Reviewer's report

Title: Matrix-metalloproteinases-1, -2, -3, -9, their inhibitors TIMP-1, -2, and the MMP1/TIMP1-complex in blood plasma as markers for transitional cell carcinoma of the bladder

Version: 3 Date: 2 January 2006

Reviewer: Cornelis Sier

Reviewer's report:

General
Title: Suggests that all parameters have 'marking' value, whereas only MMP-2 is actually shown to have (limited) diagnostic power. MMP-9, TIMP-1, and TIMP-2 might have additional value.

Aim: The choice of which plasma derived MMPs/TIMPs were to be evaluated for diagnostic validity in this study is rather unclear. Indicated is 'described to have an impact in bladder tumour carcinogenesis', but for instance MMP-7, MMP-10 and MMP-14 are equally, or perhaps even more important, considering the literature. Obviously, for the MMPs/TIMPs that were selected for this study, ELISA's are commercially available from EG/Amersham (coincidence?). The choice for the extra MMP-1/TIMP-1 complex ELISA is not explained, nor are the results discussed with respect to the single ELISAs for MMP-1 and TIMP-1.

Furthermore, if the goal was 'to evaluate the diagnostic validity of MMPs for EARLY diagnosis of TCC ', then there are not a lot of patients in this study. The extra and valuable information from advanced and/or metastasized stages has not been discussed sufficiently.

Data presentation: The presentation of the data in a single table is not effective. The reader simply does not have enough information to interpret the data him/herself. The value of the Discussion: The discussion is superficial with little indications of the impact of the study.

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

1 Although TCC is found primarily in males, as is the case in this cohort (45 vs 12), the patients and controls group are NOT matched for gender and age in this study. A sentence like 'There was also no statistical difference in age or sex between the healthy volunteers and the patients with TCC' is not enough to validate the approach. Especially not when a simple X2-test for gender shows that these groups are by no means comparable (P<0.001)! The fact that there were apparently no significant differences for all 7 MMP- related parameters between female and male controls (P<0.05 ?) makes an impression of statistical coincidence and could easily have been prevented by a presentation in a more controllable way.

2 Anyway, the way the results are presented, in a table with the controls as means plus 5th and 95th percentiles and the patient groups as median values with min./max., is uncommon and makes it impossible for the reader to compare the groups for him/her self.

3 If this study was meant as 'a new clinical marker'-study, it would have been nice to have a comparison with another, more or less established marker to estimate the potential of its performance. Furthermore, something clinically relevant should have been concluded. Is plasma MMP-2 determination indeed an easy and economical option for detection of early TCC for the future, or are additional (MMP) measurements always necessary? For clinicians the answer is unclear from this study. If the study was also meant to provide some info about the mechanism, considering the fact that also complexes were determined, there should have been at least some discussion about the relevance of the use of MMPs, next to their inhibitors, and the comparison with the complexes. Related to this:

4 What is the explanation for the relatively high MMP-1 and TIMP-1 levels in metastasized patients?
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
What was actually the dilution of the plasma for MMP3, none?
What is the median MMP9 level for G3 patients?
Which were the paired samples, as mentioned in the M&M section (statistical analyses)?
Specific IFCC guidelines are not in those 2 (?) references.
In the end, the conclusions are drawn out of the group of 57 non-metastasized patients? Please state more clearly.

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.