PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for SPARED trial: Randomized noninferiority phase III trial comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine (5 mg) in patients receiving cisplatin-based chemotherapy
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VERSION 1 – REVIEW

REVIEWER	Luigi Celio Department of Medical Oncology and Haematology; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
REVIEW RETURNED	10-Jul-2020

GENERAL COMMENTS	This is a study protocol that investigates the dexamethasone-sparing strategy in combination with low-dose olanzapine against CINV caused by cisplatin-based chemotherapy. To the best of my knowledge, there no randomized data currently available in the literature that evaluate efficacy of such an anti-emetic prophylaxis in the cisplatin setting. The study accrual is ongoing. For an improvement: Title: The title of the manuscript should state that a) this is a non-inferiority study, and b) the patients receive low-dose olanzapine in this study. These are the two novelties of the study. Strenghts and limitations of this study (page 8; lines 39-44): this statement is questionable. Are the authors absolutely certain that dex sparing in cisplatin can only be used if also olanzapine is administered? I am not sure about this. The study by Ito et al. (see reference 10) is an underpowered study to demonstrate non-inferiority of the dex-sparing strategy in patients receiving cisplatin (see Celio L et al. J Clin Oncol 2018:36:2741; this letter should be cited in the manuscript). I think that the current study will be the first randomized study that evaluates dex sparing in combination with low-dose olanzapine in the challenging setting of CINV caused by cisplatin. This would be really new evidence since the randomized phase III study by Hashimoto et al. (see reference 17) recently demonstrated the efficacy and tolerability of olanzapine 5 mg (the dose used in this study) in combination with palonosetron, aprepitant and 4-day dexamethasone in patients undergoing cisplatin.

	Strenghts and limitations of this study (page 8; lines 51-55): this statement is questionable. There is a lot of literature showing that there are no significant differences in anti-emetic activity between the two doses of palonosetron (0.25 mg or 0.75 mg) which are approved for the management of CINV. Introduction (pages 9-10; lines 54-58; lines 6-8): this paragraph should be reworded. The authors should clearly state that the two treatment arms in the Ito study (reference 10) are expected to have the same efficacy against acute CINV since patients receive the same antiemetic prophylaxis on day 1. During the delayed phase, the non-inferiority hypothesis of dex sparing on days 2 and 3 was not demonstrated due to the low power of the study (see also the above comments). Therefore, the authors should keep in mind that their study is an inconclusive study about the worth of dex sparing in cisplatin. Inclusion criteria (page 12; lines 48-51) in the inclusion criteria, it should be stated that eligible patients may have received previous chemotherapy of moderate or low emetic potential. Exclusion criteria (page 13; lines 38-40): as cisplatin-based chemotherapy is normally administered on a day-hospital basis, the authors should specify the reasons why the patients will be hospitalized in this study. Moreover, the authors must be aware that a large number of patients excluded for this reason would negatively impact on the generalizability of the study results. Exclusion criteria (page 14; lines 13): the authors should clarify the reasons why the investigator may deem the patient inappropriate for the study. Statistical analysis (page 19): it should clearly be stated which patients will be included in the main analysis, since both intention-to-treat and per-protocol analyses are scientifically relevant to a non-inferiority study. Although in this study the number of patients with missing data is expected to be very low among hospitalized patients, there is also a need for a statement concerning how missing data will be handled.

REVIEWER	Ajay Raghunath Monash Health, Melbourne, VIC, Australia
REVIEW RETURNED	27-Jul-2020

GENERAL COMMENTS	Comment 1: In the introduction you note >90% incidence of CINV in pts without adequate antiemetic prophylaxis. Given the effectiveness of modern anti-emetic regimens consider also presenting the risk of CINV in those receiving prophylaxis to accurately present the risks Comment 2: In the study outcome section, consider describing how adverse events will be presented as an endpoint. Will all reported adverse events be presented or only those considered a known adverse effect of the anti-emetics and if so which those will be

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer #1:
Thank you for reviewing our manuscript. We appreciate the time and effort you dedicated to providing feedback. We have addressed your recommendations below.

1. Title: The title of the manuscript should state that a) this is a non-inferiority study, and b) the patients receive low-dose olanzapine in this study. These are the two novelties of the study.

Thank you for your suggestion. We agree that this is an important distinction. We have revised the title on page 1, lines 2–4.

“Study protocol for SPARED trial: Randomized noninferiority phase III trial comparing dexamethasone on day 1 with dexamethasone on day 1-4 combined with neurokinin-1 receptor antagonist, palonosetron, and olanzapine (5 mg) in patients receiving cisplatin-based chemotherapy”

2. Strenghts and limitations of this study (page 8; lines 39-44): this statement is questionable. Are the authors absolutely certain that dex sparing in cisplatin can only be used if also olanzapine is administered? I am not sure about this. The study by Ito et al. (see reference 10) is an underpowered study to demonstrate non-inferiority of the dex-sparing strategy in patients receiving cisplatin (see Celio L et al. J Clin Oncol 2018:36:2741; this letter should be cited in the manuscript). I think that the current study will be the first randomized study that evaluates dex sparing in combination with low-dose olanzapine in the challenging setting of CINV caused by cisplatin. This would be really new evidence since the randomized phase III study by Hashimoto et al. (see reference 17) recently demonstrated the efficacy and tolerability of olanzapine 5 mg (the dose used in this study) in combination with palonosetron, aprepitant and 4-day dexamethasone in patients undergoing cisplatin.

Thank you for your word of caution. As you point out, DEX-1 was an underpowered study designed to evaluate whether multiple days of DEX administration can be spared during cisplatin (CDDP)-based regimens as patients who received CDDP-based regimens represented only 23% of the sample population. Further studies are required to evaluate whether patients receiving neurokinin-1 receptor antagonists (NK1-RA) in combination with palonosetron and dexamethasone can be spared DEX when undergoing CDDP-based regimens. Recently, the addition of olanzapine (OLZ) to triplet antiemetic therapy has provided greater benefit for CINV from HEC and has become a standard antiemetic therapy in patients receiving CDDP-based regimens. Furthermore, in previous studies, OLZ was demonstrated to be an effective agent affecting delayed CINV (see reference 4, 18). Therefore, we believe that it is undesirable to conduct a DEX-sparing study without OLZ. We believe that the addition of OLZ to triple antiemetic therapy can spare multiple days of DEX in patients receiving CDDP.

3. Strenghts and limitations of this study (page 8; lines 51-55): this statement is questionable. There is a lot of literature showing that there are no significant differences in anti-emetic activity between the two doses of palonosetron (0.25 mg or 0.75 mg) which are approved for the management of CINV.

Thank you for raising this point. We agree with you and have changed the limitation as follows on page 5, lines 102-103.

“A limitation of this study is that it was conducted solely within the Japanese population.”

4. Introduction (pages 9-10; lines 54-58; lines 6-8): this paragraph should be reworded. The authors should clearly state that the two treatment arms in the Ito study (reference 10) are expected to have the same efficacy against acute CINV since patients receive the same antiemetic prophylaxis on day 1. During the delayed phase, the non-inferiority hypothesis of dex sparing on days 2 and 3 was not demonstrated due to the low power of the study (see also the above comments). Therefore, the authors should keep in mind that their study is an inconclusive study about the worth of dex sparing in cisplatin.

Thank you. We agree that this is an important point (see above comments). We have added the following sentences on page 6, lines 123-126 and page 7, lines 135–139.

“Dexamethasone (DEX), 5-hydroxytryptamine type 3 receptor antagonists (5-HT3-RA) and neurokinin-1 receptor antagonists (NK1-RA) have been developed to inhibit CINV from HEC,[5-6]. DEX is typically administered for multiple days from the start of chemotherapy to treat CINV,[7];whereas, frequent administration of corticosteroids has been associated with many adverse effects, such as insomnia, hyperglycemia, and reduced bone mineral density,[8-10]. Therefore, corticosteroid-minimizing (DEX sparing) strategies, which administer DEX in the acute phase (day 1) and omit DEX in the delayed phase (day 2 and later), have been evaluated,[11] Our multicenter randomized double-blind comparative study (DEX-1 study) showed the complete response (CR; no emesis, no use of rescue medication) rate in the overall phase of DEX on day 1 provided a noninferior antiemetic efficacy to a treatment of DEX on day1-3 when combined with NK1-RA and palonosetron (Palo) for patients receiving HEC including AC and CDDP-based regimen. (44.0 % vs. 46.9 %, P = 0.007),[12] . In a subgroup analysis of patients receiving CDDP-based regimen, CR rates of acute phase demonstrated a noninferiority of DEX on day1 to day 1-3 (95.6 % vs 95.6 %, P = 0.007); whereas, CR rates of the overall and delayed phases DEX on day 1 were lower than those DEX on day 1-3 (57.8 % vs 66.7 %, P = 0.272; 57.8 % vs 68.9 %, P = 0.349, respectively). However, the DEX-1 study was underpowered to evaluate whether multiple days of DEX can be spared for CDDP-based regimens because patients who received the CDDP-based regimen represented only 23% of the total sample population,[13]. Therefore, the plausibility of DEX sparing in CDDP remains inconclusive. “

5. Inclusion criteria (page 12; lines 48-51) in the inclusion criteria, it should be stated that eligible patients may have received previous chemotherapy of moderate or low emetic potential.

Thank you for your recommendation. We have added the following parenthetical statement on page 9, lines 189-190.

“Patients with malignant tumor, excluding those with hematologic malignancies or those receiving first-line treatment with CDDP >50mg/m2 (previous use of moderate or low emetic chemotherapy is permitted).”

6. Exclusion criteria (page 13; lines 38-40): as cisplatin-based chemotherapy is normally administered on a day-hospital basis, the authors should specify the reasons why the patients will be hospitalized in this study. Moreover, the authors must be aware that a large number of patients excluded for this reason would negatively impact on the generalizability of the study results.

Thank you for your point. In this study, patients are required to use an electronic device to enter the electronic patient reported outcomes (ePRO) system. We provide them with electronic devices. Therefore, patients in this study need to be hospitalized for 120 hours after starting CDDP. We recognize that this will negatively impact the generalizability of the study results. We added the following sentence on page 10, lines 209-210.

“Patients who cannot be hospitalized until after 120 hours have passed since starting CDDP administration as the study requires daily use of an electronic patient reported outcome (ePRO) system.”

7. Exclusion criteria (page 14; lines 13): the authors should clarify the reasons why the investigator may deem the patient inappropriate for the study.

Thank you for your point. We have added the following on page 11, lines 223-225.

“Patients deemed ineligible for the study by the investigator (e.g., patients who are unable to maintain medication adherence or who may experience difficulty using electronic devices).”

8. Statistical analysis (page 19): it should clearly be stated which patients will be included in the main analysis, since both intention-to-treat and per-protocol analyses are scientifically relevant to a non-inferiority study. Although in this study the number of patients with missing data is expected to be very low among hospitalized patients, there is also a need for a statement concerning how missing data will be handled.

Thank you for your comment. As you indicated, a noninferiority trial’s use of the full analysis set is generally not conservative, and its role should be carefully considered (ICH E9). However, we plan to use a full analysis set to estimate the effect of a treatment policy that is best assessed by evaluating on the basis of intention-to-treat a subject. With regard to missing data for our primary endpoint (i.e., complete response [CR] or not), because the subject whose primary endpoint is missing will not benefit from the protocol treatment, we will impute “non-CR” for the data. Based on the above, the following sentences have been added to the last section of “Statistical analysis” on page 16–17, lines 348–352.

“We will use a full analysis set. It consists of the registered participant population who received at least a part of the protocol treatment; however, participants who were deemed as ineligible for the study after registration and those who were not administered CDDP-based regimens will be excluded from the analysis set. For the primary analysis, we will impute non-CR for missing primary endpoints.”

Response to Reviewer #2:
Thank you for reviewing our manuscript. We appreciate the time and effort you have dedicated to providing insightful feedback on ways to strengthen our paper. We have answered each of your points below.

1. In the introduction you note >90% incidence of CINV in pts without adequate antiemetic prophylaxis. Given the effectiveness of modern anti-emetic regimens consider also presenting the risk of CINV in those receiving prophylaxis to accurately present the risks

Thank you for your suggestion. We have added the following sentence regarding the incidence of CINV in those receiving prophylactic antiemetics on page 6, lines 114–117.

“Highly emetogenic chemotherapy (HEC), including cisplatin (CDDP)-based regimen and anthracycline plus cyclophosphamide (AC) regimen, can lead to a >90 % incidence of emesis in patients without an adequate antiemetic prophylaxis,[3]. When patients were administered prophylactic antiemetics prior to HEC treatment, the incidence of emesis (or requiring additional antiemetics) was found to be 35% according to a recent study.[4]”

2. In the study outcome section, consider describing how adverse events will be presented as an endpoint. Will all reported adverse events be presented or only those considered a known adverse effect of the anti-emetics and if so which those will be

Thank you for the opportunity to clarify this topic. We will report only adverse events considered to be known as adverse effects from the antiemetics in CTCAE and PRO-CTCAE. We added the following sentence regarding the study endpoints on page 15, lines 317–318.

“Study Endpoints
The primary endpoint is CR rate (no emesis and no rescue medications) during the delayed phase (24 to 120 hours post-CDDP administration). Secondary endpoints are as follows: (1) CR rate during

the acute phase (24 hours post-CDDP administration) and the overall phase (120 hours post-CDDP administration); (2) complete control (CC; no emesis, no rescue use, and no significant nausea) rate; (3) total control (TC; no emesis, no rescue use, and no nausea) rate; (4) no emesis rate and no nausea rate in the overall, acute, and delayed phase; (5) time to treatment failure (i.e., time to first emesis or using rescue, whichever occurred first); and (6) severity of nausea during the overall phase. Adverse events are associated with antiemetic therapy (CTCAE v4.0 Japanese Clinical Oncology Group [JCOG] version and the PRO-CTCAE v1.0.)."

VERSION 2 – REVIEW

REVIEWER	Luigi Celio Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, ITALY Italfarmaco SpA, Advisor Kyowa Kirin srl, Advisor
REVIEW RETURNED	20-Sep-2020

GENERAL COMMENTS	No further comments