Reviewer's report

Title: Multicenter phase II study of weekly docetaxel, cisplatin, and S-1 (TPS) induction chemotherapy in locally advanced squamous cell cancer of the head and neck

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Reviewer: Harry Quon

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General Comments:
The authors are to be congratulated for their efforts to investigate alternative induction chemotherapy strategies that offer an improved therapeutic ratio to that of what is regarded as the gold standard of TPF where the 5-fluorouracil (5-FU) is often regarded as contributing to significant acute toxicities. Despite recent negative though underpowered randomized trials evaluating the role of induction chemotherapy to concurrent chemoradiotherapy, there remains sufficient provocative evidence suggesting that both induction and possibly concurrent chemotherapy may have activity in reducing the rate of distant relapses. Thus, the study of induction chemotherapy continues to be a potentially rich therapeutic strategy.

Randomized evidence suggest that taxanes added to a PF backbone is important but can contribute to increased myelotoxicity. Thus, reducing the myelotoxicity observed with TPF may be realized with studies evaluating substitutions for 5-FU. S-1 is an oral mixture of tegafur (5-fluorouracil prodrug), gimeracil (reversible inhibitor of dihydropyrimidine dehydrogenase that is involved in 5-FU metabolism) and oteracil potassium (inhibiting 5-FU phosphorylation reducing GI toxicity). In this context, the phase II study reported by Bae et al. is of clinical significance.

With mature follow-up enrolling and treating 35 patients of which 30 were evaluable due to 5 (17%) not completing the induction chemotherapy with 3 patients due to chemotherapy-related grade 4 toxicity, the authors observed an overall 85.7% response rate after the weekly regimen x 2 weeks over 3 week cycles x 3 cycles The authors also reported favourable rates of grade 3/4 neutropenia and febrile neutropenia. Non-significant decrease in the EORTC QLQ C30 global score was observed and was consistent with the suggestion that this regimen may be less toxic and better tolerated overall. Of note was that the majority of the enrolled subjects were with oropharynx primaries where the majority were in fact HPV negative and had a significant history of tobacco exposure history. This observation is particularly relevant as the relative pattern of relapse demonstrated that all relapses were local-regional without any observed distant relapses. Thus, despite administering a lower docetaxel dose-intensity, comparable if not favourable activity was observed potentially in a
more prognostically adverse patient population to other docetaxel/platinum-based induction regimens.

Specific Comments

Major Compulsory Revisions

1) Page 6: it is noteworthy that the investigators used the presence of grade 3 mucositis or dysphagia which is typically regarded as an accepted serious but manageable and expected toxicity associated with concurrent chemoradiotherapy. For this to constitute a planned interruption in the radiotherapy introduces the risk of increased local-regional relapses due to the influence of accelerated tumour repopulation. In fact, 6/30 (20%) evaluable patients demonstrated radiotherapy interruptions due to the criteria of grade 3/4 mucositis and the dominant pattern of relapse was local-regional. As such, it is important to report how many did in fact have grade 3 or was it grade 4 mucositis that lead to the planned interruption. Moreover, it is important assess if this may have contributed to the increased relative local-regional pattern of relapse. This is also important as the most significant observation (though limited by the sample population) is the absence of distant relapses observed raising questions as to whether this regimen may in fact be as active (based on the primary endpoint of overall response rate) or possibly more active than the TPF regimen.

2) What proportion of the enrolled subjects were resectable vs. technically unresectable vs. regarded as functionally unresectable.

2) The authors need to include a concluding stating as to whether or not they accepted their hypothesis or not. based on their statistical plan. This is important as the authors conclude that the regimen merits further randomized clinical evaluation.

3) Please comment on how mucositis was evaluated and scored and by whom and was there rater reliability performed.

Minor Essential Revisions

1) re: Table 3: Please clarify in the figure legend how 9 weeks was referenced to the treatment regimen

2) Table 4: "Trombocytopenia"

3) remove additional survival figure at the end of the manuscript

Discretionary Revisions

1) Minor grammatical errors ie. pg 11"...Future studies are need to..."

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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.