Research Article

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Evaluation of a neurokinin-1 antagonist in preventing multiple-day cisplatin-induced nausea and vomiting

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Abstract: Objective. To perform a prospective non-randomized comparison of the effectiveness and safety of combined neurokinin-1 antagonist aprepitant treatment with the standard multiple-day cisplatin regimen for the prevention of cisplatin-induced nausea and vomiting (CINV). Methods. Patients being administered 3-day cisplatin-based chemotherapy (25 mg/m²/d) who had never received aprepitant were given either the standard regimen (tropisetron and dexamethasone) or the aprepitant regimen (aprepitant plus tropisetron and dexamethasone). The primary endpoint was the complete response (CR) in the overall phase (OP, 0–120 h) between the combined aprepitant triple regimen group and the standard group. Secondary endpoints were the CR in the acute phase (AP, 0–24 h) and delay phase (DP, 25–120 h) between the two groups. The first time of vomiting was also compared by Kaplan–Meier curves. The impact of CINV on the quality of life was assessed by the Functional Living Index-Emesis (FLIE). Aprepitant-related adverse effects (AEs) were also recorded. Results. A CR was achieved by 80.0% in the aprepitant group compared with 56.0% in the standard group during the OP (P =0.018) as well as during the DP. However, during the AP, the aprepitant and standard therapy groups achieved identical CR rates (98.0%, P =1.000). A longer time to first emesis was documented for the aprepitant group than for the standard group. No effect of CINV on quality of life as assessed by FLIE was reported by 44.7% of aprepitant therapy patients and 24.0% of standard therapy patients (P=0.035). The main aprepitant-related AEs were fatigue and constipation, but there was no significant difference between groups. Conclusion. Combined aprepitant therapy is recommended for the prevention of multiple-day CINV because of its improved CINV control rate and safety.

Keywords: Aprepitant; CINV; Multiple-day cisplatin chemotherapy

1 Introduction

Cisplatin-based chemotherapy regimens play an important role in cancer treatment, and a higher platinum dose delivery was shown to be beneficial at maintaining treatment efficacy [1]. However, it may decrease patient quality of life and affect chemotherapy dependence if cisplatin-induced nausea and vomiting (CINV) are not sufficiently prevented [2,3]. Although a combination of aprepitant, a 5-HT3 receptor antagonist, and dexamethasone (DXM) showed high efficacy in single-day cisplatin chemotherapy in the aprepitant multinational randomized double-blind placebo-controlled trial, the combination of 5-HT3 receptor antagonist and dexamethasone remains a standard in multiple-day chemotherapy (MDC) [4-6]. With the aim of overcoming CINV, we conducted a non-randomized study to evaluate the efficacy of apreiptant combined with the standard regimen in patients receiving 3-day cisplatin-based chemotherapy.
2 Patients and methods

2.1 Patients

Patients older than 18 years with a Karnofsky performance scale ≥60 scheduled to receive 3-day cisplatin-based chemotherapy (25 mg/m²/d) were enrolled in the study. All patients had histologically confirmed solid tumors. Females of childbearing potential had negative beta human chorionic gonadotropin blood tests. Primary exclusion criteria were: evidence of alcohol abuse, symptomatic primary or metastatic central nervous system metastasis, the administration of chemotherapy of moderate or high emetogenicity within the past 6 days, the scheduled administration of radiation therapy to the abdomen/pelvis within 1 week or chemotherapy within 3 weeks, the scheduled administration of single-day cisplatin chemotherapy, active infection or other uncontrolled disease, concurrent medical conditions precluding dexamethasone administration, and abnormal laboratory values including: white blood cell count <3,000/mm³ and absolute neutrophil count <1,500/mm³, platelet count <100,000/mm³, aspartate aminotransferase >2.5 x upper limit of normal (ULN), alanine transaminase >2.5 x ULN, bilirubin >1.5 x ULN, or creatinine >1.5 x ULN. Patients were stratified into the aprepitant regimen group or control group according to clinical characteristics such as gender, age, alcohol use, and history of motion sickness.

2.2 Study design and medications

This non-randomized study was conducted at the Medical Oncology Department of Ordos Central Hospital in Inner

| Characteristics                              | Aprepitant regimen (n=50) | Standard therapy (n=50) | P       |
|----------------------------------------------|--------------------------|-------------------------|---------|
| Age(years)                                   |                          |                         |         |
| Mean                                         | 54.9±11.0                | 57.3±9.2                | 0.546   |
| Gender                                       |                          |                         |         |
| Female                                       | 21(42.0)                 | 13(26.0)                | 0.139   |
| Male                                         | 29(58.0)                 | 37(74.0)                |         |
| History of motion sickness                   | 4(8.0)                   | 2(4.0)                  | 0.678   |
| History of nausea with pregnancy in female   | 16(37.1)                 | 8(40.0)*                | 0.713   |
| History of vomiting with pregnancy in female | 7(25.0)                  | 3(15.0)*                | 0.713   |
| Alcohol use                                  |                          |                         |         |
| No consumption                               | 28(56.0)                 | 16(32.0)                | 0.106   |
| <1 drinks per week                           | 8(16.0)                  | 14(28.0)                |         |
| 1-4 drinks per week                          | 2(4.0)                   | 2(4.0)                  |         |
| ≥4 drinks per week                           | 12(24.0)                 | 18(36.0)                |         |
| Smoking status                               |                          |                         |         |
| No Smoking                                   | 22(44.0)                 | 17(34.0)                | 0.580   |
| ≥400                                        | 21(42.0)                 | 24(48.0)                |         |
| 0-400                                        | 7(14.0)                  | 9(18.0)                 |         |
| Type of malignance                           |                          |                         | 0.423   |
| Lung cancer                                  | 24(48.0)                 | 29(58.0)                |         |
| Others                                       | 26(52.0)                 | 21(42.0)                |         |
| Chemotherapy cycle                           |                          |                         | 0.082   |
| 1                                           | 19(38.0)                 | 19(38.0)                |         |
| 2-3                                          | 26(52.0)                 | 18(36.0)                |         |
| ≥4                                          | 5(10.0)                  | 13(26.0)                |         |

P values were generated using Fisher’s exact test for characteristics with two groups and with the chi-square test for characteristics with multiple groups

Notes: *: A female patient was without pregnancy history

HNPCC: head and neck squamous cell carcinoma
From June 2014 to December 2016, patients were consecutively included if they received 3-day cisplatin-based chemotherapy (25mg/m²/d) and had not been previously treated with aprepitant. The study was approved by the local ethics committee and all patients gave written informed consent for participation in the study.

Patients in the control group received an injection of tropisetron hydrochloride (Beijing Shuanglu Pharmaceutical Co. Ltd., China) and aprepitant (EMEND, MSD Sharp & Dohme, Haar, Germany). The medication procedure is listed in Table 2. Dexamethasone was reduced to half dosage in the aprepitant group because of the previously demonstrated inhibition of CYP3A4 by aprepitant in DXM pharmacokinetics [7].

### 2.3 Procedures and assessments

Patients have recorded and self-reported times and dates of vomiting or retching episodes, and use of rescue therapy from the time of chemotherapy infusion (0 h) until day 6. Patients were contacted on the mornings of days 2–6 to ensure compliance. Functional Living Index-Emesis (FLIE) questionnaire scoring was self-administered early on day 6, directly following the completion of the final self-reports [8]. FLIE is a validated emesis- and nausea-specific questionnaire with nine nausea domain questions (items) and nine vomiting domain questions (items) [9,10]; ‘no impact of CINV on daily life’ represented mean scores >6 on a 7-point scale (>108 in total).

All patients underwent post-treatment examination on days 6–8 and follow-up on days 19–21 to record the occurrence of adverse events (AE) related to aprepitant treatment.

### 2.4 Statistical analysis

The sponsor managed the data and performed the analyses for this study. The primary endpoint for the efficacy analysis was the proportion of patients with a complete response (CR), defined as no vomiting or use of rescue therapy. Secondary endpoints included CR in the acute phase (AP, 0–24 h following chemotherapy) and the delay phase (DP, 24–120 h following chemotherapy), no vomiting (vomiting, dry heaves, or retching) in any phase, the impact of CINV on daily life during the overall phase (OP, FLIE questionnaire total score >108), and the time to first vomiting.

Treatment comparisons were made using logistic regression models that included terms for treatment, gender, age, alcohol use, and history of motion sickness. All comparisons used a two-sided significance level of 5%. Tests of significance were based on logistic regression models, and nominal P values were reported. Kaplan–Meier curves of time to first emesis were constructed for both groups. Fisher’s exact test was used to compare the percentage of patients who achieved CR or experienced aprepitant-related AEs between the two groups.

### 3 Results

#### 3.1 Patients

A total of 100 patients completed the clinical observation. Of these, 50 received the aprepitant triple regimen, and the remaining 50 received the standard regimen (control group). Baseline characteristics were comparable between the two groups. Primary cancer diagnoses were also similar, with lung cancer being the most common disease. No significant differences between groups were reported for alcohol use, history of motion sickness, or

| Table 2: The Medication Procedures |
|-----------------------------------|
| **Day 1** | **Day 2** | **Day 3** | **Day 4** |
| a4prepitant125mg po | a4prepitant80mg po | a4prepitant80mg po |
| tropisetron5mg iv | tropisetron5mg iv | tropisetron5mg iv |
| dexamethasone6mg po | dexamethasone3.75mg po | dexamethasone3.75mg po |
| tropisetron5mg iv | tropisetron5mg iv | tropisetron5mg iv |
| dexamethasone10.5mg po | dexamethasone7.5mg po | dexamethasone7.5mg po |

| standard group |
|----------------|
| Day 1 | Day 2 | Day 3 | Day 4 |
| tropisetron5mg iv | tropisetron5mg iv | tropisetron5mg iv |
| dexamethasone10.5mg po | dexamethasone7.5mg po | dexamethasone7.5mg po |
| a4prepitant125mg po | a4prepitant80mg po | a4prepitant80mg po |
| tropisetron5mg iv | tropisetron5mg iv | tropisetron5mg iv |
| dexamethasone6mg po | dexamethasone3.75mg po | dexamethasone3.75mg po |
| tropisetron5mg iv | tropisetron5mg iv | tropisetron5mg iv |
| dexamethasone10.5mg po | dexamethasone7.5mg po | dexamethasone7.5mg po |
vomiting associated with pregnancy. Only female patients were assessed for nausea or vomiting during pregnancy.

3.2 Efficacy

A CR during the OP (primary endpoint) was exhibited by 80.0% (40/50) of patients receiving the aprepitant triple regimen and 56.0% (28/50) of those receiving the standard regimen ($P =0.018$; Figure 1). Similarly, CR during the DP was significantly higher in the aprepitant regimen group than in the standard therapy group (80.0% vs. 56.0%, $P =0.018$). During the AP, however, the aprepitant and standard therapy groups exhibited identical CR rates (98.0%, $P =1.000$). Within the aprepitant group, the proportion of patients achieving a CR was highest in males (93.1% [27/29]) versus females (61.9% [13/21]) ($P=0.011$). Moreover, a higher treatment benefit in the standard group was also observed in males (70.3% [26/37]) compared with females (13.3% [2/15]) ($P=0.000$).

3.3 Comparison of FLIE index

During the OP, a higher percentage of no vomiting was reported in the aprepitant regimen group than in the standard regimen group (82.0% [41/50] vs 70.0% [35/50], respectively), although this was not significant ($P=0.241$). Fewer uses of rescue treatment were reported in the aprepitant regimen group than in the standard regimen group (6.0% vs. 14.0%, respectively, $P =0.318$) during the OP. More patients taking the aprepitant regimen reported no vomiting and no significant nausea compared with the standard regimen group, though the difference did not reach significance during the OP (36.0% vs. 30.0%, $P =0.318$).

According to FLIE, reports of no impact of CINV on daily life were exhibited by 44.7% (21/47) of patients in the aprepitant triple regimen group and by 24.0% (12/50) of those in the standard regimen group ($P =0.035$). Three FLIE questionnaires could not be analyzed in the aprepitant regimen group because of incorrect marking. The comparison of the FLIE index of nausea and vomiting between the two groups is shown in Table 3.

3.4 Comparison of time to first vomiting

Kaplan–Meier curves of time to first emesis were similar between the two groups up to 72 h, after which longer times to first emesis were observed in the aprepitant regimen group ($P =0.201$). The first emesis events were

![Figure 1: Comparison of the complete response rate between the two groups](image1)

![Figure 2: Comparison of time to first vomiting between the two groups](image2)

| Items          | Aprepitant regimen | Standard regimen | P    |
|----------------|--------------------|-----------------|------|
| Nause FLIE Score | 46.67±13.77        | 42.01±12.12     | 0.150|
| Vomiting FLIE Score | 53.32±12.71        | 47.34±13.31     | 0.066|
| FLIE Score      | 99.97±22.49        | 88.95±24.75     | 0.080|

Notes: FLIF: functional living index-emesis
observed in 30.0% (15/50) and 18.0% (9/50) of patients in the standard group and aprepitant group, respectively.

3.5 Tolerability

The most common aprepitant-related AEs were fatigue and constipation which occurred in 16.0% (8/50) and 16.0% (8/50) of patients, respectively, in the aprepitant regimen group versus 8.0% (4/50) and 14.0% (7/50), respectively, in the standard regimen group (P = 0.10 for both). There was no significant difference in the AEs that occurred between the two groups.

4 Discussion

Clinical guidelines from the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology [11], the American Society of Clinical Oncology [12], and the National Comprehensive Cancer Network have recommended antiemetic therapy for HEC (highly emetogenic chemotherapy) that includes the 3-day aprepitant regimen [13]. However, the majority of trials have investigated patients receiving their first cycle of single-day chemotherapy, and MDC is one of the most neglected areas of antiemetic research. Indeed, a 5-HT3 antagonist plus dexamethasone still routine therapy for current MDC [14]. Additionally, previous investigations into the prevention of multiple-day CINV were either retrospective or single-arm observations [14,15]. We therefore conducted a non-randomized study to evaluate the effect and safety of combined neurokinin-1 antagonist aprepitant therapy for the prevention of multiple-day CINV.

The primary and secondary endpoints adopted in this study were in accordance with the 052, 054 multinational randomized double-blind placebo-controlled trial [4,5]. Different time cut-off points between the AP and DP are reported in multiple-day CINV clinical trials [14,15], but here we defined the AP as 0–24 h following chemotherapy. Tropisetron was chosen as a 5-HT3 inhibitor because ondansetron, tropisetron, and dolasetron exhibited similar efficacies in postoperative nausea and vomiting prevention meta-analysis [16].

The current findings are consistent with previous reports for single-day chemotherapy, demonstrating that aprepitant treatment regimens achieved better CR rates during the OP and DP following initial chemotherapy treatment [4,5,17]. Conversely, our CR rates during the AP did not show a significant improvement, which is in accordance with the report of Zhang et al. [17]. Furthermore, our CR rates during the AP differ from our previous clinical observation [18], perhaps because we included patients who received high-dose cisplatin as well as lower-dose cisplatin and anthracyclines. The aprepitant regimen group in the present study achieved a high level of overall benefit (24.0%), which was identical to that seen in the 052, 054 clinical study although significantly higher than the minimum clinical relevant difference of 10% previously reported in the Chinese population [4,5,17]. Similarly, the 80.0% CR achieved during OP was consistent with the 81.5% previously reported by Zhang et al. but higher than the 58.5% reported by the Sun Yat-Sen University Cancer Center [14,15].

In this study, patients in both the aprepitant regimen group and the standard group exhibited higher CR rates during the AP and OP phases than in previous phase III trials. Nevertheless, the primary endpoint reached statistical significance in our study as well as in previous trials. The smaller sample sizes of our study may explain the higher CR rate. Alternatively, it may reflect the fact that acute nausea and vomiting are alleviated more by 3-day cisplatin than single-day treatment [19]. Another reason for the difference may be variations in time cut-off points between the AP and DP; indeed, Gao et al. found that the CR declined by ~20% when the AP cut-off point changed from 24 h to 72 h [20]. Furthermore, the different 5-HT3 and DXM dosages used in our study may have affected the results compared with previous 3-day CINV prevention clinical studies. The observed superiority of aprepitant in male rather than female patients also differed from the findings of previous studies [4,5,6], and may reflect the initial imbalance between male and female patients.

Patients in the aprepitant regimen group reported a significantly higher quality of life than those receiving the standard regimen (P = 0.0035). This finding differed from clinical research into single-day cisplatin chemotherapy in the Chinese population [15]. It indicates that aprepitant may help achieve a greater improvement to the quality of life in a 3-day cisplatin chemotherapy model. Kaplan–Meier curves of time to first emesis until 72 h were in accordance with the secondary endpoint CR in the AP. The trend of the two curves supports 72 h as a reasonable cut-off point between the AP and DP, although we define the AP as 0–24 h after treatment in this study. We propose that standard time cut-off points should be established by testing for the excretion of the urinary serotonin metabolite 5-hydroxyindoleacetic acid during 3-day cisplatin chemotherapy [21].

The aprepitant-related AE profile observed in 3-day cisplatin chemotherapy included fatigue and constipa-
tion, which are entirely consistent with other studies examining aprepitant-related AEs. Thus, aprepitant was generally well tolerated.

5 Conclusion

In summary, a combination therapy of the neurokinin-1 antagonist aprepitant with the traditional regimen of a 5-HT3 inhibitor and DXM improved the control of CINV and life quality associated with multiple-day cisplatin chemotherapy. Moreover, the aprepitant regimen was generally well tolerated. The improvement of uncontrolled CINV in patients receiving the combined aprepitant triple regimen remains a challenge for future research.

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Conflict of interest statement: The authors confirm that this article content has no conflict of interests.

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