Reviewer's report

Title: Phase II Trial of Weekly 24-Hour Infusion of Gemcitabine in Patients with Advanced Gallbladder and Biliary Tract Carcinoma

Version: 1 Date: 22 April 2005

Reviewer: Nicolas Tsavaris

Reviewer's report:

1. Is the question posed by the authors new and well defined?
The main point of this trial is the failure of Gemcitabine in the treatment of patients with advanced gallbladder and biliary tract carcinomas. The existing number of clinical trials is rather small and therefore, any additional information is valuable and welcome. For these reasons, the authors had to raise this point.

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
As mentioned earlier, the existing number of studies is small, and the application of continuous infusion of Gemcitabine is valuable, as another modality of drug administration. Cholangiocarcinoma and pancreatic cancer usually pose the difficulty in response evaluation in the primary tumor site, since in most cases, associated inflammation and/or necrosis, as well as other anatomical structures in the vicinity complicate interpretation of bi-dimensional measurements, thus rendering standard WHO response criteria of less importance and probably raise the necessity for applying the RECIST criteria. There is no comment about these issues in the manuscript.

3. Are the data sound and well controlled?
There are some questions about:
This study includes elderly patients until the age of 83, but for a typical phase II study the upper limit of age is usually somewhere between 70-75, thus making this inclusion criterion a serious weak point of the study.
An important point is the existence of jaundice, and its management (surgical or by endoscopy; ERCP) before the initiation of chemotherapy.
It is not clearly reported how many patients had undergone surgery before.
No mention is made about metastases and number of major metastatic sites.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Besides methodological problems that were mentioned above, there is an extensive Introduction without explaining the reason why the authors decided to apply continuous infusion of Gemcitabine. In Methods (Treatment Plan) the dose of Gemcitabine is absent, although it is included in the Abstract. The essential point is the age of patients; how many were under 75 years-old?
Some other points must be re-evaluated; for example: Alkaline Phosphatase (<129) has a median value of 443, with bilirubin: 0.7, and AST (<50): 29, it is difficult to have elevated Alkaline Phosphatase (3-fold) with normal (in the middle of normal range bilirubin and AST.
Generally, Patients & Methods need more simple and clear presentation.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
A main problem is that there are no references for other studies evaluating Gemcitabine in cholangiocarcinoma. There is a justification about this, that all except one are published between 2004-2005. Since there are relevant data, these should be compared with the results of the current study. On the other hand, authors used in discussion data (Refs 13, 14) from pancreatic cancer.
- Park JS, et al, Jpn J Clin Oncol. 2005; 23 patients, 26.1% had a PR, eight (34.8%) had SD, the median OS was 13.1 months.
- Eng C, et al, Am J Clin Oncol. 2004; 14 patients, 2 patients (13%) had SD lasting a median of 9 weeks. The median TTP was 9 weeks; median OS was 20 weeks.
- Verderame F, et al, Anticancer Drugs. 2000; 4 patients, one PR
- Tsavaris N, et al. Invest New Drugs. 2004; 30 patients, 9 PRs were observed (30.0%), 11 with SD (36.7%), and for responders OS was 17.1 months.

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

7. Is the writing acceptable? Yes.

Evaluation of response: Cholangiocarcinoma and pancreatic cancer have a serious problem in the evaluation of response in the primary tumor site, and this must be mentioned and authors have to explain how did they overcome this problem.

2. There are some critical points:
i. This study includes elderly patients until the age of 83, but for a typical phase II study the upper limit of age is usually somewhere between 70-75, thus making this inclusion criterion a serious weak point of the study.
ii. An important point is the existence of jaundice, and its management (surgical or by endoscopy; ERCP) before the initiation of chemotherapy, but in Table 1, patients had a median bilirubin 0.7. This must be clarified.
iii. It is difficult to understand how many patients underwent surgery.
iv. No mention is made about metastases and number of major metastatic sites.

3. Besides methodological problems that were mentioned above, there is an extensive Introduction without explaining the reason why the authors decided to apply continuous infusion of Gemcitabine.

4. In Methods (Treatment Plan) the dose of Gemcitabine is absent, although it is included in the Abstract. The essential point is the age of patients; how many were under 75 years-old?

5. Some other points must be re-evaluated; for example: Alkaline Phosphatase (<129) has a median value of 443, with bilirubin: 0.7, and AST (<50): 29, it is difficult to have elevated Alkaline Phosphatase (3-fold) with normal (in the middle of normal range bilirubin and AST.

6. Generally, Patients & Methods need more simple and clear presentation.

7. A main problem is that there are no references for other studies evaluating Gemcitabine in cholangiocarcinoma. There is a justification about this, that all except one are published between 2004-2005. Since there are relevant data, these should be compared with the results of the current study. On the other hand, authors used in discussion data (Refs 13, 14) from pancreatic cancer. Therefore, it is my view that the following References should be included in Reference list and discussed:
Ø Park JS, et al, Jpn J Clin Oncol. 2005; 23 patients, 26.1% had a PR, eight (34.8%) had SD, the median OS was 13.1 months.
Ø Eng C, et al, Am J Clin Oncol. 2004; 14 patients, 2 patients (13%) had SD lasting a median of 9 weeks. The median TTP was 9 weeks; median OS was 20 weeks.
Ø Verderame F, et al, Anticancer Drugs. 2000; 4 patients, one PR
Ø Tsavaris N, et al. Invest New Drugs. 2004; 30 patients, 9 PRs were observed (30.0%), 11 with SD (36.7%), and for responders OS was 17.1 months.
**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Declaration of competing interests:**

I declare that I have no competing interests