Reviewer's report

Title: CYP39A1 polymorphism protects against toxicity during intensive induction chemotherapy in patients with advanced head and neck cancer

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Reviewer: Balram Chowbay

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The authors investigated the impact of candidate genetic variants in ERCC2, ERCC1, XRCC1 and CYP39A1 on docetaxel-induced leucopenia in 78 patients who were treated with TPF (taxane, cisplatin and 5-fu) induction chemotherapy for advanced head and neck cancer. The authors reported a significant relationship between genotype A of the CYP39A1 rs7761731 with a higher incidence of toxicity during treatment. My comments are appended below.

Major Compulsory Revisions

1. The authors mentioned that CYP39A1 SNP influenced the metabolism of docetaxel but there was no available data supporting the role of CYP39A1 in docetaxel metabolism. A few lines of evidence or postulation in the discussion section will be helpful.

2. Apart of CYP39A1, there were also several reports on the effects of other docetaxel metabolizing enzymes eg. CYP3A4/5 and transporters ABCB1 or SLCO1B3 on docetaxel PK and PD in other patient populations. While the authors did not screen for these candidate SNPs, the authors should make an effort to highlight this in the discussion. Several papers for reference are:
   Br J Clin Pharmacol. 73, 606-618 (2012)
   Cancer Chemother Pharmacol. 67, 1471-1478 (2011)

3. It is known that interethnic variability in SNP frequency exists. Therefore the authors should include the ethnicity breakdown of the patients for future reference.

4. The candidate SNP analysis has no correction for multiple comparisons which seriously confounds the findings of this study. The effect of rs7761731 on toxicity may be a chance effect, especially when the sample size is small in this pilot study. These findings ought to be investigated in a larger, well powered study. Furthermore, it is very difficult to pinpoint docetaxel as the causative drug responsible for the observed leucopenia when the patients received other myelosuppressive drugs such as platinum and 5-FU.

5. The authors should include pharmacokinetics data as such analysis will provide a better insight regarding the pharmacogenonomomics-pharmacokinetics-toxicity relationship.

Minor Essential Revisions
1. The footnotes under Table 1 do not correspond to the table content.
2. There is no table or figure depicting the effect of rs7761731 on leucopenia and endpoint of infections or death. Table 3 is redundant.

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, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests'