

July 13, 2016

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 26831-07132016.doc).

Title: Efficacy of Japanese Traditional (Kampo) Medicine for Treating Chemotherapy-Induced Peripheral Neuropathy: A Retrospective Case Series Study

Author: Yumiko Kimata, Keiko Ogawa, Hideki Okamoto, Atsushi Chino, Takao Namiki

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 26831

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been changed into retrospective study.

2 Revision has been made according to the suggestions of the reviewers.

Response to reviewer 00742507

We thank reviewer 00742507 and add the sentence "See the content of each Kampo formula at:

http://dentomed.u-toyama.ac.jp/en/medical_information_on_kampo_formulas/"

(page 13, 7 lines from the bottom) because we afraid it takes too much space if we include all content of all Kampo formulae. This is the website for public benefits run by Toyama University School of Medicine.

Response to reviewer 00004208

We are so much grateful for the comments of reviewer 00004208.

Response to reviewer 03580207

Reviewer 03580207's points are quite reasonable and we thank reviewer 03580207, which should refine our article further.

- 1) We changed the format into retrospective study. Thanks a lot.
- 2) We rewrote the symptom evaluation as "the effectiveness of the Kampo treatment was self-evaluated by the patients in this study. They described their unpleasantness mixed with pain, numbness, and pins-and-needles sensation and those symptoms were prone to change into each other even during the Kampo treatment. The patients in the clinical records, therefore, described the improvement of symptoms how many percent of symptom reduction or how

many points of the 11-Point Numerical Rating Scale for Pain Intensity (NRSI) was gained in terms of the total unpleasantness including pain, numbness, and pins-and-needles sensation comparing before and after the Kampo treatment. In this retrospective study covering 5 years, their improvement of symptoms was equally defined as signifying a "major response" when the whole unpleasantness showed reduction by 50% or more, a "minor response" when the reduction was less than 50%, and "no response" when they felt no positive response, comparing before and after the Kampo treatment. When the pain, numbness, and pins-and-needles sensation were present at two or more sites, we used an averaged evaluation." (page 14, 4 lines from the top).

- 3) As we also answer reviewer 00742507, there are too many Kampo formulae showing up in this article and we afraid it takes too much space if we include all content of them. We, therefore, add the sentence "See the content of each Kampo formula at: http://dentomed.u-toyama.ac.jp/en/medical_information_on_kampo_formulas/" (page 13, 7 lines from the bottom). If both of the reviewers still prefer including the content of Kampo formulae in this article, we would like to think it over.

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

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July 25, 2016

Dear Editor-in-chief,

Please find attached the revised manuscript in Word format (file name: 26831-Review 20160725.doc).

Title: Efficacy of Japanese Traditional (Kampo) Medicine for Treating Chemotherapy-Induced Peripheral Neuropathy: A Retrospective Case Series Study

Author: Yumiko Kimata, Keiko Ogawa, Hideki Okamoto, Atsushi Chino, Takao Namiki

Name of Journal: *World Journal of Clinical Cases*

ESPS Manuscript NO: 26831

Revision has been made according to the editor-in-chief's review report. As the editor-in-chief pointed out, there might not have been enough information that Kampo is treated the same as conventional Western medicine in Japan and several Kampo formulae have lately accumulated the clinical evidence by randomized controlled trials not only in Japan but in other countries. Asian traditional medicine such as Kampo and traditional Chinese medicine are supposed to be included in ICD-11 by WHO. We, therefore, added the sentences and references as follows: "Conventional medical doctors in Japan introduce patients to Kampo experts when the Kampo medicines prescribed by them are not effective enough or when conventional medicine cannot improve patients' symptoms [18]. Quality control of the herbs used in Kampo has been established for both extract granules and decoctions, and the safety and reliability of Kampo have been well-established through the strict monitoring of side effects under the control of the Japanese Ministry of Health, Labor, and Welfare in the same way as conventional medicines are used [19]. In addition, the clinical efficacy of some Kampo medicines, especially daikenchuto and yokukansan, has been demonstrated in many clinical trials done in the USA and Japan by conventional medical doctors using the standard methods of conventional medicine [18,20-23]" (page 17, the first line from the top).

18 **Kono T**, Kanematsu T, Kitajima M. Exodus of Kampo, traditional Japanese medicine, from the complementary and alternative medicines: is it time yet? *Surgery* 2009; **146**: 837-840 [PMID: 19744449 DOI: 10.1016/j.surg.2009.06.012]

19 **Cameron S**, Reissenweber H, Watanabe K. Asian medicine: Japan's paradigm. *Nature* 2012; **482**: 35 [PMID: 22297961 DOI: 10.1038/482035a]

20 **Iturrino J**, Camilleri M, Wong BS, Linker Nord SJ, Burton D, Zinsmeister AR.

Randomised clinical trial: the effects of daikenchuto, TU-100, on gastrointestinal and

colonic transit, anorectal and bowel function in female patients with functional constipation. *Aliment Pharmacol Ther* 2013; **37**: 776-785 [PMID: 23451764 DOI: 10.1111/apt.12264]

21 **Manabe N**, Camilleri M, Rao A, Wong BS, Burton D, Busciglio I, Zinsmeister AR, Haruma K. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. *Am J Physiol Gastrointest Liver Physiol* 2010; **298**: 970-975 [PMID: 20378829 DOI: 10.1152/ajpgi.00043.2010]

22 **K. Iwasaki**, Satoh-Nakagawa T, Maruyama M, Monma Y, Nemoto M, Tomita N, Tanji H, Fujiwara H, Seki T, Fujii M, Arai H, Sasaki H. A randomized, observer-blind, controlled trial of the traditional Chinese medicine Yi-Gan San for improvement of behavioral and psychological symptoms and activities of daily living in dementia patients. *J Clin Psychiatry* 2005; **66**: 248-252 [PMID: 15705012]

23 **Mizukami K**, Asada T, Kinoshita T, Tanaka K, Sonohara K, Nakai R, Yamaguchi K, Hanyu H, Kanaya K, Takao T, Okada M, Kudo S, Kotoku H, Iwakiri M, Kurita H, Miyamura T, Kawasaki Y, Omori K, Shiozaki K, Odawara T, Suzuki T, Yamada S, Nakamura Y, Toba K. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukan-san, in the treatment of the behavioural and psychological symptoms of dementia. *Int J Neuropsychopharmacol* 2009; **12**: 191-199 [PMID: 19079814 DOI: 10.1017/S146114570800970X]

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

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