Reviewer's report

Title: Phase I/II study of first-line irinotecan combined with 5-fluorouracil and folinic acid Mayo Clinic schedule in patients with advanced colorectal cancer

Version: Date: 27 February 2004

Reviewer: Halfdan Sorbye

Reviewer's report:

General

The authors have combined irinotecan with the Mayo clinic schedule of 5-FU and folinic acid as first line therapy in colorectal cancer. This is a relevant study and such data have not been published previously. The phase I data however are not homogeneous due to different administrations of 5-FU and folinic acid. The phase II data are sounder and seen well controlled. The discussion and references included are up to date.

The results of this study show that the combination of irinotecan with the Mayo schedule is a highly toxic schedule. 3/49 patients died due to toxicity, 9/49 patients did not receive two full cycles and incidences of 3-4 haematological and non-haematological toxicity were very high. Median survival was disappointingly low, only 12 months. The report should serve as a warning to other clinicians not to use this combination.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The phase I part of this study was not done with identical administration of 5FU and Leucovorin. 9 patients received 5FU/FA as a 2-hour infusion (a deGramont regimen), whereas 14 patients received 5FU/FA as a 15-min infusion. These administrations are very different in effect and especially in toxicity. Is seems therefore not correct to combine the results from these different patients in the phase I part. The phase II data however are much more sound, all patients have received 5FU/FA as a 15-min infusion.

The phase I data should therefore mainly be removed from the paper, and presented in a condensed summery in the background or result part explaining the selected irinotecan dose for the phase II study. The paper should focus on the phase II data.

2. Abstract: 72 patients did not receive 5FU as a bolus infusion, 9 patients received a 2-hour infusion.

3. Abstract: This referee disagrees with the conclusion. In my opinion the conclusion of this paper is that irinotecan combined with the Mayo schedule is very toxic and should not be used further.

4. Methods page 5 last sentence, concerning tumor imaging: Where all tumor lesions evaluable after WHO criteria? What was the maximum time interval allowed from tumour imaging until inclusion into the study. Ultrasound is usually not recommended for tumor imaging in experimental clinical studies. When was US allowed to be used?

5. Methods page 6 2nd paragraph. Why did infusion of irinotecan vary between 30- 90 min. Why did the authors not choose a standard infusion time?

6. Methods page 7: As suggested in 1, remove phase I design.

7. Methods page 7: 2nd last sentence. Description of dose-reduction rules is not satisfactory. Please specify what grade was necessary for dose reduction. Were leucovorin doses ever reduced? How many dose-reductions were allowed?

8. Methods page 8, 2nd paragraph, 5th sentence. When calculating time to progression, all deaths
not only deaths due to malignant disease must be used.
10. Results page 12, 2nd paragraph. Most others studies use confirmed responses at > 4 weeks from the first response. The confirmed responses must therefore also be presented.
11. Figure 1. As stated in 8 all deaths should be used in calculating TTP. Why are 2 patients censored at 1 month, and one at 3 months? Are these the patients who died due to toxicity? If so calculation of TTP should be redone including all deaths. This figure should not at this point have any censored patients.
12. Table 2 should be removed.
13. Table 5. Confirmed responses both in evaluable and ITT should be presented

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

1. Abstract: Response rate for ITT should be mentioned.
2. Methods page 8, 2nd paragraph. What version of NCI-CTC was used?
3. Methods page 8 2nd paragraph, 2th sentence. Minor response is not a WHO criteria.
4. In general results should be presented mainly in table or in text, not both. Therefore 6 last sentences in page 9 should be removed.
5. Page 11-12. Toxicity data should mainly be presented in text or in table, not both as done in this paper.
6. Results page 12, 2nd paragraph. 17/49 patients were not evaluable. This is a very high number and of concern. Why did method of tumor assessment differ in as many as 9 patients? Why was it not possible to do a tumor assessment even if the method differed?
7. Page 14 last sentence and page 15 1st paragraph should be removed. This study provides no significant data and analysis showing less toxicity among the 9 patients with the 2-hour FU infusion.
8. Page 15 2nd paragraph, 2nd sentence. The data show early death in patients treated with irinotecan, not in the patients treated with oxaliplatin.
9. Conclusion: In this referees opinion this study is important as it shows that the combination of irinotecan with the Mayo schedule is a highly toxic schedule. Median survival was disappointingly low, only 12 months. The conclusion should be that irinotecan combined with the Mayo schedule is very toxic and should not be used further.
10. Table 1. Organ involved. Median number is not of interest, it must be separated into 1, 2 or = 3 lesions.

Discretionary Revisions (which the author can choose to ignore)

1. Background 2nd paragraph page 4: This paragraph could be removed, as it concerns mainly irinotecan monotherapy and not irinotecan used in combination chemotherapy.
2. Figure 2. Since the last inclusion, almost 3 years have gone. Why are so many patients still censored at 10 months? If possible an updated figure with fewer patients censored would be of interest, especially to see the fraction of long time survivors.
3. Table 1 page 26. What does a median time from first metastasis diagnosis of 1 month mean? Median time to what?
4. The phase II data from table 3 and 4 could be presented as one table.

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: Acceptable

Statistical review: No

Declaration of competing interests:

The referee has received financial research funding from Sanofi Synthelabo, Aventis Pharma and Roche AS.