Author's response to reviews

Title: A case of metastatic renal cell carcinoma and bile duct carcinoma treated with a combination of sunitinib and gemcitabine

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Author's response to reviews: see over
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Editor-in-Chief
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Dear Sir,

We are sending the revised version of our previously submitted manuscript entitled “A case of metastatic renal cell carcinoma and bile duct carcinoma treated with a combination of sunitinib and Gemcitabine” (MS: 2049847659118272). We thank editors and reviewers for reviewing our manuscript and providing valuable suggestions for our paper. We have addressed all comments by reviewers and carefully revised the manuscript. Revised parts were typed with red. Please find a point-by-point response for each concern as described in the following pages. We hope that the revised version of our paper is now suitable for publication in BMC Cancer and we look forward to hearing from you at your earliest convenience.

Sincerely yours,

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To reviewer #1:

Thank you very much for your favorable comments on our manuscript (MS: 1016215166109790). We revised the manuscript carefully following your kind suggestions. Please find point-by-point replies below.

**Major Revisions:**

1. **The combination therapy of sunitinib and gemcitabine was terminated on Day 13 after its initiation. Did the patient receive any subsequent therapies after that? If yes, can the author please describe the subsequent therapies? Please also clarify whether there was a long-term treatment effect given the short period of the combination therapy?**

After the recovery from severe adverse events by the combination therapy of sunitinib and gemcitabine, the patient had started subsequent chemotherapy by single agent temsirolimus. It could successfully control tumor growth for around 12 months. She is now under best supportive care 3 years after the initial chemotherapy. This suggests that a long-term survival could be possibly achieved not only by the initial combination chemotherapy but also the subsequent therapy. Therefore, we revised the sentence of the last part of “case report” as below:

Page 8, Case report: She had subsequent temsirolimus monotherapy from January 2012 and it achieved tumor control for about 21 months. She is now under best supportive care 3.5 years after the initial chemotherapy.

2. **Treatment-induced toxicities from the combination therapy seemed severe. What would the author recommend to another patient with similar disease?**

Thank you very much for a clinically important question. The present case suffered severe treatment-induced toxicities, however, it is not totally convincing that the combination therapy with the two agents potentially too toxic because the previous studies assessing the combination therapy showed modest toxicity profiles (Reference No.13, 14). Therefore, we think that the present severe toxicity may partially be caused by the characteristic of this patient in association with serum sunitinib concentration and SNPs. We need to be especially careful to treat patients with similar diseases by employing decreased doses of sunitinib 25 mg/body on days 1-14 and gemcitabine 750 mg/m$^2$ on days 1 and 8, every 3 weeks, otherwise we would select single agent specific for one of the diseases.
To reviewer #2:

Thank you very much for your important comments on our manuscript (MS: 1016215166109790). We revised the manuscript carefully following your kind suggestions. Please find point-by-point replies below.

Reviewer's report:

1. That the combination of sunitinib and gemcitabine might be feasible has been shown by various publications, such as:

We appreciate your valuable comments with a publication list of the combination therapy of sunitinib and gemcitabine. All of these studies employed combination chemotherapy aiming improvement of efficacy against various solid tumors. Among them, triplet regimens consisting of sunitinib, gemcitabine and cisplatin or capecitabine exhibited prominent toxicity and they were recognized to be difficult to continue the further studies. Doublet regimen of sunitinib and gemcitabine showed modest toxicity but could not achieve superior efficacies. Considering that these attempts to examine the combination therapy have been performed, it could be one of the possible choices to treat the present case harboring double primary cancers of RCC and BDC.

In our original manuscript, we discussed the differences between the present case and the findings in the references No.2 (Brell JM et al) and No.3 (Michaelson MD et al) of your list. Since the other three papers (No. 1, 4, 5) were published after the submission of our manuscript on January 10th, 2014, we could not refer them. Therefore, we add a description of these three papers in the last part of discussion and in the references part as below.

Examination of the serum concentration of sunitinib and SNPs had not been carried out in these studies. In addition, patients suffered remarkably various toxicities such as the present case were not reported. We thus believe that the present report has scientific significance.

Page 15-16, Discussion: After submission of this manuscript, several clinical studies employed the combination of sunitinib and gemcitabine had been published. A randomized phase II study in advanced pancreatic cancer demonstrated the combination regimen could not show sufficient superior efficacy compared to gemcitabine monotherapy but was associated with more toxicity [27]. Triplet regimens consisting of the combination and cisplatin or capecitabine in advanced solid tumors exhibited prominent toxicities suggesting difficulties of further developments of triplet regimens [28, 29].
Page 26, References:

2. The authors cannot conclude from one case only that the combination of sunitinib and gemcitabine might be more effective to sunitinib alone. The same is regarding side effects or behaviour of plasma levels of sunitinib.

We agree that observation from a single case cannot conclude superiority of the combination regimen comparing with sunitinib alone. Since we did not intended to emphasize clinical benefit of the doublet regimen in the original manuscript, the description regarding efficacy in the case report part have revised to be more adequate as below.

Page 4, Abstract: Although unknown synergistic mechanisms of these agents may be involved, severe toxicities might be possibly associated with high sunitinib exposure.
Page 8, Case report: The response of the lung metastases of RCC and no significant change for BDC were confirmed on day 35.

We also understand your opinion that relationship between side effects and plasma levels of sunitinib cannot be conclusive from a single case experience. We examined plasma concentration of sunitinib and SNPs in order to explore the reasons for intense side effects. Few reports of clinical study performing these analyses have been available possibly because of only limited number of patients suffered such severe adverse events. Therefore, accumulation of clinical experiences and analyses from the individual cases is thought to be significant. We expect the present case report could provide information in case of the appearance of similar adverse events. We thus carefully revised the conclusion part to be without exaggeration.

Page 16, Conclusions: Possible mechanisms of high exposure of sunitinib might include gene polymorphisms of drug-transporters, but unknown mechanisms induced by the combination use of two drugs should be investigated.
To reviewer #3:

Thank you very much for your critical comments on our manuscript (MS: 1016215166109790). We revised the manuscript carefully following your kind suggestions. Please find point-by-point replies below.

Reviewer's report:
1. The treatment was only 13 days of sunitinib treatment and two doses of gemcitabine. It's quite different from common clinical practices. Clinically, we usually need about 2-3 months' treatment to evaluate the response.

The combination chemotherapy of sunitinib and gemcitabine for the present case was terminated on the day 13 because of severe adverse events, and the same treatment regimen could not be resumed. As the reviewer pointed out, evaluation of the response is usually performed every 2 or 3 months in the clinical practice. In the present case, CT scan examinations immediately after the termination of the combination therapy were required for assessing the organ damages induced by adverse events. We simultaneously examined the response of the tumors in these images.

The present report would like to demonstrate appearance of intense toxicities even after short-term therapy and possible association with plasma concentration of sunitinib. Following your important comment, we carefully revised the description about efficacy of this short-term combination therapy in the case report part as below. Additionally, in order to clarify the reasons for survival, information of the subsequent therapy was added in the case report part as below:

Page 4, Abstract: Although unknown synergistic mechanisms of these agents may be involved, severe toxicities might be possibly associated with high sunitinib exposure.

Page 8, Case report: She had subsequent temsirolimus monotherapy from January 2012 and it achieved tumor control for about 21 months. She is now under best supportive care 3.5 years after the initial chemotherapy.

2. The CT scan for lung metastasis showed a tumor became smaller, but the other tumor seems unchanged. It's hard to conclude a "partial response" by RECIST criteria.

Since the total of the longer axis of lung metastatic lesions reduced more than 30%, we originally described as partial response. However, no significant size reduction of BDC lesion was observed. Following your suggestion, we revised the explanation regarding the response as below:

Page 8, Case report: The response of the lung metastases of RCC and no significant change for BDC were confirmed on day 35.

3. The SNP study didn't show any predictive value for sunitinib treatment efficacy. So there is little value in contribution to current medical knowledge or a change in clinical practice.

We understand your opinion that SNPs study could not provide predictive values for sunitinib treatment efficacy from a single case experience. We examined plasma concentration of sunitinib and SNPs in order to explore the reasons for intense side effects. Few reports of clinical study
performing these analyses have been available possibly because of only limited number of patients suffered such severe adverse events. Therefore, accumulation of clinical experiences and analyses from the individual cases is thought to be significant. We expect the present case report could provide information in case of the appearance of similar adverse events. We thus carefully revised the conclusion part to be without exaggeration.

Page 16. Conclusions: Possible mechanisms of high exposure of sunitinib might include gene polymorphisms of drug-transporters, but unknown mechanisms induced by the combination use of two drugs should be investigated.