Antiemetic Prophylaxis for Chemoradiotherapy-induced Nausea and Vomiting (C-RINV) in Locally Advanced Head and Heck Squamous Cell Carcinoma: a Prospective Phase Ⅱ Trial

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Research

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Abstract

Background There is sparse research reporting effective interventions for preventing nausea and emesis caused by concurrent chemoradiotherapy (CCRT) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). This phase Ⅱ trial was conducted to provide the direct evidence for the current practice of prescribing antiemetic in patients with LA-HNSCC receiving CCRT.

Methods Treatment-naïve LA-HNSCC patients received intensity-modulated radiotherapy with concomitant cisplatin 100 mg/m² every 3 weeks for two cycles. All patients were given orally aprepitant 125 mg once on d1, then 80mg once on d2-5; ondansetron 8 mg once on d1; and dexamethasone 12 mg once on d1, then 8mg on d2-5. The primary endpoint was complete response (CR). Pursuant to δ=0.2 and α=0.05, the expected CR rate was 80%.

Results A total of 43 patients with LA-HNSCC were enrolled. The median age was 53 years old, and 86.0% were male. All patients received radiotherapy and 86.0% of patients completed both cycles as planned. The overall CR rate was 86.0% (95% CI: 72.1-94.7). The CR rates for cycles 1 and 2 were 88.4% (95% CI: 74.9-96.1) and 89.2% (95% CI: 74.6-97.0). The complete protection rate in the overall phase was 72.1% (95% CI: 56.3-84.7). The emesis-free response and nausea-free response in overall phase were 88.4% (95% CI: 74.9-96.1) and 60.5% (95% CI: 44.4-75.0), respectively. The adverse events related to antiemetics were constipation (65.1%) and hiccups (16.3%), but both were grade 1-2. There was no grade 4 or 5 treatment-related adverse event with antiemetic usage.

Conclusion The addition of aprepitant into ondansetron and dexamethasone provided effective protection from nausea and emesis in patients with LA-HNSCC receiving radiotherapy and concomitant high-dose cisplatin chemotherapy. Randomised phase 3 studies are required to further define the potential role of NK_1RA in chemoradiotherapy setting.

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Background

Amongst the background of advances in new antiemetic agents, the efficacy of antiemetics in preventing chemotherapy-induced nausea and vomiting (CINV) has been substantially improved [1]. Aprepitant was the first Neurokinin-1 receptor antagonist (NK_1RA) that block the binding of substance P to prevent emesis. The addition of NK_1RAs improved complete response (no emesis and no rescue medication) by 8–20% after highly emetogenic chemotherapy (HEC) [2]. The current Multinational Association of Supportive Care in Cancer/ European Society for Medical Oncology (MASCC /ESMO) and NCCN guidelines also recommend a triple regimen consisting of 5-HT3RA, dexamethasone and NK_1RAs to prevent nausea and vomiting induced by HEC, e.g., cisplatin [3]. Conversely, little focus has centred on the antiemetic prophylaxis in radiotherapy. As a result, radiation-induced nausea and vomiting (RINV) is often

underestimated by clinicians [4]. A cross-sectional study demonstrated one third of patients experiencing RINV would like additional treatment[5]. Nevertheless, evidence for the guideline recommendations is scarce, and little is known about the combination and optimal duration of antiemetic agents [6]. In chemoradiotherapy setting, RINV can be exacerbated by concomitant chemotherapy to higher levels, which has been confirmed by prior studies, though the pathophysiological mechanism is not well understood [7–9].

With regard to locally advanced head and neck squamous cell carcinoma (LA-HNSCC), cisplatin-based concurrent chemoradiotherapy (CCRT) remains the standard treatment modality. However, nausea and vomiting induced by CCRT are common toxicities, with deleterious effects on treatment compliance and quality of life. Several prospective studies have demonstrated that the incidence of nausea and vomiting during cisplatin-based CCRT are 48%-66% and 30%-47% [10–13]. Thus, there is a pressing need for optimization of antiemetic treatment to address chemoradiotherapy-induced nausea and vomiting (C-RINV). Recent evidence has emerged that NK_1RAs improve the control of C-RINV in certain tumors. To date, only five published prospective studies have reported the efficacy and safety of NK_1RAs for the prophylaxis of C-RINV, two of which focused on cervical cancer, and the remainder included multiple-site tumors [14–18]. The above studies demonstrated the superiority of NK_1RAs in the prevention of nausea and vomiting as well as their high tolerance, yet whether different tumors, various chemotherapy regimens, as well as different radiation schedules would yield similar results remains unknown.

In our preliminary trial, 13 patients with LA-HNSCC receiving CCRT with triweekly cisplatin were administrated with triple antiemetic regimen consisting of NK_1RA (aprepitant), 5-HT_3RA (ondansetron) and dexamethasone. The results highlight only 1 case developed vomiting and 2 cases required rescue antiemetic treatment. No significant adverse event was observed. On the basis of the above results, a prospective trial was conducted to explore whether the addition of aprepitant could provide effective protection against C-RINV in patients with LA-HNSCC.

Materials And Methods

Study design and participants

This study was investigator initiated and designed as a prospective single arm, open label phase Ⅱ trial to evaluate the efficacy and safety of aprepitant combined with ondansetron and dexamethasone for the prevention of nausea and vomiting induced by concurrent chemoradiotherapy in LA-HNSCC. All patients were fully informed about the study and signed informed consent. The study was conducted in accordance with the Declaration of Helsinki and the international standards of Good Clinical Practice and approved by the local ethics committee.

The eligible patients were aged 18 to 70 years old with histologically confirmed squamous cell carcinoma of the head and neck (nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, nasal cavity and

paranasal sinuses), and were stage Ⅱ- IVB for nasopharynx site or stage III-IVB for other sites based on the American Joint Committee on Cancer 7th Edition (AJCC 7th). Patients had the Eastern Cooperative Oncology Group (ECOG) performance status 0-1; had adequate organ and bone marrow function; must have been able to swallow tablets; had the life expectancy of at least 12 weeks; and would receive CCRT as planned after multi-disciplinary team (MDT) discussion. Fertile male and female patients volunteered to use effective contraception during the study and within 90 days of the last medication. The exclusion criteria included other medical histories of malignancy apart from non-melanoma skin cancer, cervical carcinoma in situ, and early-stage cured prostate cancer; nausea and emesis occurred 24 hours before the start of CCRT; corticosteroid or benzodiazepines used; any medicine which affected metabolism through drug-metabolising enzymes CPY3A4 and CYP2D6 except for nighttime sedatives; severe cardiovascular, pulmonary, diabetes, mental and other diseases; perinatal women or rejection of taking contraception during treatment; drug and/or alcohol addiction; symptomatic brain metastasis; gastrointestinal obstruction; hypocalcemia or any other conditions that could provoke emesis.

Procedures

Intensity-modulated radiotherapy (IMRT) using simultaneously integrated boost was administered to all patients. The target delineation and dose prescription followed the principles of radiotherapy for head and neck cancer at our center [19]. The delineation of normal organs adhered to the international consensus on delineation of organs at risk in the head and neck regions [20], and the standard of dose limitation referred to the QUANTEC. Concurrent chemotherapy was administrated with cisplatin 100 mg/m^2 (given evenly on days 1-3) every 3 weeks for two cycles. All patients received hydration and diuretic therapy during the administration of cisplatin. The chemotherapy-induced toxicities had to be restored to grade 0-2 prior to the start of the subsequent cycle. The chemotherapy was terminated if the toxicities were not restored to grade 0-2 within 14 days of the beginning of the next cycle. If grade 4 hematological toxicities or ≥ grade 3 non-hematological toxicities occurred in the previous cycle, the dose of subsequent cycle had to be reduced by 25%.

The recruited patients were subjected to unified antiemetic treatment (Fig. 1). The doses, duration and scheduling of antiemetics in our study basically followed the MASCC/ESMO guidelines for multiple-day cisplatin chemotherapy.[21] A combination of ondansetron, dexamethasone and aprepitant was applied for acute nausea and vomiting, dexamethasone and aprepitant for delayed nausea and vomiting. Aprepitant was administrated orally once daily for the 2 days after chemotherapy (days 4-5). The antiemetic regimen was maintained in the subsequent cycle until chemotherapy was stopped or severe drug-related side effects occurred. Rescue antiemetic therapy was permitted for grade 3 nausea (National Cancer Institute Common Toxicity Criteria for Adverse Events, NCI CTCAE, version 4.0) or poor antiemetic effects (criteria: emesis > 2 times/24 hours, and continuous vomiting within 5 minutes is regarded as one time).

Assessment

Patients were obligated to complete daily diaries per cycle that recorded nausea, vomiting or dry retches including the time, frequency, degree or score, and application of rescue medication. The weekly

evaluation of treatment-related toxicities was predicated on NCI CTCAE version 4.0. To assess the degree of nausea and vomiting, the MASCC Antiemesis Tool (MAT) scale was completed respectively by patients during chemotherapy and during the period from the 2nd day to 4th day after the last administration of cisplatin. At baseline, on day 7 of the first cycle and the second cycle, the Functional Living Index-Emesis (FLIE) questionnaire was employed to evaluate the effect of nausea and emesis on the quality of life. The overall quality of life was assessed each week during treatment (week 1–7) by using the questionnaires of the European Organization for Research and Treatment of Cancer (EORTC), Quality of Life Core 30 items (QLQ-C30) version 3.0 and Quality of Life Head and Neck 35 items (QLQ-H&N35) version 1.0.

Outcomes

The primary endpoint was complete response (CR) defined as no emesis and no use of rescue therapy during concurrent chemoradiotherapy. The secondary endpoints were as follows: CR for each cycle; complete protection (CP), denoted as no emesis, no rescue medication and no more than mild nausea (grade 1 premised on CTCAE 4.0); emesis-free response, which refers to no vomiting or dry retches during treatment; nausea-free response, signified as no nausea during treatment; and treatment-related toxicities. Other secondary endpoints consisted of the degree of nausea and vomiting evaluated by the MAT scale, as well as the quality of life using the FLIE, EORTC QLQ-C30 and QLQ-H&N35 questionnaires (results not reported here).

Statistical analysis

The Simon two-stage design was adopted to estimate the sample size [22]. Pursuant to $\delta = 0.2$ and $\alpha = 0.05$, the expected CR rate was 80%. If the CR was less than 60%, the study protocol was declared invalid. In the first stage, 17 patients were enrolled. If more than 13 patients achieved CR, 26 patients would remain enrolled.

Demographic and clinical characteristics were outlined using median (range) for continuous variables and frequency (percentage) for categorical variables. The percentages of patients with CR or CP, emesis-free response, and nausea-free response for every cycle and overall phase were estimated along with 95% confidence intervals (CIs). The corresponding 95%CIs were calculated using the Binomial test of one-sample nonparametric tests. The treatment-related toxicities and adverse events were summarised as frequency (percentage). Statistical analyses were conducted using SPSS software (version 26.0; SPSS, Inc).

Results

Between March 2018 and January 2020, 16 of 17 patients recruited in stage 1 achieved CR and thereafter 26 patients were further enrolled in stage 2. Baseline characteristics are reported in Table 1. The median age was 53 years old (range: 18-66), and 86.0% were male. 40 patients in total were treated with definitive CCRT, while the remaining 3 patients who were to receive planned definitive CCRT were re-examined and the efficacy thereof evaluated when the cumulative PTV dose reached around 50Gy, followed by conversion to surgery after MDT discussion. The median radiation dose was 69.96Gy (range: 53-

73.92Gy). All patients received radiotherapy and the first cycle of cisplatin, while 6 patients terminated the subsequent cycle of chemotherapy. Among the 37 patients who received the second cycle of chemotherapy, different degrees of delayed chemotherapy occurred in 21 (56.8%) patients (median: 7 days; range: 2-14 days). The reasons for delay or discontinuation are displayed in Table 2. Cisplatin dose changes were reported in 11 (29.7%) of 38 patients during the second cycle. All patients completed antiemetic treatment as planned.

Table 1
Baseline demographic and clinical characteristics

Characteristics	***N*=43**
Age, years	53 (18-66)
Gender	
Male	37 (86.0%)
Female	6 (14.0%)
ECOG performance status	
0	5 (11.6%)
1	38 (88.4%)
Tumor location	
Nasopharynx	23 (53.5%)
Oropharynx	9 (20.9%)
Hypopharynx	8 (18.6%)
Larynx	1 (2.3%)
Paranasal sinuses	2 (4.7%)
TNM classification (AJCC 7th)	
	3 (7.0%)
	16 (37.2%)
A	17 (39.5%)
B	7 (16.3%)
Completed cycles	
One cycle	43 (100%)
Two cycles	37 (86.0%)
Total dose of cisplatin, mg	300 (150-360)
Dose of cycle 1	150 (120-180)
Dose of cycle 2	150 (90-180)

Data are *n*, *n* (%), or median (range). ECOG=Eastern Cooperative Oncology Group. CCRT= Concurrent Chemoradiotherapy.

Table 2
Reasons for chemotherapy delay or discontinuation

Reasons	Numbers
Chemotherapy delay	21
Hematologic toxicities	12
Hepatic function damage	3
Patient autonomy	3
Gastrointestinal reactions	2
Asthenia/fatigue	1
Chemotherapy discontinuation	6
COVID-19 pandemic	2
Thromboembolic event	1
Hepatic dysfunction	1
Malnutrition	1
Patient refusal	1

The overall CR rate of this study achieved 86.0% (95% CI: 72.1%-94.7%), exceeding the expected CR rate. Table 3 lists the secondary efficacy endpoints. The CR rate for cycle 1 was 88.4% (95% CI: 74.9%-96.1%), while there was a slightly higher CR rate (89.2%, 95% CI: 74.6%-97.0%) for cycle 2. The CP rate in the overall phase was 72.1% (95% CI: 56.3%-84.7%), while the data of cycle 1 and cycle 2 were 76.7% (95% CI: 61.4%-88.2%) and 86.5% (95% CI: 71.2%-95.5%), respectively.

Table 3
Secondary efficacy endpoints

	No. of patients (percentage)	95% CI
Complete response		
Days 1-3 of cycle 1	39 (90.7%)	77.9%-97.4%
Days 1-7 of cycle 1	38 (88.4%)	74.9%-96.1%
Days 1-3 of cycle 2	34 (91.9%)	78.1%-98.3%
Days 1-7 of cycle 2	33 (89.2%)	74.6%-97.0%
Emesis-free response		
Days 1-3 of cycle 1	40 (93.0%)	80.9%-98.5%
Days 1-7 of cycle 1	39 (90.7%)	77.9%-97.4%
Days 1-3 of cycle 2	34 (91.9%)	78.1%-98.3%
Days 1-7 of cycle 2	34 (91.9%)	78.1%-98.3%
Nausea-free response		
Days 1-3 of cycle 1	30 (69.8%)	53.9%-82.8%
Days 1-7 of cycle 1	26 (60.5%)	44.4%-75.0%
Days 1-3 of cycle 2	32 (86.5%)	71.2%-95.5%
Days 1-7 of cycle 2	29 (78.4%)	61.8%-90.2%
Complete protection		
Days 1-3 of cycle 1	36 (83.7%)	69.3%-93.2%
Days 1-7 of cycle 1	33 (76.7%)	61.4%-88.2%
Days 1-3 of cycle 2	33 (89.2%)	74.6%-97.0%
Days 1-7 of cycle 2	32 (86.5%)	71.2%-95.5%

The emesis-free response in overall phase achieved 88.4% (95% CI: 74.9%-96.1%). The emesis-free response rates for cycle 1 and 2 were 90.7% (95% CI: 77.9%-97.4%) and 91.9% (95% CI: 78.1%-98.3%), respectively. Of the five patients with emesis, grade 2 emesis occurred in three patients, the remaining two patients experienced grade 1 emesis, and all patients did not receive rescue antiemetics. The median time from cisplatin administration to emesis was the 3rd day (day 1-day 6), while the median duration time of emesis was 2 days (1-6 days).

The nausea-free response in the overall phase was 60.5% (95% CI: 44.4%-75.0%). The nausea-free response rate for cycle 1 also achieved 60.5% (95% CI: 44.4%-75.0%), whereas the incidence of no nausea for cycle 2 increased by nearly 18% (78.4%; 95% CI: 61.8%-90.2%). The distribution of patients with different grades of nausea appertaining to the nausea visual analog scale (NVAS) was reported in the Fig. 2 (1-3 points: 7 cases; 4-6 points: 7 cases; 7-10 points: 3 cases). The median score of nausea founded on the NVAS was 4 points (range: 1-10). Regarding the patients with nausea, the same one patient developed severe nausea (NVAS score up to 10 points) in both cycles and was administrated with rescue treatment. The median time of the nausea episode was the 2nd day (day 1-day 6), while the median duration time of nausea was 3 days (1-7days).

Grade 1–2 adverse events that presented in at least 10% patients included dermatitis, mucositis, dry mouth, leucopenia, anaemia, hepatic dysfunction, appetite loss, constipation, and hiccups (Table 4). The most frequent grade 3 adverse events were mucositis (20.9%) and leucopenia (14.0%). Grade 3 dermatitis, hepatic dysfunction, and appetite loss were less than 5%, and no grade 4 or 5 adverse event was recorded. The adverse events related to antiemetics were constipation (65.1%) and hiccups (16.3%), but both were grade 1-2. Further, no infusion site infection or allergic reaction emerged during treatment.

Table 4
Treatment-related toxicities

Toxicities	Grade 1	Grade 2	Grade 3
Dermatitis	28 (65.1%)	14 (32.6%)	1 (2.3%)
Mucositis	13 (30.2%)	18 (41.9%)	9 (20.9%)
Dry mouth	14 (32.6%)	29 (67.4%)	0
Leucopenia	13 (30.2%)	14 (32.6%)	6 (14.0%)
Anaemia	11 (25.6%)	2 (4.7%)	0
Hepatic dysfunction	8 (18.6%)	3 (7.0%)	2 (4.7%)
Loss of appetite	18 (41.9%)	10 (23.3%)	2 (4.7%)
Constipation	15 (34.9%)	13 (30.2%)	0
Hiccups	4 (9.3%)	3 (7.0%)	0

Data are *n* (%). Incidences of grade 1–2 adverse events in at least 10% of patients and all grade 3 adverse events. No grade 4 or 5 adverse event was observed.

Discussion

To the best of our knowledge, this is the first prospective trial to evaluate the efficacy and safety of a NK_1 receptor antagonist (aprepitant) combined with ondansetron and dexamethasone to prevent nausea and vomiting for patients with HNSCC receiving triweekly cisplatin chemoradiotherapy. The primary endpoint

met the target, with the overall CR rate achieving 86.0%, revealing that the triple antiemetic regimen provided effective protection against chemoradiotherapy-induced nausea and vomiting in patients with LA-HNSCC. Prior research has indicated that the addition of an NK_1RA into 5-HT_3RA and dexamethasone improves antiemetic efficacy in patients with cervical cancer receiving radiotherapy with weekly cisplatin chemotherapy [17, 23]. Similar results have now been extended to patients with HNSCC receiving IMRT and triweekly cisplatin chemotherapy.

The primary endpoint of the present trial was complete response, which has used in most clinical antiemetic trials. The “no emesis” represented the control of emesis, while “no use of rescue therapy” as an alternative marker also reflected control of nausea to a certain degree. In the present trial, only 5 patients experienced grade 1 to 2 emesis, and one patient with severe nausea received rescue treatment. Prior prospective studies on NK_1RAs for prophylaxis of C-RINV observed that the CR rate was between 48% and 76% [14–16, 18]. As against the data of the above studies, our results exhibit that the triple antiemetic regimen achieved excellent antiemetic efficacy. One possible explanation is that the 5-day antiemetics administration increased the cumulative dose of the aprepitant and dexamethasone under the premise of multiple-day cisplatin chemotherapy, potentially having a stronger antiemetic effect. With regard to the secondary endpoints, CP is also a reliable endpoint to evaluate the overall control of nausea and vomiting, often being employed in clinical trials of CINV. The CP rate of this study achieved 72%, which was higher than the data reported in several trials on aprepitant for prevention of CINV [24, 25]. However, the concept of “mild nausea” is not objective enough, whether it is based on grade 1 of CTCAE or NVAS < 25mm [26]. Conversely, “no vomiting” and “no nausea” are relatively objective indicators, being adopted as secondary endpoints in our study. In the overall phase, 88.4% of patients developed no emesis, higher than the 66%-73% reported in previous studies on NK_1RAs for prevention of C-RINV [15, 17, 18, 27]. Although the overall nausea-free response rate was only 60.5%, this is approximately consistent with the 40%-61.5% reported in preceding research on NK_1RAs for prevention of C-RINV [16, 18, 27].

The control rates of nausea and vomiting under our triple antiemetic regimen were also superior to the data reported in previous studies on concurrent chemoradiotherapy for head and neck squamous cell carcinoma. In actuality, many studies have reported treatment-related toxicities such as nausea and vomiting while publishing primary endpoints, yet few studies specified the antiemetic regimens. In the RTOG 0129 trial [11], 361 patients were subjected to standard fractionation irradiation with a median dose of 69.8Gy and concomitant triweekly cisplatin chemotherapy, and granisetron or ondansetron was used as the antiemetic regimen. In this condition, 65.9% of patients developed nausea and 46.8% of patients experienced vomiting. Further, the incidences of grade 3 nausea and grade 3-4vomiting were both close to 20%. These results implied that single-agent 5-HT_3RAs were insufficient to control nausea and vomiting caused by concurrent chemoradiotherapy in head and neck squamous cell carcinoma. In a randomized phase 3 trial [13], the CCRT arm was subjected to radical radiotherapy (66-70Gy) with concurrent weekly cisplatin (30 mg/m^2). Employing ondansetron and dexamethasone as antiemetics, the overall incidences of nausea and vomiting were 47.7% and 30%, and the incidences of grade 3 nausea and grade 3-4

vomiting were only 1% and 1.5%. As well as the addition of dexamethasone, the reduction of nausea and vomiting could also be attributed to the weekly cisplatin chemotherapy regimen. A preceding meta-analysis compared weekly low-dose (≤ 50 mg/m^2) and triweekly high-dose cisplatin (100 mg/m^2) for CCRT in LA-HNSCC, and demonstrated the weekly regimen did lead to a substantially lower proportion of severe nausea and/or vomiting (3% vs 16%) [28]. However, the antiemetic efficacy was still superior to the above study under the premise of administrating the stronger emetic triweekly cisplatin regimen in the present study, illustrating that the addition of aprepitant into ondansetron and dexamethasone could more effectively control nausea and vomiting. In a further randomized phase 3 trial [29], Tang et al also divided 100 mg/m^2 of cisplatin into three days, and the antiemetic regimen stipulated adding metoclopramide on the basis of ondansetron/ granisetron and dexamethasone. The proportion of patients with nausea and vomiting were both around 80%, and the incidence of grade 3 nausea was only 9%, but the incidence of grade 3-4 vomiting was up to 18%. Numerically, although the triple regimen containing metoclopramide could be more effective in preventing severe nausea, poor prevention of the overall occurrence of nausea and vomiting was demonstrated, in addition to a failure to effectively prevent severe vomiting. Conversely, the majority of patients with nausea presented mainly mild and moderate levels in the present study. Despite the determination of the degree of nausea being subjective, only one patient required rescue antiemetics, and no patient discontinued treatment due to nausea or vomiting, thereby objectively illustrating that the triple regimen containing aprepitant could effectively control the occurrence of severe nausea and vomiting.

Recently, another prospective study evaluating the antiemetic efficacy of aprepitant in patients with LA-HNSCC receiving radiotherapy and concurrent weekly cisplatin (50 mg/m^2) chemotherapy was exhibited at the 2020 Annual Meeting of the American Society of Clinical Oncology (ASCO) [27]. The incidences of no nausea and no vomiting were 57.7% and 73.2% in patients receiving aprepitant, 5-HT$_3$RA and steroids. The similar antiemetic regimen demonstrated poorer control of nausea and vomiting during concurrent weekly cisplatin and radiation compared with our study. In general, whether horizontally compared with the studies of NK$_1$ RAs for prophylaxis of C-RINV, or longitudinally compared with prior studies of CCRT for head and neck squamous cell carcinoma, our study administrated a triple antiemetic regimen consisting of aprepitant, ondansetron and dexamethasone and presented high antiemetic efficacy. Yet, the incidence of nausea in our study notably remained close to 40%. A small randomized controlled trial had revealed that the addition of olanzapine increased the control rate of nausea from 40–71% [16]. In future research, we will consider adding olanzapine to optimise this antiemetic regimen.

In terms of treatment compliance and toxicities, 86.0% of patients completed both cycles of chemotherapy in the present study. Of the six patients who discontinued chemotherapy, only three did so as a result of treatment related adverse events. Owing to the antiemetics that were given together with cisplatin, it was difficult to classify adverse events into antiemetics-related or cisplatin-related, especially fatigue, appetite loss and hepatic dysfunction. Nevertheless, constipation and hiccups with incidences of 65.1% and 16.3% were primarily regarded as antiemetics-related adverse events. The high incidence of constipation could be attributed to an increase of cumulative dose for 5-day administration of

antiemetics, in addition to the non-use of prophylactic laxatives. Dexamethasone-induced hiccups are not an uncommon symptom in patients with cancer, Vardy et al. reported a 25% incidence of hiccups after dexamethasone administration [30]. Liaw et al. also discovered that more than 40% of patients treated with cisplatin developed hiccups, and 90% of hiccups eased after discontinuation of dexamethasone [31]. As against the data of the above studies, the incidence of hiccups in the present study was not unacceptable. A randomized trial confirmed that replacing dexamethasone with methylprednisolone does not compromise the antiemetic efficacy, but reduces the occurrence of hiccups. Hence, if there is a concern that hiccups would affect the quality of life, using methylprednisolone instead of dexamethasone could also be considered [32]. Although grade 3 mucositis and leucopenia also exceeded 10%, both toxicities were recognised as being related to concurrent chemoradiotherapy. Overall, the present study demonstrated that the triple regimen is still well tolerated in HNSCC patients.

Notwithstanding the above, several limitations still exist in the present study. Firstly, 3-day administration of cisplatin was primarily owing to the naïve population tolerance and the recommendation of the local ethics committee, which had already been utilised in another large prospective trial [29]. The 5-day antiemetic regimen in the present study was designed based on the 3-day administration of cisplatin. Thus, for the more extensively used single-day cisplatin administration, the question of whether this triple antiemetic regimen can achieve the same efficacy as the present study requires further research to answer. Further, the present study was a single-arm phase 2 trial without an optimal control group. When analysing the efficacy, only comparison with historical data was possible. For this reason, further phase 3 randomized controlled trials must be conducted in the future.

Conclusions

The present study extends the combination of aprepitant, ondansetron and dexamethasone as antiemetic prophylaxis to patients with HNSCC receiving IMRT and high-dose cisplatin chemotherapy. The addition of aprepitant into ondansetron and dexamethasone provides effective protection from emesis and nausea in patients with LA-HNSCC receiving radiotherapy and concomitant high-dose cisplatin chemotherapy. Treatment-related toxicities are mainly mild to moderate and tolerable. Randomized phase studies are required to further define the potential role of NK_1RAs in a chemoradiotherapy setting for HNSCC.

List Of Abbreviations

CINV, chemotherapy-induced nausea and vomiting; NK1RA, neurokinin-1 receptor antagonist; HEC, highly emetogenic chemotherapy; MASCC /ESMO, Multinational Association of Supportive Care in Cancer/ European Society for Medical Oncology; RINV, radiation-induced nausea and vomiting; LA-HNSCC, locally advanced head and neck squamous cell carcinoma; CCRT, concurrent chemoradiotherapy; C-RINV, chemoradiotherapy-induced nausea and vomiting; AJCC 7th, American Joint Committee on Cancer 7th Edition; ECOG, Eastern Cooperative Oncology Group; MDT, multi-disciplinary team; IMRT, intensity-

modulated radiotherapy; NCI CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; MAT, MASCC Antiemesis Tool; FLIE, Functional Living Index-Emesis; EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, Quality of Life Core 30 items; QLQ-H&N35, Quality of Life Head and Neck 35 items; CR, complete response; CP, complete protection; NVAS, nausea visual analog scale; ASCO, American Society of Clinical Oncology.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Approval No.17-115/1371).

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is included within the article.

Competing interests

The authors have declared no conflicts of interest.

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Authors' contributions

Zekun Wang: data analysis and interpretation, manuscript preparation and editing.

Junlin Yi, Ye Zhang: conception and design, quality control of data and algorithms, manuscript review and final approval.

Wenyang Liu, Jianghu Zhang, Xuesong Chen, Jingbo Wang, Kai Wang, Yuan Qu, Xiaodong Huang, Jingwei Luo, Jianping Xiao, Guozhen. Xu, Li Gao: data acquisition and manuscript review and final approval.

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Figures

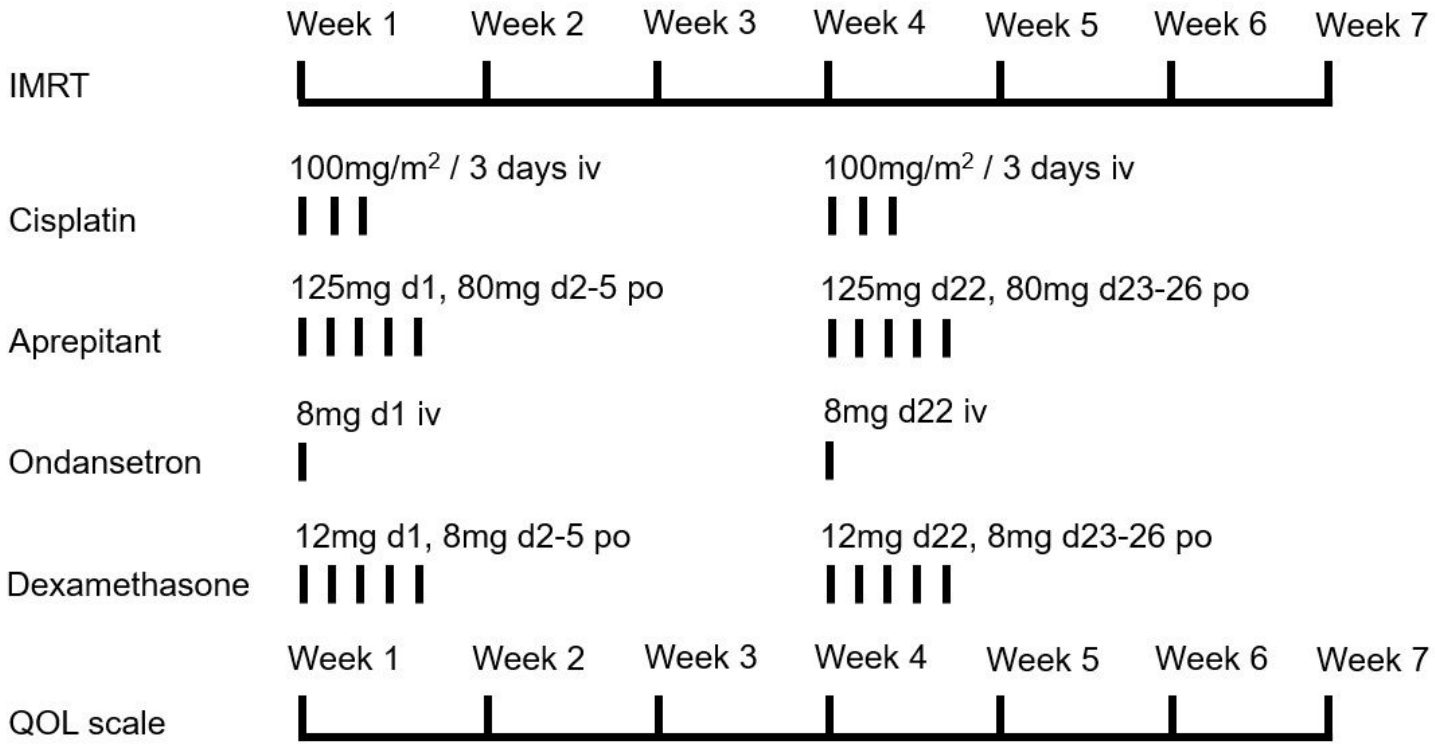

Figure 1

The trial procedure Abbreviation: IMRT: Intensity-modulated radiotherapy; QOL: Quality of Life

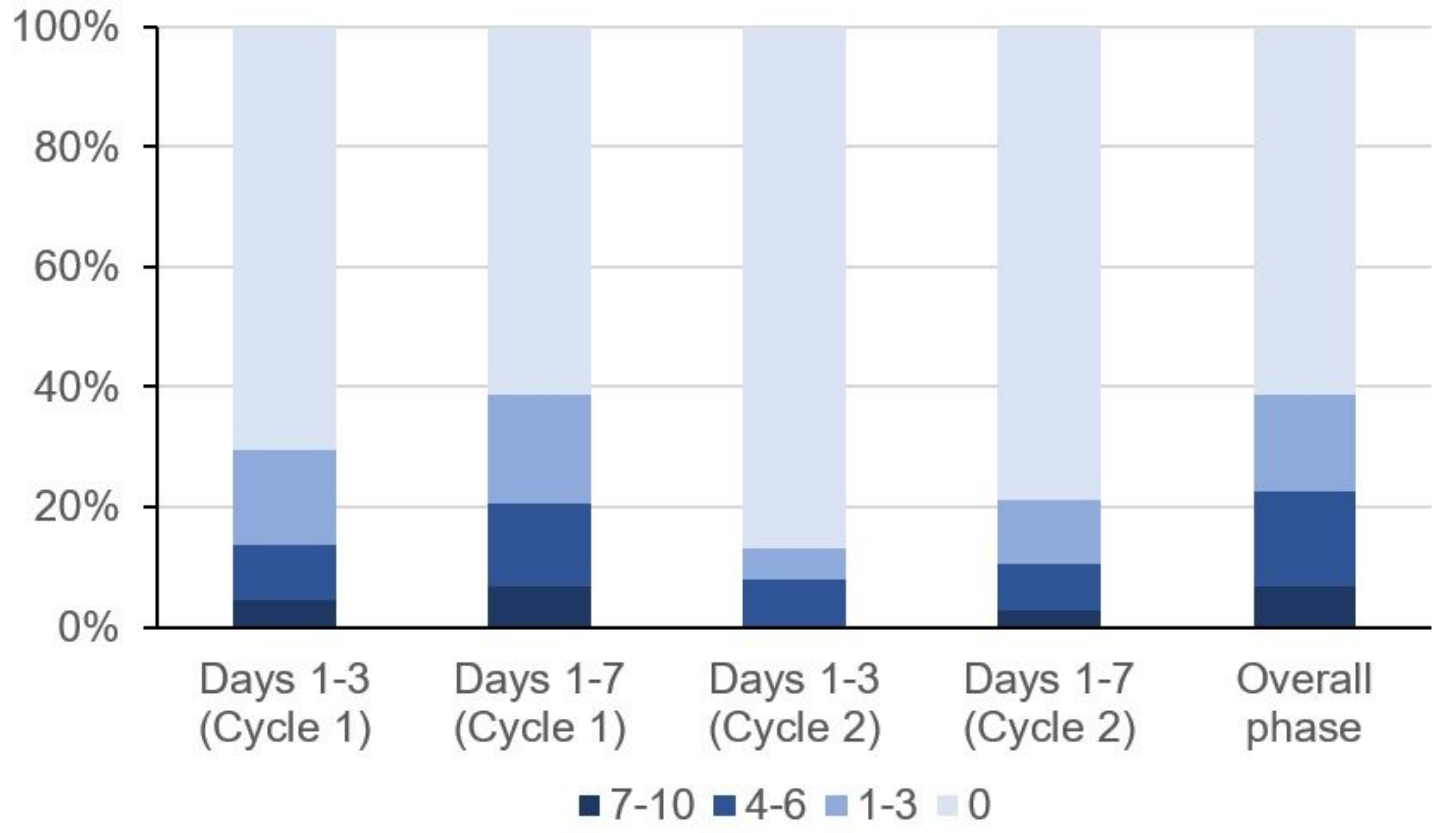

Figure 2

The distribution of patients with different grades of nausea based on the NVAS score