**Author's response to reviews**

**Title:** A Phase II Study of LFP Therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-Dose Consecutive (Cisplatin) CDDP) in Advanced Biliary tract Carcinoma

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**Version:** 10  **Date:** 13 January 2006

**Author's response to reviews:** see over
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Version: 4 Date: 15 November 2005

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Reviewer's report

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Version: 6 Date: 13 January 2006
Reviewer's report
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Version: 4 Date: 15 November 2005
Reviewer: Nicolas Tsavaris

Reviewer's report:
This is an extensive analysis of continuous infusion of 5FU + CDDP for advanced Billiary tract Carcinoma. In a group patients, of which 26% was previously treated by chemotherapy or radiotherapy, an interesting response rate of 42% was found. My main objection is that this study reports rather on the use of the pump than the basic points of such a study. These points would be:
1. Generally the Tables and Figures is of low quality with poor legends, without explanation of abbreviations, which makes it very difficult reading and understanding them.
   You are right. We add to full spelling of abbreviations and rewrite the Tables. If it is difficult to read, please see additional file Tables1-6 for BMC.

2. Table 1 regarding the clinical characteristics of patients is inadequate; specifically there is no mention of disease extension (i.e. local or metastatic), of performance status and of the number of patients who had undergone surgery.
   Disease extension was such that 11 patients (BDca: 7, GBca: 4), had only primary or local recurrence 11, 14 patients had only metastatic disease (BDca:9, GBca: 5), another 17 patients (BDca:11, GBca: 6) had both diseases (See; Patient characteristics in the manuscript). Disease extension is also defined in Table 2. The number of patients who had undergone surgery was 16 (= the number of postoperative recurrence). Unresectable in Table1 means that the patients with locally advanced or both locally advanced and metastatic disease. Therefore unresectable could not undergo initial operation. ECOG PS is added to Table 1.

3. It is very difficult to evaluate the response rate in local disease pancreatic and biliary carcinomas. Authors used RECIST criteria, and they present overall response rate 42.9% which is very high for this type of cancer. This means that 18 patients which showed partial response had a more than 50% decrease in the sum of the products of the largest perpendicular diameters of the measurable lesions sustained for at least 1 month. This is not clear enough in the “material and methods” and the “results” sections.
   We evaluate anti-tumor effect according to RECIST criteria. Patients with a complete response (CR) or a partial response (PR) required a confirmatory disease assessment at least one month later. The overall response rate of our study is relatively high for this type of tumor. However, our LFP method has achieved more than a 50% overall response rate in other tumors such as esophageal, gastric or colon cancers. Biliary tract cancer may be more malignant than other types of cancer.

4. The authors do not give any information about the 11 (26%) patients with previous therapy (radiotherapy/chemotherapy/ surgery).
   We added these descriptions about these patients such that Two of 4 patients experienced surgery before these chemotherapy (i.e. postoperative recurrence). Seven of BDca patients had palliative radiotherapy. Three of these seven underwent surgery before
radiation (i.e. postoperative recurrence).

5. PS is absent from Table 1, but it appears in Table 4.
   ECOG PS is added to Table 1.

6. In Table 3 there is no explanation for ascites and jaundice, were they the result of therapy (drug toxicity) or the outcome of the disease progression?
   The occurrence of ascites and jaundice may be partly because of the outcome of the disease progression. But drug toxicity is not absolutely denied. Therefore we include these into toxicity.

7. It is not clearly stated how was toxicity evaluated; was it expressed in respect with the administered courses of therapy or according to the number of patients?
   We expressed the Toxicity in relation to number of patients in all the courses of therapy.

8. The separation of patients in two groups ( >2 and <2A) is rather confusing. They refer to patients with only one course (<2) and 2 and more courses of therapy. From another point of view this means responders and no responders. The questions are firstly, when, how and by which criteria did the authors evaluated disease progression; and secondly why did they compare responders and no responders to chemotherapy, and included this element to survival and prognostic factors analysis?
   You are right. We exclude this description.

9. The authors quote mild toxicity, mainly Grade 1 and 2. On the other hand, they used low doses of chemotherapy. It is well established in most types of malignant tumors that by increasing the dose intensity of chemotherapy one might achieve better response rate. Why did the authors avoid to increase the doses of the administered drugs, although it was allowed at this phase of a study?
   These doses were determined based on our experience of the previous LFP therapy for other digestive organ cancers, such as gastric cancer. Our main objective is to establish patient-friendly chemotherapy. Therefore, we think that the feasibility and longer survival rate is more important than the response rate. As a result, we do not increase the dose of the anti-cancer agent during the chemotherapy protocol, even if the toxicity is low.

10. In Discussion I would expect a comment on the study by Kim et al. 2003, who had also used CDDP and Capecitabine, and reported RR 21.4% (half of the present study).
   Kim’s regimen is also interesting since oral capesitabine was used and we plan to use oral S-1 in the next chemotherapy. However, our results showed higher response rate and lower toxicity than Kim’s.

1. Is the question posed by the authors new and well defined?
   Yes

2. Are the methods appropriate and well described, and are sufficient details provided to
replicate
the work?
Yes, but there are some methodological problems mentioned above.

3. Are the data sound and well controlled?
It is a fair presentations of data, because authors have been oriented mainly to technical administration of drugs, with pour presentation of therapy’s results.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes, but see above.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes, but it needs to explain and support the findings of this effort, more.

6. Do the title and abstract accurately convey what has been found?
Yes

7. Is the writing acceptable?
Yes

-Major Compulsory Revisions
Better quality of Tables and Figures, with brief legends, with explanation of abbreviations. More details of clinical characteristics, and evaluation of response. Think and decide about pretreated patients including in the study, also explain the relation of ascites and jaundice with disease or drug toxicity. More details about toxicity, and make clear its evaluation. Delete or re-write some consusing points such as the separation of patients in two groups ( >2 and <2 courses). Explain why they avoided to increase the doses of the administered drugs, or how they chose this doses. Discuss the response rate in correlation with other studies with platinum derives.

All the corrected parts including language corrections are all underlined in this manuscript. Please see the manuscript file.

Level of interest -An article of importance in its field -An article whose findings are important to those with closely related research interests
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
Quality of written English: Needs some language corrections before being published
Statistical review: Yes
Declaration of competing interests:
'I declare that I have no competing interests'
Reviewer's report
Title: A Phase II Study of LFP Therapy (5-FU (5-fluorourasil) continuous infusion (CVI) and Low-Dose Consecutive (Cisplatin) CDDP) in Advanced Biliary tract Carcinoma
Version: 4 Date: 14 November 2005 Reviewer: Vittorio Gebbia

Reviewer's report:
General
The paper is well written an reported data from a phase II trial employhg infusional 5-fluorouracil and cisplatin in biliary tract carcinomas. Results are interesting and in line with other reports.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
none

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Some engligh language mistakes. The discussion section may be reduced in size and length since it deals a lot on the use of venous catheters and about other drugs such as S-1.

Discretionary Revisions (which the author can choose to ignore)

Version: 6 Date: 13 January 2006

All the corrected parts including language corrections are all underlined in this manuscript. Please see the manuscript file.

What next?: Accept after minor essential revisions

Level of interest: An article whose findings are important to those with closely related research interests Quality of written English: Needs some language corrections before being published Statistical review: No Declaration of competing interests: 'I declare that I have no competing interests'