Author's response to reviews

Title: Gemcitabine versus gemcitabine based combination chemotherapy in advanced pancreatic cancer- Indirect comparison

Authors:

Asma Sultana (asultana@liv.ac.uk)
Paula Ghaneh (P.Ghaneh@liverpool.ac.uk)
David Cunningham (David.Cunningham@rmh.nhs.uk)
Naureen Starling (Naureen.Starling@rmh.nhs.uk)
John P Neoptolemos (j.p.neoptolemos@liv.ac.uk)
Catrin Tudur Smith (cat1@liverpool.ac.uk)

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Author's response to reviews: see over
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The Editor,

BMC Cancer

Re: MS: 8540915911643260- Gemcitabine based combination chemotherapy in advanced pancreatic cancer- Indirect comparison, Sultana A et al.

Authors responses to the reviewers.

Referee 1 Comments for the Authors.

Minor Essential Revisions

1. Ref. [2] has been published as a full paper in Annals of Oncology (Epub ahead of print) in the meantime: the author should therefore revise the introduction and also the discussion section by including the data from this trial (a randomised phase II study including a comparison of a gemcitabine + capecitabine regimen versus a modified gemcitabine + oxaliplatin regimen)

Response

The reference has been updated to include the recent abstract (Epub ahead of print) in the Annals of Oncology, and both the introduction and discussion sections (page 7; paragraph 1) have been revised, with this added. The full paper is yet to be published (checked October 2007 to January 2008 issues).

Discretionary Revisions

1. Perhaps the title of the paper should be changed to "Gemcitabine based combination chemotherapy in advanced pancreatic cancer - indirect comparison" as this is the main topic of the article.

   This suggestion has been taken, and the title altered.

2. A HR of 1.17 (although with a wide 95% CI) in favour of gem + cap over gem + 5-FU is interesting. Perhaps the authors would like to (shortly) discuss this observation with regard to a possible higher clinical activity for an oral fluoropyrimidine compared to infusional 5-FU in advanced pancreatic cancer.

   This is expanded upon on page 8 of the revised discussion.
3. Ref. [3] and [5]: Incorrect citation; only volume, but not number of the journal issue is cited.

The references have been amended to include the number of the journal issue.

**Referee 2 Comments for the Authors.**

**Major Compulsory Revisions**

The discussion needs to expand on the implications of these findings:

1) No combination was found to be significantly superior to others. Is this due to sample size? What were the statistical limitations of the comparison?

Quote revised discussion page 7; paragraph 2: “The lack of significant differences on indirect comparison is probably due to the already highlighted observation that this method tends to yield results that are less statistically significant than in a direct comparison [1]. Indeed, it can be shown that one directly randomised trial is as precise as an indirect comparison based on four randomised trials of the same size.

2) How, if at all, does this change practice?

Quote revised discussion page 8; paragraph 2: “In the light of level I evidence demonstrating that gemcitabine based combinations have a modest survival advantage over single agent gemcitabine, the current study indicates which combinations may be more efficacious.”

3) What is the way forward?

Quote revised discussion page 9; paragraph 2:

The findings of our original meta-analyses, as well as the trends observed on our adjusted indirect comparisons support the use of gemcitabine in combination with either capecitabine or a platinum compound in clinical practice. Future randomised controlled trials will now likely to be centred on the exploitation of novel targets or biology (such as Telovac) [2] in this chemo-resistant cancer, probably on a cytotoxic backbone of a gemcitabine combination.

4) Why is there a trend for superiority for capecitabine and not for 5-FU?

Quote revised discussion page 8; paragraph 1: “A note-worthy observation on indirect comparison was that overall survival with gemcitabine combined with the fluoropyrimidine 5FU was inferior (though not statistically significant) to gemcitabine plus another fluoropyrimidine capecitabine (HR 1.17). A likely explanation is that capecitabine, an oral prodrug of 5FU, has the advantage of an element of tumour targeting, leading to enhanced selectivity and better tolerability [3]. The higher levels of thymidine phosphorylase (the final requisite enzyme for conversion of capecitabine to 5FU) observed in tumours compared to normal tissue may account for the improved targeting.

Another possibility is the mode of delivery of 5FU versus capecitabine. The 5FU trials have involved bolus 5FU schedule [4] or 24 hour infusion [5], with the exception of one trial where 5FU was given by continuous infusion [6]. In contrast,
the administration of capecitabine is more analogous to the delivery of 5FU by continuous protracted venous infusion, with the added ease of oral administration.

5) What is the role for a randomised controlled trial in light of these findings and the conclusions by Song et al. that "Adjusted indirect comparisons usually but not always agree with the results of head to head randomised trials" (Discussion, page 6)

Quote revised discussion page 8; paragraph 2: “A previous study which examined direct versus adjusted indirect comparison concluded that the two may not always agree [1]. Therefore the trends observed on our adjusted indirect comparisons need further evaluation”

Salient points of this expanded discussion need to also be included in the Conclusions.

The conclusion has been amended to include salient points from the revised discussion.

Minor Essential Revisions

1) The randomised control trial referred to on page 3 (Background, reference [2] and on page 6, last paragraph) is a randomised phase II study rather than a phase III study. This needs to be made explicit as the implications are quite different.

The text of the paper has been amended to include the fact that the study is a phase 2 trial

2) A table of selected studies would strengthen the manuscript.

A table of included studies has been added.

REFERENCES

2. Telovac: A prospective, phase III, controlled, multicentre, randomised clinical trial comparing combination Gemcitabine and Capecitabine therapy with concurrent and sequential chemoimmunotherapy using a telomerase vaccine in locally advanced and metastatic pancreatic cancer