## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Clinical trial protocol of doublet therapy and olanzapine for carboplatin-induced nausea and vomiting in patients with thoracic cancer: a multicenter phase II trial |
| **AUTHORS** | Iihara, Hirotoshi; Shimokawa, Mototsugu; Gomyo, Takenobu; Fujita, Yukiyoshi; Yoshida, Tsutomu; Funaguchi, Norihiko; Minato, Koichi; Kaito, Daizo; Osawa, Tomohiro; Yamada, Momoko; Hirose, Chiemi; Suzuki, Akio; Ohno, Yasushi |

## VERSION 1 - REVIEW

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| **REVIEWER** | Rudolph Navari<br>University of Alabama Birmingham |
| **REVIEW RETURNED** | 19-Dec-2018 |

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| **GENERAL COMMENTS** | I assume this is a description of the proposed study with no results at this point? |

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| **REVIEWER** | Luigi Celio<br>Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy |
| **REVIEW RETURNED** | 30-Dec-2018 |

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| **GENERAL COMMENTS** | This paper reports the study protocol of a phase II trial that evaluates the antiemetic efficacy of a three-drug regimen containing olanzapine in patients receiving carboplatin-based chemotherapy for thoracic cancer. The study is ongoing.<br>Specific criticisms:<br>Introduction (lines 55-58 on page 4; line 4 on page 5): the sentence should be rephrased as it is not correct. MASCC classifies carboplatin as moderately emetogenic with an acute emetic risk at the upper limit of the MEC category regardless of the carboplatin dose (see reference 2) . ASCO classifies carboplatin at a dose of □≥4 mg/mL/min as highly emetogenic (see reference 1).<br>Introduction (lines 7-19; page 5): for the sake of clarity, the sentence should be rephrased as “....have recommended emesis prophylaxis using a three-drug regimen ....in patients receiving carboplatin-based chemotherapy.”<br>Introduction (lines 43-46; page 5): this statement is entirely debatable as the use of an antiemetic must be based on the expected risk of CINV for a patient and not only on the cost of the drug. In light of this, if thoracic cancer patients treated with |

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| | carboplatin have an inherent risk of CINV that can make the use of an NK-1RA unnecessary, the authors should explain the reason why they are evaluating the addition of olanzapine in this setting. This is a very important issue as currently available evidence on olanzapine supports the use of olanzapine instead of an NK-1RA in the management of CINV (see reference 2).<br>Introduction (lines 4-10; page 6): the sentence should be rephrased as it is not correct. The Navari study was a superiority study that could not demonstrate equivalence between the two treatment arms (see reference 10). Since in the Navari study palonosetron and dexamethasone were administered only on day 1 in patients treated with HEC regimens and receiving olanzapine on day 1 through 4, the authors should explain the clinical rationale for using granisetron with additional doses of dexamethasone. It is well known that granisetron plus dexamethasone is significantly less effective than palonosetron plus dexamethasone in the setting of CINV caused by HEC (Saito M et al. Lancet Oncol 2009;10:115-124). There also randomised data demonstrating that palonosetron plus 1-day dexamethasone is not inferior to palonosetron plus 3-day dexamethasone in female patients receiving AC-based HEC (Aapro M et al. Ann Oncol 2010;21:1083-1088). Last but not least, in light of the use of immunotherapy in combination with chemotherapy for lung cancer, it is extremely important to reduce the total dose of dexamethasone administered during each treatment cycle. The authors should comment on these specific issues that can impact the clinical relevance of the study findings to the management of CINV in the setting of thoracic cancer (namely lung cancer).<br>Introduction (lines 10-19; page 6): the sentence should be rephrased as references 11-14 cited in the text do not refer to European studies.<br>Introduction (lines 34-46; page 6): although the cost of drugs is an important aspect in the presence of increasingly limited health budgets, it cannot be the only rationale for this study. See the above comments.<br>End points (lines 58 on page 7; lines 4-7 on page 8): the definition of complete control is not correct. Complete control is defined as no emetic episodes, no rescue medication use, and no more than mild nausea.<br>End points (lines 16-19; page 8): it seems to be questionable assessment of TTF in this single-arm study.<br>End points (lines 22-26; page 8): I do not understand the meaning of this sentence. The authors should specify in the text what they intend to evaluate and the tools used for evaluation.<br>Exclusion criteria (line 19; page 10): the statement “patients deemed inappropriate for the study by the investigator” should be better clarified.<br>Table 1 is not cited in the text. |

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| **REVIEWER** | Julia E. Inglis<br>University of Rochester Medical Center, United States of America |
| **REVIEW RETURNED** | 14-Feb-2019 |

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| **GENERAL COMMENTS** | Good and adequate protocol. Objective may not be very relevant. Limitations of the protocol were not described adequately and aspects of participant consent and ethics in recruitment were not explained. |

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| **REVIEWER** | Massimo Di Maio<br>Department of Oncology, University of Turin, Italy |
| **REVIEW RETURNED** | 28-Apr-2019 |

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| **GENERAL COMMENTS** | The authors are conducting a phase II, single arm trial testing the combination of 5HT3, dexamethasone and olanzapine in the prevention of emesis of patients with thoracic malignancies receiving carboplatin. The rationale and study hypothesis are well described.<br>The limitations of the study (single arm, open label) are explicited in the paper.<br>I have some comments:<br>1. what is the rationale for the e.v. and oral dose of dexamethasone adopted?<br>2. page 9, row 22-25: the sentence is not clear, please explain better: severity of what? The sentences are probably referred to patients' questionnaires, but it is not clear.<br>4. considering that the trial is presented as ongoing, I suggest to use verbs at present instead of past.<br>3. could the authors specify the software used for sample size calculation? |

## VERSION 1 – AUTHOR RESPONSE

Reviewer #1

I assume this is a description of the proposed study with no results at this point?

=> As you pointed out, our manuscript is study protocol. This study is currently ongoing. There are no results at this time. Therefore, the following sentences were added (from line 4 to line 8 of page 14 in the revised version):

Trial status

February 2018: protocol approval by the Ethics Committee.

February 2018: Start of inclusion.

December 2019: End of inclusion.

We will submit the manuscript during the first half of 2020.

Reviewer #2

Introduction (lines 55-58 on page 4; line 4 on page 5): the sentence should be rephrased as it is not correct. MASCC classifies carboplatin as moderately emetogenic with an acute emetic risk at the upper limit of the MEC category regardless of the carboplatin dose (see reference 2) . ASCO classifies carboplatin at a dose of ≥4 mg/mL/min as highly emetogenic (see reference 1).

=>We summarized the guidelines for carboplatin in the table below. Based on this table and your suggestions, the sentences were modified as followed (from line 8 of page4 to line 1 of page 9 in the revised version):

“Carboplatin (CBDCA) administered to achieve an area under the blood concentration-time curve (AUC) of ≥4 mg/mL/min is ranked as the highest risk drug among the moderately emetogenic chemotherapy (MEC) agents and/or the highly emetogenic chemotherapy (HEC).” ----------> “ In recent guidelines, carboplatin (CBDCA) is reclassified at the upper limit of the moderately emetogenic chemotherapy (MEC) category and/or the highly emetogenic chemotherapy (HEC) [1-3].”

| Guideline | Emetic Risk Classification | Three Drug Regimen Recommendation |
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| MASCC | MEC | regardless of the carboplatin dose |
| ASCO | MEC | a dose of ≥4 mg/mL/min |
| NCCN | HEC<br>MEC | a dose of ≥4 mg/mL/min<br>one of the choices |

Introduction (lines 7-19; page 5): for the sake of clarity, the sentence should be rephrased as “....have recommended emesis prophylaxis using a three-drug regimen ....in patients receiving carboplatin-based chemotherapy.”

=>Thank you for your suggestion. With your suggestions and the above changes, the sentences were modified as followed (from line 1 to line 7 of page 5 in the revised version):

“The American Society of Clinical Oncology (ASCO) [1], the Multinational Association of Supportive Care in Cancer (MASCC) [2], and the National Comprehensive Cancer Network (NCCN) [3] have recommended emesis prophylaxis using a three-drug combination therapy including 5-hydroxytryptamine-3 receptor antagonist (5-$HT_3$RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist ($NK_1$RA).” ----------> “The Multinational Association of Supportive Care in Cancer (MASCC) (regardless of the CBDCA dose) [1], the American Society of Clinical Oncology (ASCO) (CBDCA at a dose of ≥4 mg/mL/min) [2], and the National Comprehensive Cancer Network (NCCN) (CBDCA at a dose of ≥4 mg/mL/min) [3] have recommended emesis prophylaxis using a three-drug regimen including 5-hydroxytryptamine-3 receptor antagonist (5-$HT_3$RA), dexamethasone (DEX), and neurokinin-1 receptor antagonist ($NK_1$RA) in patients receiving CBDCA-based chemotherapy.”

Introduction (lines 43-46; page 5): this statement is entirely debatable as the use of an antiemetic must be based on the expected risk of CINV for a patient and not only on the cost of the drug. In light of this, if thoracic cancer patients treated with carboplatin have an inherent risk of CINV that can make the use of an NK-1RA unnecessary, the authors should explain the reason why they are evaluating the addition of olanzapine in this setting. This is a very important issue as currently available evidence on olanzapine supports the use of olanzapine instead of an NK-1RA in the management of CINV (see reference 2).

=>As you pointed out, the cost aspect is not the only problem for prophylaxis of CINV. For $NK_1$RA, there are problems with drug-drug interaction, and some cases. It is difficult to use. Therefore, we believe that the development of antiemetic therapy without $NK_1$RA is necessary.

The evidence for olanzapine is mainly for HEC. As the effects of $NK_1$RA differ among MEC agents (CBDCA alone is a strong recommendation for $NK_1$RA use), we consider that the effect of olanzapine is different for each agent. Therefore, we believe that the effects of olanzapine should also be considered for each emetic risk, or each agent. For those reasons, the following sentences were added (from line 17 of page 5 to line 1 of page 6 in the revised version):

Furthermore, because of the inhibition of cytochrome P450 3A4, clinically significant pharmacokinetic interactions of apreitant (APR) and fosaprepitant have been reported not only general agents but also chemotherapy agents [9]. Therefore, the development of antiemetic therapy without $NK_1RA$ is beneficial in complicated cancer chemotherapy.

Introduction (lines 4-10; page 6): the sentence should be rephrased as it is not correct. The Navari study was a superiority study that could not demonstrate equivalence between the two treatment arms (see reference 10).

=>As you pointed out, the Navari study could not demonstrate that olanzapine regimen is superior to aprepitant regimen. Therefore, the sentences were revised as follows (from line 5 to line 11 of page 6 in the revised version):

“Navari et al. reported that 10mg OLZ combined with palonosetron (PALO) and DEX has an equivalent antiemetic effect to an antiemetic regimen consisting of PALO, DEX, and aprepitant (APR), in CR rate, and excellent in control of nausea in highly emetogenic chemotherapy (HEC)” ----------> “ Navari et al. performed a phase III trial to confirm the superiority of 10mg OLZ combined with palonosetron (PALO) and DEX to an antiemetic regimen consisting of PALO, DEX, and APR in highly emetogenic chemotherapy (HEC). The study could not demonstrate that the OLZ regimen is superior to the APR regimen. However, the CR rates for the acute, delayed, and overall period were not significantly different between the OLZ regimen and the APR regimen. On the other hand, the OLZ regimen showed excellent control of nausea in the delayed and overall period”

Since in the Navari study palonosetron and dexamethasone were administered only on day 1 in patients treated with HEC regimens and receiving olanzapine on day 1 through 4, the authors should explain the clinical rationale for using granisetron with additional doses of dexamethasone. It is well known that granisetron plus dexamethasone is significantly less effective than palonosetron plus dexamethasone in the setting of CINV caused by HEC (Saito M et al. Lancet Oncol 2009;10:115-124). There also randomised data demonstrating that palonosetron plus 1-day dexamethasone is not inferior to palonosetron plus 3-day dexamethasone in female patients receiving AC-based HEC (Aapro M et al. Ann Oncol 2010;21:1083-1088). Last but not least, in light of the use of immunotherapy in combination with chemotherapy for lung cancer, it is extremely important to reduce the total dose of dexamethasone administered during each treatment cycle. The authors should comment on these specific issues that can impact the clinical relevance of the study findings to the management of CINV in the setting of thoracic cancer (namely lung cancer).

=>In recent years, immune checkpoint inhibitor (ICI) in combination with chemotherapy is available in clinical setting for lung cancer. Arbour et al. reported that baseline corticosteroid use of ≥ 10 mg of prednisone equivalent was associated with poorer outcomes in patients with non-small-cell lung cancer who were treated with ICI (J Clin Oncol. 2018;36:2872-2878) . Therefore, there is a concern that DEX as emesis prophylaxis may affect the effects of ICI combination chemotherapy.

The noninferiority of DEX sparing on day 2 and 3, combined with PALO has been demonstrated for MEC in randomized control trials (Aapro et al. Ann Oncol 2010;21:1083-1088, Celio et al. Support Care Cancer. 2011 19:1217-25, Komatsu et al. Cancer Sci. 2015 ;106:891-5) . Therefore, to use PALO can reduce corticosteroid.

Among the ICI combination therapies, the pembrolizumab combined with CBDCA and pemetrexed is one of the most used regimens for advanced non–small-cell lung cancer. In the KEYNOTE-189 trial that proved the effectiveness of this regimen, for prophylaxis of cutaneous reaction, the administration of DEX 8 mg per day for 2 days besides DEX of day 1 used for antiemetic therapy had been regulated

by the protocol (Gandhi et al. N Engl J Med. 2018;378:2078-2092). In consideration of these, DEX is administered for 3 days in our protocol.

About $5HT_3RA$, the effectiveness of olanzapine combination has been revealed in both first and second generation (first generation $5HT_3RA$: Wang et al. Cell Biochem Biophys 2015; 72:471–3, Navari et al. N Engl J Med 14; 375:134–42, Tan et al. J Exp Clin Cancer Res. 2009;28:131) . Therefore, the first-generation $5HT_3RA$ is administered in our protocol.

For those reasons, the following sentences were added (from line 6 of page 7 to line 1 of page 8 in the revised version):

In recent years, immune checkpoint inhibitor (ICI) in combination with chemotherapy is available in clinical settings for lung cancer. Arbour et al. reported that baseline corticosteroid use was associated with poorer outcomes in patients who were treated with ICI [19]. Therefore, there is a concern that DEX as emesis prophylaxis may affect the effects of ICI combination chemotherapy. The noninferiority of DEX sparing on day 2 and 3, combined with PALO has been demonstrated for MEC in randomized control trials [20-22]. Therefore, to use PALO can reduce corticosteroid. Among the ICI combination therapies, the pembrolizumab combined with CBDCA and pemetrexed is one of the most often used regimens for advanced non–small-cell lung cancer. In the KEYNOTE-189 trial that proved the effectiveness of this regimen, for prophylaxis of cutaneous reaction, the administration of DEX 8 mg per day for 2 days besides DEX of day 1 used for antiemetic therapy had been regulated by the protocol [23]. Therefore, we plan to administer DEX for 3 days.

The efficacy of OLZ has been demonstrated in both combinations with the first and second generation $5HT_3RA$ in HEC [11-18, 24]. Therefore, granisetron (GRN) was chosen as $5HT_3RA$ in the study.

Introduction (lines 10-19; page 6): the sentence should be rephrased as references 11-14 cited in the text do not refer to European studies.

=>The sentence was corrected, as you suggested (from line 12 of page 6 in the revised version):

“in Europe and the United States,” ---------->” in the United States and Asia,”

Introduction (lines 34-46; page 6): although the cost of drugs is an important aspect in the presence of increasingly limited health budgets, it cannot be the only rationale for this study. See the above comments.

=> As you pointed out, the cost aspect is not the only problem for prophylaxis of CINV. Therefore, we made the revision above.

End points (lines 58 on page 7; lines 4-7 on page 8): the definition of complete control is not correct. Complete control is defined as no emetic episodes, no rescue medication use, and no more than mild nausea.

=>The definition of complete control was corrected, as you suggested (from line 6 to line 8 of page 9 in the revised version):

“complete control rate (defined as the absence of nausea and emetic episodes and no use of rescue medication during the overall assessment period).” ---------->” complete control rate defined as

no significant nausea, no emetic episodes, and no use of rescue medication for the acute, delayed, and overall assessment periods."

End points (lines 16-19; page 8): it seems to be questionable assessment of TTF in this single-arm study.

=> We deeply appreciate your kind advice. Our research has already been started. Although this is a single arm study, TTF will be evaluated as an exploratory indicator that is used to reveal when a patient will become non-CR.

End points (lines 22-26; page 8): I do not understand the meaning of this sentence. The authors should specify in the text what they intend to evaluate and the tools used for evaluation.

=>Thank you for your suggestion. The sentences were modified as followed (from line 13 to line 15 of page 9 in the revised version):

"Severity has been classified into a four-grade categorical scale, including nausea, anorexia, sleepiness, and the impact on life. Patient satisfaction with antiemetic therapy." ---------->" The levels of nausea, anorexia, sleepiness, impact on life severity, and patient satisfaction with antiemetic therapy are also classified using a four-grade categorical scale. These data are collected from patient diaries."

Exclusion criteria (line 19; page 10): the statement "patients deemed inappropriate for the study by the investigator" should be better clarified.

=>Thank you for your suggestion. The following sentences were added (from line 9 to line 10 of page 11 in the revised version):

(From daily behavior, patients who may not be able to keep medication adherence and/or fulfill patient diary etc.)

Table 1 is not cited in the text.

=>According to your comment, we inserted the following sentences (from line 16 of page 11 in the revised version):

The study antiemetics administrations are shown in Table 1.

Reviewer #3

Good and adequate protocol. Objective may not be very relevant.

=> Thank you for your suggestion. The cost aspect is not the only problem for prophylaxis of CINV. For $NK_1RA$, there are problems with drug-drug interaction, and some cases. It is difficult to use. Therefore, we believe that the development of antiemetic therapy without $NK_1RA$ is necessary. Therefore, the following sentences were added (from line 17 of page 5 to line 1 of page 6 in the revised version):

Furthermore, because of the inhibition of cytochrome P450 3A4, clinically significant pharmacokinetic interactions of apreitant (APR) and fosaprepitant have been reported not only general agents but also chemotherapy agents [9]. Therefore, the development of antiemetic therapy without NK1RA is beneficial in complicated cancer chemotherapy.

Limitations of the protocol were not described adequately and aspects of participant consent and ethics in recruitment were not explained.

=>Thank you for your suggestion. The following sentences were added:

And the study is conducted within the Japanese population. (from line 15 of page 4 in the revised version)

A signed informed consent form is obtained from all patients before enrollment. (from line 12 of page 13 in the revised version)

Reviewer #4

what is the rationale for the e.v. and oral dose of dexamethasone adopted?

=>In Japan, Europe, United Sates, and other countries, dexamethasone injection is provided as dexamethasone sodium phosphate. For example, 8 mg of dexamethasone sodium phosphate (Injection) contains 6.6 mg of dexamethasone. Bioavailability of oral dexamethasone is about 80%. Therefore, dexamethasone sodium phosphate (Injection) 6.6 mg has almost the same effect as oral dexamethasone 8 mg. Therefore the following sentences were added (from line 21 of page 11 to line 2 of page 12 in the revised version):

Dexamethasone injection is provided as dexamethasone sodium phosphate. The 8 mg of dexamethasone sodium phosphate contains 6.6 mg of dexamethasone.

page 8, row 22-25: the sentence is not clear, please explain better: severity of what? The sentences are probably referred to patients' questionnaires, but it is not clear.

=>Thank you for your suggestion. The sentences were modified as followed (from line 13 to line 15 of page 9 in the revised version):

“Severity has been classified into a four-grade categorical scale, including nausea, anorexia, sleepiness, and the impact on life. Patient satisfaction with antiemetic therapy.” ----------> ”The levels of nausea, anorexia, sleepiness, impact on life severity, and patient satisfaction with antiemetic therapy are also classified using a four-grade categorical scale. These data are collected from patient diaries.”

considering that the trial is presented as ongoing, I suggest to use verbs at present instead of past.

=> According to your suggestion, we changed some verbs from past tense to present tense (underlined with blue letters).

could the authors specify the software used for sample size calculation?

=>The following sentences were added, as you suggested (from line 4 to line 5 of page 13 in the revised version):

A sample size calculation was performed by SAS 9.4 (Cary, NC, USA).

**VERSION 2 – REVIEW**

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| **REVIEWER** | Luigi Celio<br>Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy |
| **REVIEW RETURNED** | 04-Jun-2019 |

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| **GENERAL COMMENTS** | The reviewer completed the checklist but made no further comments. |

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| **REVIEWER** | Massimo Di Maio<br>Department of Oncology, University of Turin |
| **REVIEW RETURNED** | 04-Jun-2019 |

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| **GENERAL COMMENTS** | The reviewer completed the checklist but made no further comments. |