Low-dose Dexamethasone with Fosaprepitant and Palonosetron to prevent Cisplatin-induced nausea and vomiting in head and neck cancer patients

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Abstract

***Objective*:** To determine if a lower dose of dexamethasone can be used in combination with fosaprepitant and palonosetron for cisplatin induced nausea and vomiting in head and neck cancer patients, we conducted a single-center, two-arm, cross-over comparison study.

***Methods*:** Patients were randomly assigned to either standard dose dexamethasone group: intravenous 9.9 mg on day 1 and 6.6 mg on days 2-4 or low dose dexamethasone group: intravenous 3.3 mg on days 1-4 for the first course, and crossed over to the other treatment for the second course. The primary endpoint was complete response (CR) in the overall period.

***Results*:** Twenty-five patients were screened for the study and 22 were evaluable. Eleven patients were randomly assigned to the standard dose dexamethasone group and 12 patients to the low dose dexamethasone group. The CR rate in the overall period was 86% in the standard dose group and 73% in the low dose group, showing no significant difference (p=0.61).

***Conclusion*:** The efficacy of low-dose dexamethasone with fosaprepitant and palonosetron was not inferior to that of the standard dose dexamethasone in the highly emetogenic cisplatin-based treatment for head and neck cancer patients.

Keywords: head and neck cancer, CINV, dexamethasone, HEC, aprepitant, fosaprepitant

Introduction

Nausea and vomiting are the most feared and distressing side effects of chemotherapy [1,2]. Cisplatin (CDDP), an important drug for head and neck cancer treatment, is classified as highly emetogenic chemotherapy (HEC). Even with the appropriate use of currently available antiemetic therapy, head and neck cancer patients still suffer from chemotherapy-induced nausea and vomiting (CINV).

Combination of a 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RA) and a corticosteroid has made it possible to prevent CINV especially in the acute phase [3]. Recently, the addition of a neurokinin-1 receptor antagonist (NK-1 RA), such as aprepitant or its prodrug fosaprepitant, to 5-HT3 RA and dexamethasone was found to be effective against acute and delayed emesis [4-7]. Therefore,-current anti-emetic guidelines updated from ASCO, MASCC/ESMO and NCCN recommend a three-drug regimen of a 5-HT3 RA, dexamethasone, and a NK-1 RA for preventing CINV caused by HEC [8-10].

However, the adequate dose of dexamethasone for the triple-drug therapy is not well-defined. In a dose-response study, when used with a 5-HT3 RA, dexamethasone at 20 mg had the highest antiemetic effect against acute CINV [11]. Aprepitant and fosaprepitant are one of commonly used NK-1 RA. Pharmacokinetic study demonstrated that when used in combination with aprepitant, the blood concentrations of dexamethasone doubled in 1-2 days [12].-From these studies, when aprepitant or fosaprepitant was added to 5-HT3 RA and dexamethasone, the dose of dexamethasone was simply determined to be half of the conventional two combination dose. In other words, when aprepitant or fosaprepitant is used as one of NK-1 RA, the additive effect of aprepitant or fosaprepitant on

dexamethasone and 5-HT3 RA may not be taken into account.

To our knowledge, this is the first study aimed at determining if a lower dose of dexamethasone in combination with palonosetron and fosaprepitant can be as effective as the standard dose of dexamethasone in CDDP-containing chemotherapy for head and neck cancer patients. Lowering the dexamethasone dose can reduce complications such as obesity and gastrointestinal ulcers caused by steroids [13], thereby enabling a safer treatment with fewer adverse events.

Patient and Methods

Study Design: This study was a single-center, two-arm, cross-over comparison study conducted at the Hiroshima University Hospital, with a washout period of at least two weeks.

All patients provided written informed consent to participate in the study. The study was approved by the Ethics Committee of the Hiroshima University Hospital and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients: CDDP-naive patients between 20 to 75 years of age at the time of registration, who had histologically confirmed head and neck cancer with Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of ≤2, and were scheduled to receive two courses involving CDDP ≥60 mg/m^2 as first line (all patients received docetaxel ≥60 mg/m^2 and 5-fluorouracil ≥600 mg/m^2) were eligible to participate. The primary exclusion criteria included the following: vomiting and/or nausea 24 hours before infusion of CDDP; a symptomatic primary or metastatic CNS malignancy; uncontrolled diabetes mellitus; an active infectious disease; any uncontrolled disease other than

malignancy that the investigator determined might pose an unwarranted risk. Patients being treated with pimozide (contraindication for co-administration of aprepitant and fosaprepitant) were also excluded.

Procedures: All patients were given 150 mg fosaprepitant and 0.75 mg palonosetron intravenously, once on day 1 in both cycles as baseline antiemetic prophylaxis. Using the minimization method, patients were assigned to either a standard dexamethasone dose group or a low dexamethasone dose group for the first course, and then crossed over to the other group for the second course. Patients in the standard group received 9.9 mg of intravenous dexamethasone on day 1 followed by another intravenous dose of 6.6 mg on days 2-4. This dosing of dexamethasone was compliant with the current guidelines [8-10]. On the other hand, patients in the low dexamethasone arm received 3.3 mg of intravenous dexamethasone on days 1-4 (Figure 1). This dose of dexamethasone was calculated based on the finding that 6.6 mg of intravenously delivered dexamethasone and 13.2 mg of it administered with granisetron were almost equally efficacious in the treatment of CDDP-containing chemotherapy for head and neck cancer [14]. Moreover, a pharmacokinetic study showed that aprepitant increased the blood levels of dexamethasone by approximately two-fold via a CYP3A4 interaction on days 1-2 [12].

Assessment: For 5 days after administration of chemotherapy, patients kept a diary to report the date and time of any episodes of emesis and/or retching. Patients documented the intensity of nausea daily using a validated 100-mm horizontal visual analog scale [VAS] The use of rescue therapy also recorded and the permitted rescue included 7.67 mg of oral metoclopramide up to twice a day and

3.3 mg of dexamethasone given intravenously. Use of any other 5-HT3 receptor antagonists were excluded.

Response definitions: The response criteria outlined above were applied to the acute phase (day 1), the delayed phase (days 2-5), and the overall study period (days 1-5). The primary endpoint was determined by the number of patients achieving complete response (CR), defined as no emetic episodes and no use of rescue medication, in the overall study period (days 1-5). Secondary endpoints included (1) no emesis, (2) no use of rescue therapy and (3) the intensity of nausea degree using VAS score in the overall period.

Statistical analysis: The primary and secondary efficacy variables were analyzed per protocol set (PPS). The binary efficacy was considered for a carry-over effect by performing a Mainland-Gart test and analyzed by using the Fisher's exact test. Another secondary endpoint, the degree of VAS score, was analyzed by using a non-parametric test of the Mann–Whitney U test. A mixed linear model was used to evaluate the associations between the intervention and the VAS score. The model included variables for the group, time, and drug dose as the fixed effects and patients as the random effect. The analyses were reported as median and range values and were considered significant only for $P < 0.05$. All statistical analysis was performed by using JMP® 7 (SAS Institute Inc., Cary, NC, USA). Patients included in this study were the same as those included in a previous study, which reported the dose of dexamethasone and granisetron in 40 patients [14]. Therefore, no formal sample size calculation was performed for this study and the present study was designed to collect 40 patients.

Results

Patient characteristics: Patients were enrolled from 1 June 2012 and followed up until 31 May 2014. Twenty-five patients were screened for inclusion, and two were found to be ineligible. The remaining 23 were randomly assigned to one of the two treatment cycles. Eleven patients were randomly assigned to the standard dose dexamethasone group. One patient declined to continue participating in the study due to adverse effects of chemotherapy. Twelve patients were randomly assigned to the low dose dexamethasone group. Twenty-two of the 25 patients who entered the study were fully evaluable and completed 2 cycles of chemotherapy including CDDP (Figure 2.). Patient characteristics are listed in Table 1. Baseline and demographic characteristics were generally similar between the two groups. Especially, the dose of CDDP for all patients was ≥60 mg/m^2 (mean 68.4 mg/m^2 range 60-80).

Antimetric outcomes

1) *Complete response*

Figure 3 shows results for primary endpoint. During the acute phase, in the first and second cycles, the CR rates were 95% and 86% in the standard and low dose dexamethasone groups, respectively showing no significant difference between the two groups (p=0.61). During the delayed phase, the CR rates were 86% and 73% in the standard and the low dose dexamethasone groups, respectively with no significant difference between the two groups (p=0.46). During the overall period, the CR rates were 86% and 73% in the standard and the low dose dexamethasone groups, respectively with no significant difference between the two groups (p=0.61).

2) *Other endpoints*

Table 2 shows results for other endpoints. During the acute phase, in the first and second cycles, the

percentages of patients with no emesis were 100% in both the groups. During the delayed phase, the percentages of patients with no emesis were 91% in both the groups, and similar result was obtained during the overall period.

During the acute phase, in the first and second cycles, the percentage of patients with no use of rescue therapy were 95% and 86% in the standard and the low dose dexamethasone groups, respectively with no significant difference between the two groups (p=0.61). During the delayed phase, the percentage of patients with no use of rescue therapy were 86% and 82% with no significant difference between the two groups (p=1.0), and similar result was obtained during the overall period.

Figure 4 and 5 shows the VAS during the overall period. The median value of VAS score during the overall period did not show any significant differences between the two treatment groups in reports of overall.

Discussion

This study compared the efficacy of low-dose dexamethasone regimen with the standard dexamethasone regimen combined with fosaprepitant and palonosetron as an antiemetic treatment for CINV in patients with head and neck cancers who received HEC including CDDP in a randomized, crossover study design. Our findings demonstrated that the low-dose dexamethasone regimen might be as effective as the standard dose regimen when dexamethasone combined with fosaprepitant and palonosetron. The CR (defined as no emetic episodes and no use of rescue medication) rates for the two regimens showed no significant differences during acute, delayed and overall phases. Furthermore, the two groups showed no significant differences in the episodes of emesis, use of rescue and the VAS score for daily nausea intensity during the entire study.

For cancer patients receiving CDDP-based HEC, CINV is the most distressing adverse effect of chemotherapy. Antiemetic treatment regimens consisting of NK-1 RA, 5-HT3 RA and dexamethasone have been shown to be more effective compared to regimens that comprise of only 5-HT3 RA and dexamethasone in both the acute and delayed phases, thus current guidelines recommend a three-drug regimen including a NK-1 RA, 5-HT3 RA and dexamethasone for preventing CINV due to HEC [8-10]. Aprepitant and its prodrug fosaprepitant are the NK-1 RA that can be used for CINV prevention and aprepitant boosts the blood levels of dexamethasone during days 1-2 [12]. Thus the dose of dexamethasone when combined with aprepitant should be half the dose when dexamethasone is used only with 5-HT3 RA. In other words, if the additional effect of aprepitant as one of NK-1 RA is taken into consideration, the dose of dexamethasone may be further reduced. Dexamethasone causes side effects such as insomnia, gastric distress, agitation, peptic ulcer disease, and hyperglycemia. The present study was designed to discern whether a lower dose of dexamethasone in the triple therapy could result in an overall efficacy that is comparable to the standard regimen.

A previous study has documented that oral administration of 8 mg dexamethasone once a day, on days 1-4 had equivalent efficacy to an oral administration of 16 mg on days 1-4 combined with granisetron for CDDP-based HEC in 36 head and neck cancer patients [14]. In addition, a pharmacokinetic study in healthy subjects reported that aprepitant doubled the blood levels of dexamethasone on days 1-2. Thus, the low dose group in our study received 3.3 mg of dexamethasone intravenously on days 1-4.

Although no significant differences were found between the two groups, CINV occurred in fewer patients in the standard dexamethasone group in our study. Similar findings were noted in other

studies that compared 8 mg and 16 mg of oral dexamethasone for CDDP-based HEC [14]. Compared to the dose of 100 mg/m^2 CDDP used for standard chemotherapy, the mean dosage of CDDP used in our study was 68.4 mg/㎡, which was given in combination with docetaxel and 5-fluorouracil. Therefore, the efficacy of the low dose dexamethasone regimen should be evaluated cautiously, when considering for use with high dosage CDDP therapies. According to recent guidelines, olanzapine is listed as a fourth recommended drug for HEC treatment, and further reduction of CINV can be expected by using olanzapine in combination[8-10]. Although this study was examined with three agents without olanzapine, when used combination with fosaprepitant, 5-HT 3 RA and olanzapine, the dose of dexamethasone may be further reduced. Further research is expected for this question in the future.

Dexamethasone has several adverse effects of corticosteroids some of which include insomnia, indigestion/epigastric discomfort, peptic ulcer disease, hyperglycemia, agitation, increased appetite, weight gain and acne [13]. Therefore, our findings that the low dose dexamethasone regimen may be equivalent to the standard dose dexamethasone regimen for patients receiving CDDP-based treatment will help reduce the dexamethasone-induced side effects.

Some limitations of our study should be acknowledged. It should be noted that: a) all but four of the patients were men, b) the mean age of the patients was greater than 60 years in each arm, and c) approximately 50% of patients in each arm had a daily intake of alcohol. It is well known that male sex, age older than 50 years and regular alcohol consumption are all factors associated with a lower risk of CINV [15]. However, 1) male, 2) customary drinking history are considered to be high risk factors in head and neck cancer, and head and neck cancer patients often have these factors. The major limitation was a small sized and single-center study. A certain high CR ratio was obtained in

both the standard and low dexamethasone group in the course of the trial. Subjects in this study were head and neck cancer patients who often have predisposition to lower vomiting risk, as described above, compared with other carcinomas, so even if the number of cases increased further, it was predicted that similar results could be obtained. Therefore, it was thought that choosing subjects to be administered clinically and reducing the dosage was more beneficial in terms of cost and side effects, so the trial was discontinued without prolonging the accumulation period of the case. Large-scale randomized crossover trials are needed to evaluate the adequate dosage of dexamethasone combined with aprepitant and 5-HT3 RA for HEC including with high dose of CDDP.

In conclusion, the current study reported that when combined with fosaprepitant and palonosetron, the low dose dexamethasone was not inferior to the standard dose dexamethasone in the CR rate, percentage of no emesis and no rescue, and VAS score of nausea intensity in the acute, delayed and overall phases in the CDDP-based treatment of head and neck cancer patients. In combination with fosaprepitant and palonosetron, it may be possible to reduce the dose of dexamethasone for the additional effect of aprepitant when treating head and neck cancer patients who have lower nausea risks than other cancer patients.

Our findings also indicated that patients who cannot receive standard treatment because they can not use high-dose corticosteroids due to aging or complications can also undergo standard treatment by using low dose dexamethasone.

Disclosure of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Editor-in-Chief, Acta Oto-Laryngologica actaoto@informa.com

Reviewer(s)' Comments to Author:

I have no further comments.