Title: Phase I study of intermittent and chronomodulated oral therapy with capecitabine in patients with advanced and/or metastatic cancer

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

Please find enclosed the revised version of the Original Article “Phase I study of intermittent and chronomodulated oral therapy with capecitabine in patients with advanced and/or metastatic cancer” signed by Daniele Santini, Bruno Vincenzi, Gaia Schiavon, Annalisa La Cesa, Simona Gasparro, Angelo Vincenzi and Giuseppe Tonini. As requested we have followed the reviewers’ suggestions and described how each criticism was dealt in the following lines. The major changes along all the text are underlined.

REVIEWER NUMBER 1

Major Concerns:
Author’s concern: “The MTD and DLTs were assessed after 2 cycles (6 weeks). The authors didn’t explain why they evaluated both after 6 weeks……”

My response:
1) We used the same methodology used by Mackean M et al in his phase I study on intermittent capecitabine (Mackean M et al, J Clin Oncol, 1998). The author considered two cycles (6 weeks) for evaluating both MTD and DLTs.
2) All the phase I studies consider the first two cycles for evaluating the MTD and DLTs
3) In any case the cumulative toxicity is reported in the present Paper during the text and summarized in the Table number 5. The cumulative toxicity is a different parameter and do not correspond with the DLT and MTD.

Author’s concern: “A grade IV fatigue is, per definition, a DLT. But couldn’t this due to tumour progression? Did it resolve after chemotherapy discontinuation?”

My response:
1) The patient didn’t show any disease progression while experiencing grade IV fatigue
2) Moreover, grade IV fatigue completely resolved after chemotherapy discontinuation
Author’s concern: “….Does the patient still prefer the oral medication if he has to stay awake until 11pm for his last dose?”

My response:
1) In the previous phase II study (D. Santini et al., Oncology, 2005) and in the present phase I study we performed a sub analysis about the compliance of the last dose (11pm) of capecitabine. Among more than 100 patients treated with chronomodulated capecitabine, only 8 patients asked us to anticipate the dose administration to 10pm.

Author’s concern: “ You already conducted a phase II study with good results. Why did you initiate a phase I study thereafter?”

My response:
1) Because the aim of the present study is only to establish the MTD of chronomodulated capecitabine when used as single agent and to demonstrate that this MTD is superior than that reported by Mackean M et al when capecitabine is administered with the standard non chronomodulated schedule.

Minor Concerns:
We have followed all the suggestions of the reviewer and all the suggested modifications during the text are underlined.

We decided to maintain the Table number 4 because we think that it’s very important to describe and summarize the cumulative and late toxicity of chronomodulated capecitabine. This table shows that long term administration of chronomodulated capecitabine is feasible and safe.

Reviewer Number 2

Major Concerns:
Author’s concern: “What is the rationale for chronomodulating capecitabine?”

My response: the rationale of chronomodulating capecitabine is reported during the “Introduction Section” and is discussed during the “Discussion Section”.

Author’s concern: “Please provide scientific data that demonstrates that dose-intensity with capecitabine matters or it doesn’t”
My response: Scheithauer W. et al. in his randomized phase II study (J Clin Oncol. 2003 Apr 1;21(7):1307-12), clearly demonstrated that the increase of capecitabine dose-intensity translates into an increase of response rate and into a significantly longer median progression-free survival time. The author conclude his report with this sentence “The dose-intensified bimonthly capecitabine arm, however, seems to be more effective in increasing both response rate and progression-free survival time”.

Author’s concern: “Would saturation of enzymes in tumour be rate-limiting for more 5-FU to form...?”

My response: Yuko Tsukamoto et al. (Pharm Res. 2001 Aug;18(8):1190-202) clearly demonstrated that there is a direct correlation without any plateau between the dose of capecitabine administrated and the AUC of 5-FU in the tumour tissue (Figure above). This is an indirect demonstration that the enzyme saturation in not rate-limiting.

![AUC of 5-FU vs Dose of Capecitabine](image)

**Fig. 16.** Simulation for 5-FU AUC in blood (---), the GI (-----), and tumor tissue (-----) after administration of capecitabine, docetaxel, and 5-FU in humans. The estimation was performed by assuming a patient (70 kg body weight) to have a tumor of 20 g. The bar shows the reported clinical dose range for each drug.

Author’s concern: “Limit and shorten sections of the Paper(e.g., patient selection etc....)”

My response: I followed this suggestion where possible and where this suggestion did not induce conflicts with the suggestions of reviewer number 1.
**Author’s concern:** “There was no PK done….”

**My response:** we completely agree with the reviewer and for this reason we stressed this limit during the “Discussion Section”: “Pharmacologic studies were not performed in this study, but it is likely that such studies would have contributed much information at this point in the development of this regimen”.

**Author’s concern:** “Comment on other strategies to make dosing more predictable like flat doses programs….”

**My response:** the aim of this study was exclusively to determine the MTD of a new way of administering capecitabine. The “flat doses” programs are very interesting and promising in cancer chemotherapy. The combination of chronomodulation with the “flat dose” administration of drug could represent a strategy that warrant further investigation in future clinical trials.

**As suggested by the reviewers and by the the BioMed Central Editorial Team we performed a complete revision of the English language with the help of a native English speaking colleague.**

We thank you very much for the reviewer’s criticisms that were very useful in improving our manuscript.

Awaiting your final decision,

Sincerely yours,

Daniele Santini, MD, PhD

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