Reviewer’s report

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

Version: 2  Date: 19 July 2015

Reviewer: Mei-Kim Ang

Reviewer’s report:

In this research article, the authors present a retrospective analysis of 78 patients with head and neck cancer treated with induction TPF. The purpose of the study was to evaluate genetic polymorphisms associated with efficacy and toxicity during induction chemotherapy.

This clinical question is relevant, even as the role of induction chemotherapy in HNSCC is still being debated. Induction chemotherapy with TPF is recognized as a highly active chemotherapy regimen and may be useful particularly in patients with locally advanced disease deemed unresectable and/or where frontline radiotherapy may be associated with significant toxicities as well. However, TPF despite its efficacy, is known to have significant toxicities particularly that of myelosuppression.

With respect to the manuscript, it requires major compulsory revisions.

1) Title & Conclusion

Line 1: “CYP39A1 polymorphism protects against toxicity…. “
Line 314 : “this is the first report of a gene polymorphism protective against docetaxel-induced toxicity…. ”

In this study, the results report that CYP39A1 homozygosity is associated with higher incidence of grade 3 or 4 leucopenia, infections or death.

a. However, this does not lead to a conclusion of protective effect of CYP39A1 polymorphism
b. The results are not specific to docetaxel chemotherapy as patients were all treated with triplet regimen of TPF.

2) Abstract

In general, the abstract is too brief and needs more details.

a. Background: Please state what toxicity that docetaxel is associated with, and what is the purpose/ rationale of the study
b. Methods: more information about the patient population should be included: what was the induction chemotherapy regimen utilized, what their subsequent treatment after induction chemotherapy was. The primary objective/ endpoint(s)
of study should be included, and what were the genetic polymorphisms being evaluated and method used for that.

c. Results:
   i. “Overall response rate was high with 78.1% and 88.5% of the patients were able…” : this sentence is confusing and will be better to rephrase it.
   ii. Please report all results that are related to primary endpoint and objective of the study?.

I. For example, as this study is evaluating toxicities of induction chemotherapy, will be relevant to report what these were
   II. Similarly line 91: “…incidence of toxicity during treatment” : to clarify what toxicities these were
   III. As the study also evaluated efficacy of therapy according to ERCC, XRCC gene polymorphisms, this data should be included (if this is a primary endpoint of the study).

3. Background
   a. Line 100: “cytostatic regimens” : please clarify this term, as usually standard chemotherapy would be regarded as “cytotoxic” chemotherapy (and in fact the term cytotoxic chemotherapy is used in line 115)
   b. Line 101, 104: Minor grammatical errors need correction
   c. Line 122-124 : Only 1 reference cited for docetaxel-related toxicity especially neutropenia leucopenia, although there are several other references and case series in the literature that can be included.

4. Patients and methods
   a. Please state how many cycles of induction chemotherapy were planned and what was the subsequent therapy after induction/ how this was decided.
   b. Please define how response was evaluated
   c. Please could you state the primary (and secondary, if any) objectives of the study.
   d. The evaluation of efficacy endpoints eg response and survival in association with ERCC and XRCC SNPs were not described as part of the methods section although the results were reported in brief (line 208). Please include in methods.
   e. Line 160-166 :
      a. Line 160: use of term “cytostatic” is incorrect
      b. There are several other reports in the literature of other SNPs that have been studied in the context of docetaxel toxicity, and which are linked to docetaxel metabolism and drug transportation: CYP3A4, CYP3A5, ABCB1, SLCO1B3, ABCC2, (Choi, Cancer Res Ther 2015; Kiyotani K, Cancer Sci 2008), however none of these were evaluated in the present study. The study will be more complete if other docetaxel-related SNPs were evaluated, and not just 1 possible SNP associated with Docetaxel related toxicity
f. Line 167: use of formalin fixed tissue samples is not standard methodology to evaluate SNPs. Can authors describe method used, and previous experience and quality of data obtained using this method?

g. Line 171: not enough information is supplied on methodology of SNP analysis, primers, reagents used etc.

5. Results

a. Table 1:

i. For “Sex”, “treatment after TPF”, the numbers in the columns are confusing. Please state no. of patients and give % only in brackets. Please give no. and % of patients with stage I/II/III and IV disease.

ii. How many patients had unresectable disease? This is relevant to interpretation of the overall survival and PFS data

b. Line 185: please state % of patients with PR and % of patients with CR, and how/ when response was measured

c. Line 193: was LRC with/ without concomitant cisplatin an objective of the study? If so, please define it in methods section

d. Line 208 - 210:

i. Which SNPs were evaluated in association with efficacy/ response/ LRC/ PFS and OS?

ii. How were the SNPs assessed in their relationship to response/LRC/PFS and OS? Was it by univariable, or multivariable analysis? Please could you give the relevant detailed data including hazard ratios, p-values, what were other significant variables affecting outcomes that were evaluated.

e. Line 213: please give detailed breakdown of all toxicities of induction TPF, according to CTCAE grading (line 148), in table format

f. Line 231: was effect of SNP CYP39A1 on leucopenia assessed to be independent of other clinical factors eg age, sex etc.?

6. Discussion

a. Line 241, 279: grammar

b. Line 242: “treatment related toxicity” – is this referring to RT toxicity or induction chemotherapy toxicity. The sentence is confusing

c. Line 259: see 5 (c)

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests