Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-901.

Reviewer A

A well written prospective early phase trial of Kampo to assess hot flash benefit, a significant unmet clinical need. The data are clearly reported as well as the study's limitations.

(**Reply**)

Thank you for reviewing our manuscript. The present study demonstrated that Keishibukuryogan is an effective and safe treatment for hot flashes in PC patients receiving ADT. We believe that this medicine can be the one of the treatment option for hot flashes in PC patients.

Reviewer B

1. This manuscript looks at the effectiveness of a traditional Japanese Kampo medicine in reducing hot flashes in prostate cancer patients undergoing ADT. Overall, it is clear that this medicine has little to no side effects, and does have some benefit in reducing the strength of hot flashes, although not reproducible in a more objective AMS scale.

(**Reply 1**)

Thank you for reviewing our manuscript. The present study demonstrated that Keishibukuryogan is an effective and safe treatment for hot flashes in PC patients receiving ADT. In accordance with your comments, an objective tool for evaluating hot flash has been not currently available, and so we used a daily describing their hot flashes in addition to AMS scale; The diary included information regarding the strength, frequency, and mean duration of hot flashes. The hot flash strength was assessed by the visual analog scale (VAS), and duration was described in three categories: <3 min, 3 to 5 min, or >5 min.

2. Unfortunately, this study suffers from significant inherent sample size calculation and recall bias. The author needs to explain how the sample size of 30 patients is derived? Is it from a statistical point of view, or a pilot study?

(**Reply 2**)

Setting of sample size has described in patients and methods （Page 6, Line 10-14, which was

described by red color.）. Unfortunately, in accordance with reviewer's comments, sample size was not established based on scientific proof. The sample size was calculated based on the number of patients undergoing hormone therapy per year at research facilities and incidence rate of hot flashes, which was set as the number of cases considered to be practicable in daily medical practice within the registration period. This was a prospective observational pilot study. In addition, the present result is certainly affected by recall bias, and then we have added this comment in limitations.

3. Separately, because of the nature of a one-sided study, there is no baseline comparisons of what the patients may have felt should there be a placebo control. The subjective improvement in strength of hot flushes may simply be a 'feel good' effect of having an oral supplement, and therefore, was evidently not reproducible in the objective AMS scale. The author needs to compare with a placebo study group to objectively appreciates the real benefit of this medicine.

(**Reply 3**)

According to the reviewer's comments, the present study was a single-arm cross-sectional one and not a randomized controlled trial. Therefore, the efficacy of TJ-25 may include some placebo effects. In addition, no objective scales for authorizing hot flash symptoms have been currently available, which is also a subject of the present study. Therefore, we used diary data including frequency, strength, and duration of hot flashes per day as one of the study outcomes, in addition to AMS scale. Although it is very difficult make placebo formulation of any herbal medicines, we also consider it necessary to carry out open-label RCT to validate the results of this study. On the other hand, we hope that this study will become a pilot study for the next RCT and can be used as a statistical data for setting the statistical case size. Based on the above points, the discussion part (Page 11, line 23 to Page 12, line 1, which was indicated by red-color) indicates the need for further research. Although the present study includes many limitations indicated by the reviewer, this is the first prospective pilot-study to demonstrate efficacy of TJ-25 for hot flashes among PC patients receiving ADT, and then we believe that this is valuable study.

4. The results of this study are unfortunately at most explorative, and require further work and detailed methodology to objectively review the role of complementary medicine in men with

prostate cancer undergoing ADT.

(**Reply 4**)

According to the reviewer's comments, this is a single-arm cross-sectional study and not a randomized controlled trial, which is one of the limitations of this study. This point has been described in limitation (by red color). Therefore, further prospective randomized controlled trials including large numbers of participants are certainly required to validate the results of this study. This sentence is described in discussion (Page 11, line 23 ～ Page 12, line, which was indicated by red color.）