Reviewer's report

Title: Clinical implications of thymidylate synthetase, dihydrorpyrimidine dehydrogenase and orotate phosphoribosyl transferase activity levels in colorectal carcinoma following radical resection and administration of adjuvant 5-FU chemotherapy

Version: 4 Date: 24 July 2007

Reviewer: Carlo Barone

Reviewer's report:

General

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

This is a retrospective study concerning 40 radically resected patients, who received UFT for two years. Both stage II and stage III patients are included and the prognostic role of TS, DPD and OPRT was investigated as well as their relationship with the clinicopathological characteristics. Several general and specific revisions are needed.

MAJOR COMPULSORY REVISIONS

A) General

1) TS and DPD are generally evaluated by IIC or by gene expression. The method used by the authors is less frequently used, therefore they should comment its effectiveness in comparison with the other methods. The reference to the paper describing the method (# 8) is incomplete.

2) At least for TS and DPD, both retrospective and also perspective studies on their prognostic role in the adjuvant therapy are not so rare. Some of these studies are reported by the authors (#16, 20, 22, 25), but several other have been published (for example: Johnston PG JCO 1994, Edler D JCO 2001, lacopetta B BJC 2001, Casciu S Ann Oncol 2001, Allegra JC JCO 2002, Ciaparrone M Oncology 2006 for TS; Nishimura G Oncol Rep 2002, Oi K Anticancer Res 2004, Ciaparrone M Oncology 2006 for DPD). What one may conclude is that the data are conflicting (Popat S JCO 2004), but the authors should discuss how their results might help in the general interpretation of the prognostic role of TS, DPD and OPRT.

3) The discussion should be shortened; indeed, many statement are general, repetitive or even futile. Only comments regarding the study object (the prognostic role of the TS, DPD and OPRT) should be maintained. It would be useful to state the different biological role of TS (the target enzyme of 5-FU) and
of DPD/OPRT (involved in 5-FU anabolism/catabolism) as well as their independent (or not) gene regulation. It may be important to remind the role of normal colonic tissue and liver or PMNCs in the total DPD activity, but actually no difference has been found in DPD activity between the tumour and the normal tissue. On the other hand, an hypothesis or an explanation about the lower level of OPRT in normal than in neoplastic tissue could be attempted in order to understand the biological meaning of the decrease of OPRT in tumors with lymph node metastasis. Finally, the study results and size don’t allow to support definitely the centrality of OPRT activity in deciding lymphadenectomy.

B) Specific

4) Page 6, lines 9-10. The statement is incorrect: Dukes’ B is a composite of better (T3N0) and worse (T4N0) prognostic groups, as is Dukes’ C (anyTN1 and any TN2). Accordingly, in Table 1 both ss and se patients are included in Dukes’ B as in Dukes’ C, not only pT3N0 or pT3N1 as reported in the text.

5) Page 13, lines 1-3. The sentence is too strong in relation to the data and the level of evidence of the study.

6) Page 13, lines 16-18. The study results don’t support this statement, if it is an hypothesis; otherwise, it should be reinforced by some other evidence in the literature.

7) Page 15, lines 2-10. The discussion should be based on adjuvant therapy; several studies have explored this context (see # 2 above). The study results and the low number of patients suggest more cautious conclusions.

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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 ESSENTIAL REVISIONS

A) General

8) The low number of patients might influence some authors’ conclusions. For example, this could explain the lack of survival difference between Dukes’ B (22 patients) and Dukes’ C (18 patients) stage. Similarly, the prognostic evaluation of the enzymatic activities studied may be affected by the small size of the sample.

9) Throughout the manuscript a confusion emerges in the use of the term “predictive”. In an adjuvant study we can predict the outcome as far as survival is concerned. This means that one or more enzymatic activities might have a “prognostic” value. Conversely, we could predict the response only in a study involving patients with metastatic disease.

10) The Authors don’t explain the reason of the cut-off for TS and OPRT activity, that they have chosen (10.7 and 0.51, respectively). Also, they don’t show the number of patients with low TS or high OPRT activity. Figures 2a and 2b would have a poor meaning if one subgroup was very low.
B) Specific

11) The reference #1 concerns only rectal cancer. Probably, references including both colonic and rectal cancer would fit better.
12) Page 5, lines 4-7. This statement should be modified according to the above item #4.
13) Page 6, lines 16-18. It is not clear the meaning of these sentences. Are they referring to UFT absorption? What evidence supports them?
14) Page 7, lines 13-14. How was the reaction stopped? By incubation or by adding 10% active carbon suspension or both?
15) Page 10, lines 15-18. The two sentences are similar: tumours with lymph node metastasis are Dukes’ C tumours.
16) Page 12, line 13-24. It is not clear the relevance to what is discussed.

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 of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.