positive comments of reviewer 3.

**(4) Reviewer No. 02822922**

This systematic review is of great interest as it focuses on a clinical meaningful problem. Unfortunately, prognosis for patients diagnosed with pancreatic cancer is extremely poor as the majority of the patients are inoperable due to advance metastatic disease and only few respond to standard treatment (i.e. gemcitabine). However, some revisions need to be made as the review is not publishable in its current form. 1. Non-english articles should be included in the search as this is a systematic review 2. Page 5, characteristics of selected studies: line 2 authors should add references after Belgium.Canada.. etc 3. results section: when describing the results in terms of OS, the authors should detail this better (i.e. adding the number of months). Although they included a nice table, the readers should be able to get more information by reading the text only. 4. Discussion section: The first three lines belong to background and aim and should not be repeated in the discussion section. 5. English language should be properly reviewed. In details: 6. Page 7 line 17 was should be replaced by were 7. Page 8: a) line 12: tumours. This includes should be replaced by tumours including b)last line: have should be edited in has 8. Page 9: a) line 7 the results was should be replaced by were b) line 10: that is important should be that are .. c) last line again were should be replaced by was 9. Page 10, line 11: do not repeat in twice.

**Answer:** We thank the reviewer for the valuable comments. 1) We agree that inclusion of non-English articles in the systematic review would have been more optimal. However, the authors are proficient in English and Swedish only, and articles in other languages were not included for this reason. We analyzed articles in full-text, thus an English abstract was not sufficient for inclusion in this study. 2) The references have been added. 3) Outcome (survival) has been described in terms of overall survival (OS) as this is what consistently can be retained from the included papers. 4) The first three lines of the discussion have been removed. 5) The English language has now been reviewed by a professional English

language editing company. 6) This has been changed. 7) This has been changed. 8) This has been changed. 9) This has been changed. 10) This has been changed.

3 References and typesetting were corrected

4 As mentioned in 'The Revision Policies of BPG for TOPIC HIGHLIGHT', we have provided a language certificate by a professional English language editing company.

Thank you for considering publishing this systematic review in the *World Journal of Gastroenterology*.

Sincerely yours,

***Roland Andersson***

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