Author's response to reviews

Title: Polymorphisms in ERCC1, GSTs, TS and MTHFR predict clinical outcomes of gastric cancer patients treated with platinum/5-Fu-based chemotherapy: a systematic review

Authors:

    Zhen Wang Dr. (wangzhensurgeon@163.com)

Version: 2 Date: 16 September 2012

Author's response to reviews: see over
Author's response to reviews and editors
Title: Polymorphisms in ERCC1, GSTs, TS and MTHFR predict clinical outcomes of gastric cancer patients treated with platinum/5-Fu-based chemotherapy: a systematic review
Manuscript ID: 1438002268722146
Authors: Wang Zhen, Chen Jun Qiang, Jin-lu Liu, Xin-gan Qin and Yuan Huang

Author’s response to reviewers and editors:
Dear Editors:
Thanks very much for your sincere proposals. According to the advice of the two reviewers and editorial requirements, we revised our manuscript carefully. And the part of revision was marked in red letters in the revised manuscript. The following is our reply. If any problem exists, please let me know. Thank you very much!
With best wishes,
Wang Zhen

Response to reviewer Katja Ott
The advice is very good and all of us thank you very much. We revised our manuscript according to your suggestion.

Introduction:
#1 Question: Please delete the epidemiology and focus on your aims of your study.
Reply: We delete some content about epidemiology and add some content associated with our study according to your advice.

#2 Question: Add nowadays standards in neoadjuvant, perioperative and adjuvant chemotherapy and highlight the possible associations with the respective polymorphisms
Reply: We add some content according to your advice and mark it in red letters.

Palliative chemotherapy for advanced GC has been widely accepted as a standard treatment for several decades. And recent studies have demonstrated that peri-operative adjuvant chemotherapy (pre- or post-operative) can improve survival and quality of life in patients with GC [3]; however, expected survival for the advanced disease is generally poor (less than 1 year). Until now, 5-fluorouracil (5-Fu) and platinum are the most common drugs used for GC both in adjuvant and advanced settings, although there are no standard combination regimens [4]. Additionally, efficacy outcomes for a number of new agents (such as paclitaxel, oxaliplatin and capecitabine) have not shown definitive clinical benefit or superiority to older drugs in patients with advanced GC [5-7]; and in some patients therapy results in severe, unpredictable toxicity without any tumor response.

A growing body of evidence suggests that inter-individual variation in drug-metabolizing enzymes and nucleotide excision repair (NER) system may affect anticancer drug efficacy by influencing DNA repair or related enzyme activities [10]. Recently, many studies finds that genes involved in DNA detoxification (glutathione S-transferases, GSTs) and repair (excision repair cross complementing 1, ERCC1) control the effects of platinum [11, 12], while methylene tetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS) are associated with 5-Fu metabolism [11, 13].
#3 Question: Explain, why those polymorphisms were chosen

Reply: We add some content according to your advice and mark it in red letters.

Recently, many studies find that genes involved in DNA detoxification (glutathione S-transferases, GSTs) and repair (excision repair cross complementing 1, ERCC1) control the effects of platinum [11, 12], while methylene tetrahydrofolate reductase (MTHFR) and thymidylate synthase (TS) are associated with 5-Fu metabolism [11, 13]. Despite genetic polymorphism in response to platinum/5-Fu chemotherapy in GC has been reported [14], data reported so far are conflicting and critical consideration is needed before translation to the treatment of GC.

Results:

#1 Question: Please add to your subgroup analysis, the type of treatment: Preoperative versus adjuvant versus palliative.

Reply: We add subgroup analysis according to your advice. And the results are listed in Table2-5.

#2 Question: Would it be possible to define more predictive combinations of genotypes by this meta-analysis for response and/or prognosis?

Reply: This is good proposal. However, the included studies reported different genotypes and the data were confounding. Therefore we could not do meta-analysis in our study. This is our shortcoming and we discussed it in the part of discussion.

Discussion:

#1 Question: Shorten please the first part-it repeats facts of the introduction and focus on your results in combinations with literature.

Reply: We shortened the first paragraph and add some content according to your advice.

#1 Question: Address the problem of polychemotherapy: never single agents are delivered. It’s always a combination of 5-Fu and platinum containing combinations.

Reply: We add some content according to your advice and mark it in red letters.

Meanwhile, we must notice that never single agents are delivered. Poly-chemotherapy which combines several drugs (mainly 5-Fu and platinum) is the main chemotherapy regime currently. Whether the effect of genetic polymorphisms will change because of drug interactions is worthy of studying.
Response to reviewer Serah funke
Thank you very much for your good proposal. We revised our manuscript according to your advice.

**Question:** this study did not give introduction/little explanation on inherited genetic variability which may affect treatment outcomes.

**Reply:** We add some content in the part of introduction and mark it in red letters. In the part of discussion, we discussed how genetic polymorphisms affect treatment outcomes in the beginning of every paragraph.

Response to editors
1. We add a separate “conclusions section”
2. We add Authors' Contributions and Acknowledgements section.
3. We list all figure titles after the references in the manuscript file.
4. In order to minimise white space around the image, we reprocess the figures by using STATA 9.0 package instead of STATA 11.0 package.