Author's response to reviews

Title: Preliminary estimation of the prevalence of chemotherapy-induced dysgeusia in Japanese patients with cancer

Authors:

Hiroo Imai (imagen@med.akita-u.ac.jp)
Hiroshi Soeda (soeda@med.akita-u.ac.jp)
Keigo Komine (k.komine@idac.tohoku.ac.jp)
Kazunori Otsuka (kaz@med.akita-u.ac.jp)
Hiroyuki Shibata (hiroyuki@med.akita-u.ac.jp)

Version: 4 Date: 19 September 2013

Author's response to reviews: see over
Dear Dr. Sriram Yennu, and editors

Thank you for your meaningful and heart-warming advice to our manuscript. We read it carefully, and made revision according to your suggestion. We describe corrections below one by one. The changes were clarified in red.

Abstract
1) In the background section, “prompt method” was changed to “an objective method” (page 2, line 5).

2) The first sentence of methods was modified and moved to the last sentence of the background section as below.

“Therefore, we evaluated the prevalence of dysgeusia induced by recently approved chemotherapies.” (page 2, line 9)

3) The design of this study was explained in the methods section, as described below.

>A cohort study design was used to obtain pilot data to determine the prevalence of dysgeusia. (page 2, line 11)

4) The main outcome was clarified in the result section, as described below.

Dysgeusia developed in 38.8% (14/38) patients receiving chemotherapy; this prevalence was highest in the patients receiving 5-fluorouracil and its oral analogs (48.1%, 13/27). (page 3, line 4)

5) Following sentence was changed to described below.

The patients aged >70 years revealed a tendency to frequently experience dysgeusia (75.0%, 6/8). (page 3, line 8)

6) The relative risks described in abstract were deleted, and replaced by frequency and number, as described below. (page 3, line 4)

> this prevalence was highest in the patients receiving 5-fluorouracil and its oral analogs (48.1%,
Particularly, dysgeusia developed in 55.6% (10/18) patients receiving oral 5-fluorouracil analogs; however, the differences in the prevalence between the patients receiving and off chemotherapy were not statistically significant.

7) Conclusion section was totally rewritten as described below. (page 3, line 11)

An association between dysgeusia and chemotherapy may exist with regard to recently approved chemotherapeutic drugs. Therefore, routine investigations to assess dysgeusia in patients receiving chemotherapy should be performed using objective methods such as paper strip testing. Furthermore, intervention to prevent dysgeusia for protection of quality of life may be required.

Main body

1) In the background, short explanation of taste strip was added as described below. (page 5, line 1 from the bottom)

In this study, a salt-impregnated taste strip was used to evaluate dysgeusia because of its objectiveness, ease, and low cost.

2) In the result section, description about participants, detailed and unnecessary informations were deleted and rewritten as shown below. (page 11, line 4)

"Among those patients, 3 had completed chemotherapy at least 1 year prior, 2 had not started chemotherapy at the time of evaluation, 2 could not undergo chemotherapy because of severe complications such as liver dysfunction and heart failure, and 2 decided not to pursue any chemotherapy. Among 9 patients, all but one colon cancer patient (stage III) were diagnosed as stage IV."

"Among those patients, 3 had completed chemotherapy at least 1 year prior, 2 had not started chemotherapy at the time of evaluation, 2 could not undergo chemotherapy because of severe complications such as liver dysfunction and heart failure and 2 decided not to pursue any chemotherapy. Among 9 patients, all but one colon cancer patient (stage III) were diagnosed as stage IV."

All participants were diagnosed with malignancies (Table 1) and were categorized as stage IV disease.
3) The following sentence was changed as described below. (page 12, line 8)
> Pre) Even patients in the off-chemotherapy group could feel taste alteration.
> Post) Even patients in the off-chemotherapy group experienced altered taste because of their past histories of chemotherapy or other comorbidities.

4) The discussion section was totally rewritten according to suggestion.
4-1) In the first sentence, a main result was claimed as described below. (page 16, line 8)
> The prevalence of dysgeusia due to recent chemotherapy was 38.8% in our hospital.

4-2) Then, the other objective methods were explained, and finally, merits of taste strip were described.
> “Objective evaluation of the impact of taste alteration in the clinic requires several types of procedures, including electrogustometry, whole-mouth gustatory testing and magnetoencephalography [18-20]. However, because these procedures are labour-intensive, they are not suitable for routine evaluation. It was reported that among patients with phantogeusia and parageusia, 38% reported salty and 22% reported mixed sensations, such as bitter–salty or sour–sweet [21]. Evaluation of all 5 tastes including salty, sweet, bitter, sour and umami is labour-intensive. Further, it has been reported that except for umami, other tastes are sensitive to radiotherapy to the same extent [22]. Hence, other alternative approaches are warranted.

4-3) and finally, merits of taste strip were described. (page 17, line 1)
In this study, we used the Salsave kit® paper testing because of its ease of use during routine examinations [29]. This type of testing can easily diagnose dysgeusia, and the method is adequate for mass screening. In addition, this taste strip could objectively estimate the grade of dysgeusia and was suitable for follow-up testing as well.

4-4) Next, the high frequency of taste alteration induced by oral 5-FU analogues was described below. (page 17, line 5)
> Our study indicated that oral 5-FU analogs can potentially induce dysgeusia during therapy. These recently approved drugs have become important therapeutic drugs for various types of malignancies, including colorectal, gastric, mammary, and pulmonary cancers, which are the cancers with the highest incidences worldwide.
4-5) Future design of clinical study with oral 5-FU analogues to assess taste alteration together with a main outcome was concerned as described below. (page 17, line 9)

> Therefore, in conducting larger scale studies using oral 5-FU analogs, it would be necessary to evaluate dysgeusia, and the paper strip test would be convenient for assessing a larger number of participants.

4-6) Then, intervention to lessen taste alteration was followed as below.

> In addition, intervention to lessen taste alteration should be considered to support QOL for cancer patients undergoing chemotherapy. Zinc consumption has been reported to improve taste sensation affected by radiation [23]. Glutamine is also known to ameliorate neuropathy induced by cisplatin and paclitaxel in rats [24]. However, a phase III trial using oral glutamine failed to prove that it could prevent taste alteration caused by taxanes [25]. A standard treatment for taste alteration caused by cancer and cancer therapy has not yet been established [26]. The importance of supportive care during chemotherapy, such as care with antiemetics, has been recognized [27,28]. Future clinical studies in this regard are warranted.

Our study also showed that elderly patients are susceptible to taste alteration.

The final sentence was deleted.

4-7) Limitation of this study was described below. (page 18, line 5)

> Finally, our study was observational, and we did not detect any statistically significant differences with regard to the prevalence of dysgeusia between the on- and off-chemotherapy group patients, which could be attributable to the limited sample size.

Additional changes

1) Taste alteration was changed to dysgeusia
2) Corresponding author was clarified on the top page.
3) The underlying phrase was inserted as below. (page 3, line 7)

“however, the differences in the prevalence between the patients receiving and off chemotherapy were not statistically significant.”

4) “cancer patients receiving chemotherapy” was retracted from keywords, and dysgeusia was added. (page 4)

5) “grade of dysgeusia” was defined in the methods. (page 8, line 10)
6) The following sentence was moved from methods section to results section. “The relative risk of dysgeusia between the on- and off-chemotherapy groups was 1.66 (NS).” (page 13, lie 6)

7) Titles of Tables were set on the top.

I am sending herewith a revised version of research article entitled “Preliminary estimation of the prevalence of chemotherapy-induced dysgeusia in Japanese patients with cancer”, according to your kind suggestion, which I should like to submit for publication in BMC Palliative Care.

Evaluation of dysgeusia suffered from cancer chemotherapy is very important issue to be conducted to keep QOL of cancer patients. However, objective way how to assess taste alteration has no been established. Especially, we claimed that a medical oncologist should know the prevalence of dysgeusia induced by chemotherapy as a routine. Salt paper strip is easy and enough to evaluate this situation.

This manuscript has not been published or submitted elsewhere. All authors are in agreement with the content of the manuscript. We declare there is no conflict of interest in this work.

In revising this paper, we show changes point by point below.

It is my great pleasure, if you accept our revision.

Yours sincerely

Hiroyuki Shibata