Author’s response to reviews

Title: Efficacy of the combination use of aprepitant and palonosetron for improving nausea in various moderately emetogenic chemotherapy regimens

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PHAT-D-18-00204

Efficacy of the combination use of aprepitant and palonosetron for improving nausea in various moderately emetogenic chemotherapy regimens Naohisa Yoshida; Tetsuya Taguchi; Masayoshi Nakanishi; Ken Inoue; Tetsuya Okayama; Takeshi Ishikawa; Eigo Otsuji; Koichi Takayama; Haruo Kuroboshi; Motohiro Kanazawa; Yoshito Itoh
Dear Dr. Benjamin Ragen,

Editor of BMC Pharmacology and Toxicology

We are very glad to your consideration for the publication of our manuscript for BMC Pharmacology and Toxicology. We changed detail of draft according to peer review’s comments. I would like to receive good news from you.

Sincerely,

Naohisa Yoshida

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Reviewer reports:

Elpis Mantadakis, MD, PhD (Reviewer 1): The manuscript PHAT-D-18-00204 by Yoshida N et al describes the results of a retrospective, observational study that compared the efficacy of a triple anti-emetic regimen (aprepitant, palonosetron, and dexamethasone) versus the combination of palonosetron and dexamethasone in adult patients with cancer receiving moderately emetogenic chemotherapy.

Main criticism

The main problem of the study is that the patients were not randomly assigned to one of the two anti-emetic regimens and neither was the investigator blinded to the anti-emetic regimen prescribed. This is a serious problem with the study design, which in essence is a retrospective review of patient medical records, something that can certainly introduce bias. Moreover, the patient population was inhomogeneous, since it included patients with colorectal, gastric, lung, and several types of gynecological cancers. To make things worse, there was a significant difference in the median age and primary organ involved with cancer between the two groups of anti-emetics. Finally, although the exclusion criteria are clearly stated, the authors fail to explain
in Figure 1, why 134 patients with breast cancer and 50 patients with pancreatic cancer were excluded from further analysis.

Answer: We appreciate your helpful comments. In this study, all symptoms including nausea and vomiting were recorded using a questionnaire, which was used in our center since 2012 for all patients. The questionnaire was written by each patient in our center with the help of our qualified nurses who didn’t know this study. It was according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) grade ver. 4.0 after every course of chemotherapy. So, the possible bias about the evaluation of symptoms was not affected by doctors. We wrote this clearly in the Method section (Page 11, line 13-).

To decrease inhomogeneous the patient population, we performed a propensity score-matching analysis between the two groups to reduce the effect of any selection bias including sex, age, primary organ, and so on. The propensity score-matching method was proposed to evaluate statistically causal effects free from confounding effects by mathematically refashioning an observational study into a randomized study [new ref. 19,20]. Finally, we analyzed 97 patients in the two-drug group and 97 patients in the three-drug group. There were no significant differences about patient characteristics between two groups in the revised table 1. We wrote this explanation in the Method section (Page 9, line 3-).

Moreover, regarding the exclusion of 134 patients with breast cancer and patients with 50 pancreatic cancer, those cases were excluded to analyze MEC regimens using L-OHP, CDBCA, and CPT-11 in this study. We added this explanation in the Method section (Page 9, line 3-).

Reference

19. Rubin DB. Estimating causal effects from large data sets using propensity scores


Minor criticism

There are several typos and mistakes throughout the manuscript. For example, in line 49, page 9, creatinine is misspelled to creatine, in line 42, page 14, be is misspelled to ne, the units of hemoglobin in Tables 2-4 are incorrect (mg/dl instead of the correct g/dl), etc.

Answer: Thank you for your comments. We amended these parts.
Hesham Al-Sallami, PhD (Reviewer 2): The authors of the article titled "Efficacy of the combination use of aprepitant and palonosetron for improving nausea in various moderately emetogenic chemotherapy regimens" present an analysis of an observational study on the use of aprepitant vs aprepitant + palonosetron in addition to dexamethasone for the treatment of CINV.

The article is well-written and the study is interesting and may be of interest to the journal's readership. However, two major issues need to be addressed before this article is considered for publication:

What does this study add to the current literature on the use of this combo in CINV? E.g. Longo et al (IJCP 2012).

Answer: The literature by Longo et al. was written about the use of three-drug treatment including Palonosetron to the HEC regimen. Another study of three-drug treatment with palonosetron for HEC including cisplatin (>50 mg/m2) showed no nausea rates were 61.5-70.4% during 6 cycles of chemotherapy [26]. These results suggest that palonosetron might have higher efficacy against delayed nausea than first-generation 5HT3RA. According to several guidelines, three-drug treatment including palonosetron is recommended for preventing CINV due to HEC. On the other hand, three-drug treatment for MEC is controversial though the control of nausea is not enough using two-drug treatment. Thus, in this study, we analyzed the efficacy of the three-drug treatment for preventing nausea due to MEC. We concluded the three-drug treatment’s efficacy for preventing nausea was not superior than two-drug treatment including palonosetron.

We added this explanation in the Introduction and Discussion section and referred the paper by Longo et al (new ref. 26) (Page 7, line 9, Page 18, line 11).

Reference


What were the specific scores used to measure nausea and vomiting (presumably separate scores?)

Answer: Thank you for your comments. In this study, all symptoms including nausea and vomiting were recorded using a questionnaire, which was used in our center since 2012 for all patients. The questionnaire was written by each patient in our center with a help of our qualified nurses who didn’t know this study. It was according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC) grade ver. 4.0 after every course of chemotherapy. We wrote this explanation in the Method section (Page 11, line 13-).
Did all patients receive fixed doses and frequencies of the anti-emetic drugs? If not, dosage should have been included in the regression analyses.

Answer: We appreciate your comments. All patients received fixed dose of NK1RA and palonosetron and fixed frequency of them. However, among all chemotherapy, whether additional oral DEX (4-8mg) on day 2-3 days of chemotherapy was administered in both the two- and three-drug groups, were decided by each doctor according to patient characteristics. We analyzed the rates and added them in the Table 1. There was no significant difference of the rates between the two-drug and the three-drug groups before and after propensity score matching (before: 9.3% vs. 14.0%, p=0.25, after: 9.3% vs. 12.4%, p=0.49). We wrote this explanation in the Method section (Page 13, line 11).

Kawa Dizaye, PhD, MSc, HD (Clin.Pharm), BSc Pharm (Reviewer 3): Dear Authors Thanks for your clinical useful manuscript entitled (Efficacy of the combination use of aprepitant and palonosetron for improving nausea in various moderately emetogenic chemotherapy regimens)

You need to explain the significant difference in the median age and primary organ affected between the two groups. As those two parameters could effect the results of comparison between the two groups. Moreover you must take in consideration the types of cancer such as digestive organ cancers, lung cancers, and gynecological cancers which also might change the results.

Answer: We appreciate your helpful comments. As the reviewer said, the significant difference in the median age and primary organ affected our results greatly. Thus, to decrease inhomogeneous the patient population, we performed a propensity score-matching analysis between the two groups to reduce the effect of any selection bias including sex, age, primary organ, and so on. The propensity score-matching method was proposed to evaluate statistically causal effects free from confounding effects by mathematically refashioning an observational study into a randomized study [new ref. 19,20]. Finally, we analyzed 97 patients in the two-drug group and 97 patients in the three-drug group. There were no significant differences about patient characteristics between two groups in the revised table 1. We wrote this explanation in the Method section (Page 9, line 13-).

Reference

19. Rubin DB. Estimating causal effects from large data sets using propensity scores