Reviewer’s report

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

Version: 1 Date: 13 December 2005

Reviewer: birgit gruenberger

Reviewer’s report:

General
The authors describe a phase I study of intermittent and chronomodulated oral therapy with capecitabine in patients with advanced cancer. It is an interesting report but leaves several important questions unaddressed:

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The MTD and DLTs were assessed after 2 cycles (6 weeks). They authors didn’t explain why they evaluated both after 6 weeks. 6 weeks is a short period and we know that, especially in regards to hand and foot syndrome, side effects do increase with the cumulative dose of a chemotherapeutic agent. Restaging is usually performed after 9 to 12 weeks and at this time point MTD and DLT should be evaluated.
A grade IV fatigue is, per definition, a DLT. But couldn’t this be due to tumour progression? Did it resolve after chemotherapy discontinuation?
The oral chemotherapy with capecitabine is equivalent to the infusional 5-FU. An advantage is the convience of the oral administration. Does the patient still prefer the oral medication if he has to stay awake until 11pm for his last dose?
You already conducted a phase II study with good results. Why did you initiate a phase I study thereafter?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Minor revision:
Pg 2:
Methods: The first sentence should be: Patients with advanced solid tumours who had failed to response to standard therapy or for whom no standard therapy was available were eligible for this study.

Results: 2nd line: replace “dyarrhoea” with “diarrhoea”
3rd line: replaced “between” with “out of”
4th line: which doses?
5th line: please explain the lower dose steps?
Pg 3: second paragraph, last sentence: “..was less toxic to the in the intestinal tract”. What do you mean?
Third paragraph, first sentence: in which tumour entitiy does capecitabine show response rates of 25%?
Second sentence: This sould be put at the end of the second paragraph.
Page 4: 6th line: change “Authors recommend for phase II studies” to “authors recommend for further evaluation...”
2nd paragraph: TP is an abreviation which is not discribed.
Page 5: 2nd paragraph, 3rd sentence: change it to “ Pregnant or breast feeding woman or patients
with uncontrolled severe disease were excluded”.

Page 6: study design: 5th line: replace “is” with “was”
Delete the 7th sentence (“choice of...”)
Dose escalation and definition of study end points: 1st sentence: “in phase I study” should be read as “in a phase I study”

Page 7: Dose modification: the first sentence should be deleted as well as table 1. These dose modifications are standard.
Page 7: first sentence: replace “dyarrhoea” with “diarrhoea”
Second paragraph: delete the sentence “the MTD was defined..” because it was explained twice before.
Last sentence: what do you mean with: “....cancer patients are of particular note in that all had...”? 
Page 9: Discussion: line 16: PPE is an abbreviation for what?
Page 14: delete table 1
Page 18: as you evaluated the MTD after 2 cycles table 5 is of limited interest. Delete table 5

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory 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