Difference in the emetic control among highly emetogenic chemotherapy regimens: Implementation for appropriate use of aprepitant

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Abstract. Although antiemetic medication based on the emetogenicity of the cancer chemotherapy regimen is recommended, emetic control varies even among highly emetogenic chemotherapy (HEC). In the present study, we retrospectively investigated the rates of emetic control by a combination of granisetron, 5-HT_3 antagonist and dexamethasone in various HEC regimens, including 5 single-day chemotherapy regimens such as gemcitabine/cisplatin (GEM/CDDP), epirubicin/cyclophosphamide(EPI/CPA),pemetrexedorvinorelbine/cisplatin (PEM or VNR/CDDP), doxorubicin/bleomycin/vinblastine/dacarbazine (ABVd) and rituximab/doxorubicin/cyclophosphamide/vincristine/prendisolone (R-CHOP21), and 2 multiple-day chemotherapy regimens such as 5-fluorouracil/cisplatin (5-FU/CDDP) and bleomycin/etoposide/cisplatin (BEP). Complete response (no emesis, no rescue treatment) during the overall period (days 1-5) was assessed as the primary endpoint. Chemotherapy-induced nausea and vomiting was well-controlled (complete response >70%) in GEM/CDDP and R-CHOP21, but not in other regimens. The effect of a triple antiemetic medication including aprepitant (APR) was subsequently examined in patients receiving EPI/CPA and 5-FU/CDDP. Complete response was significantly improved in patients receiving 5-FU/CDDP but not in those receiving EPI/CPA, although the complete protection from vomiting significantly increased in both cases. Of note, the administration of APR for 5 days, but not for 3 days, was required to completely block the incidence of vomiting during the 7 days of the observation period in patients receiving 5-FU/CDDP. These findings suggest that APR should be used appropriately based on the emetogenicity of HEC regimens.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a frequent distressing side effect that impairs patient's quality of life and decreases medication adherence (1-3). CINV comprises the acute event that occurs within 24 h of chemotherapy, the delayed event that appears after 24 h persisting for several days, and the anticipatory symptom that develops prior to chemotherapy, particularly in patients who experienced CINV in the previous course (4). In the clinical practice guidelines for the prevention of CINV documented by the Multinational Association of Supportive Care in Cancer (MASCC) (5), the American Society of Clinical Oncology (ASCO) (6) and the National Comprehensive Cancer Network (NCCN) (7), anticancer agents are classified into four risk categories based on the emetogenicity: high emetic risk (HEC), moderate emetic risk (MEC), low emetic risk and minimal emetic risk. Prophylactic medication against CINV was recommended based on the evidence of the eligible clinical studies. For example, triple combination therapy, including neurokinin NK_1 receptor antagonist, 5-HT antagonist (granisetron) and dexamethasone (DEX), is recommended to prevent CINV associated with HEC regimens.

Aprepitant (APR) is a selective NK_1 antagonist for the substance P in the central nervous system. Several eligible clinical trials evaluating the antiemetic effect of APR in patients receiving high doses of cisplatin (≥70 mg/m^2) or anthracycline/cyclophosphamide demonstrated that APR combined with the standard antiemetic medication, comprising 5-HT_3 antagonist and DEX, significantly improved complete response (no emesis and no rescue treatment) compared to the standard antiemetic therapy (8-11). APR is shown to be effective against acute as well as delayed emesis, in which the efficacy is independent of gender (10,12). However, involvement of the NK_1-sensitive mechanism may vary among different chemotherapeutic regimens, even in the HEC regimens. In the present study, we retrospectively analyzed the rates of emetic control by a

combination therapy, comprising 5-HT_3 antagonist and DEX, in patients receiving 5 single-day treatment HEC regimens such as gemcitabin/cisplatin (GEM/CDDP), epirubicin/cyclophosphamide (EPI/CPA), pemetrexed or vinorelbine/cisplatin (PEM or VNR/CDDP), doxorubicin/bleomycin/vinblastine/dacarbazine (ABVd) and rituximab/doxorubicin/cyclophosphamide/vincristine/prednisolone (R-CHOP21), as well as 2 multiple-day chemotherapy regimens, such as 5-fluorouracil/cisplatin (5-FU/CDDP) and bleomycin/etoposide/cisplatin (BEP). Subsequently, the effect of a triple combination antiemetic therapy using APR, 5-HT_3 antagonist and DEX was prospectively investigated in breast cancer patients receiving EPI/CPA and head-and-neck cancer patients who underwent a 5-FU/CDDP regimen.

Patients and methods

Study design. This study comprises a retrospective chart review of the emetic control by a combination therapy consisting of 5-HT_3 antagonist and DEX in several HEC regimens and a non-randomized prospective study evaluating the antiemetic effect of a triple combination therapy of APR, 5-HT_3 antagonist and DEX in single- as well as multiple-day HEC regimens. The present study was carried out in accordance with the guidelines for the care for human study adopted by the Ethics Committee of the Gifu Graduate School of Medicine (Gifu, Japan), and approved by the Japanese government (no. 22-156 of the Institutional Review Board).

Patients. Patients who underwent the HEC regimen for the first time (first course) at Gifu University Hospital (Gifu, Japan) between April 14, 2009 and November 18, 2011, were the subject of the present study. The exclusion criteria were age, <18 years; patients receiving emetogenic drugs, such as opioid analgesics; patients receiving previous chemotherapy; and those with organic disorders accompanied by nausea and vomiting.

HEC regimens. As shown in Table I, HEC regimens were 5 single- and 2 multiple-day chemotherapy regimens, including GEM/CDDP (GEM 1,000 mg/m^2, days 1, 8 and 15 and CDDP 70 mg/m^2, day 1, every 28 days) for bladder cancer (13); R-CHOP21 (rituximab 375 mg/m^2, day 1; doxorubicin 50 mg/m^2, day 3; CPA 750 mg/m^2, day 3; vincristine 1.4 mg/m^2, day 3 and prednisolone 100 mg/body, days 3-7, every 21 days) for malignant B-cell lymphoma (14); EPI/CPA (EPI 90 mg/m^2, day 1 and CPA 600 mg/m^2, day 1, every 21 days) for breast cancer (15); PEM/CDDP (PEM 500 mg/m^2, day 1 and CDDP 75 mg/m^2, day 1, every 21 days) or VNR/CDDP (VNR 25 mg/m^2, days 1 and 8 and CDDP 80 mg/m^2, day 1, every 21 days) for non-small cell lung cancer (16,17) and ABVd (doxorubicin 25 mg/m^2, day 1; bleomycin 10 mg/m^2, day 1; vinblastine 6 mg/m^2, day 1 and dacarbazine 250 mg/m^2, day 1, every 14 days) for Hodgkin's lymphoma (18) for single-day regimens; 5-FU/CDDP (5-FU 800 mg/m^2, days 1-5 and CDDP 80 mg/m^2, day 1, every 21 days) for head-and-neck cancer (19); and BEP (bleomycin 30 mg/body, days 1, 8 and 15; etoposide 100 mg/m^2, days 1-5 and CDDP 20 mg/m^2, days 1-5, every 21 days) for testicular cancer (20).

Antiemetic medication. Prior to the addition of APR, a combination therapy, including granisetron (3 mg, day 1) and DEX (20 mg intravenously on day 1 and 8 mg orally on days 2-4), was a common antiemetic medication against HEC regimens. Dopamine D_2 antagonists such as prochlorperazine and metoclopramide, antipsychotic agents, including olanzapine, antihistaminic agents such as diphenhydramine and histamine H_2 blockers, including famotidine, were used as the breakthrough treatment for CINV. In a set of studies, where the antiemetic effect of APR was evaluated in patients receiving EPI/CPA or 5-FU/CDDP, APR was administered orally at 125 mg on day 1 and 80 mg on days 2 and 3 or on days 2-5 in addition to a combination therapy using granisetron and DEX.

Emetic control. Unless otherwise indicated, the incidence of CINV during the 5 days of the observation period was checked from the pharmaceutical record where clinical pharmacists recorded the symptoms and severity of adverse drug events during daily monitoring in pharmaceutical care practices. In the case of 5-FU/CDDP, the observation period was extended from 5 to 7 days). Complete response (no vomiting, no rescue treatment) during the overall (0-5 or 0-7 days) period was a primary endpoint. Complete response during acute (0-24 h after chemotherapy) and delayed (2-5 or 2-7 days) periods, and complete protection from vomiting were assessed as secondary endpoints.

Statistical analysis. Data were analyzed using the Statistics Program for Social Sciences (SPSS X, version 11) for Windows (SPSS, Inc., Chicago, IL, USA). The rate of complete response or complete protection from vomiting was compared prior to and following the addition of APR to the standard combination antiemetic therapy and statistically evaluated by Fisher's exact probability test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of the rates of emetic control response by a combination of granisetron and DEX among various HEC regimens. The efficacy of combination therapy using granisetron and DEX was evaluated in patients who received the first course of HEC regimens, excluding R-CHOP21 in which DEX was not administered. Although acute CINV was well-controlled in most cases, the complete response during the delayed period varied among various chemotherapy regimens (Fig. 1). A good overall complete response rate was observed in the GEM/CDDP (71.4%, n=14) and R-CHOP21 (73.7%, n=19) regimens, however, the rate was extremely low in BEP (12.5%, n=16) and ABVd (7.7%, n=13). The response rate was moderate in EPI/CPA (50.0%, n=20), PEM or VNR/CDDP (46.2%, n=13) and 5-FU/CDDP (27.3%, n=11).

Effect of a triple antiemetic treatment using APR, granisetron and DEX. Subsequently, the effect of adding APR to the standard combination therapy was investigated in patients receiving EPI/CPA or 5-FU/CDDP. As shown in Fig. 2A, APR caused a slight, but not significant, improvement of complete response in EPI/CPA, in which the complete response

Table I. HEC regimens, age and no. of patients.

Chemotherapy regimens	Drugs, dosage and administration	Cycle (days)	Type of cancer	Age, years (range)	No. of patients (males/females)
Single-treated regimens					
EPI/CPA	Epirubicin 90 mg/m^2, day 1 Cyclophosphamide 600 mg/m^2, day 1	21	Breast cancer	49.5 (32-70)	20 (1/19)
GEM/CDDP	Gemcitabine 1,000 mg/m^2, days 1, 8 and 15 Cisplatin 70 mg/m^2, day 1	28	Bladder cancer	71.4 (37-82)	14 (9/5)
PEM/CDDP	Pemetrexed 500 mg/m^2, day 1 Cisplatin 75 mg/m^2, day 1	21	Non-small cell lung cancer	62.9 (59-67)	9 (5/4)
VNR/CDDP	Vinorelbine 25 mg/m^2, days 1 and 8 Cisplatin 80 mg/m^2, day 1	21	Non-small cell lung cancer	61.3 (46-67)	4 (4/0)
R-CHOP	Rituximab 375 mg/m^2, day 1 Doxorubicin 50 mg/m^2, day 3 Cyclophosphamide 750 mg/m^2, day 3 Vincristine 1.4 mg/m^2 (up to 2 mg), day 3 Prednisolone 100 mg/body, days 3-7	21	Malignant lymphoma	63.6 (46-78)	19 (11/8)
ABVd	Doxorubicin 25 mg/m^2, day 1 Bleomycin 10 mg/m^2, day 1 Vinblastine 6 mg/m^2, day 1 Dacarbazine 250 mg/m^2, day 1	14	Hodgkin's lymphoma	40.9 (21-74)	13 (7/6)
Repeated treatment regimens					
5-FU/CDDP	5-fluorouracil 800 mg/m^2, days 1-5 Cisplatin 80 mg/m^2, day 1	21	Head and neck cancer	60.6 (49-71)	11 (9/2)
BEP	Bleomycin 30 mg/body, days 1, 8 and 15 Etoposide 100 mg/m^2, days 1-5 Cisplatin 20 mg/m^2, days 1-5	21	Testicular tumor	37.6 (21-56)	16 (16/0)

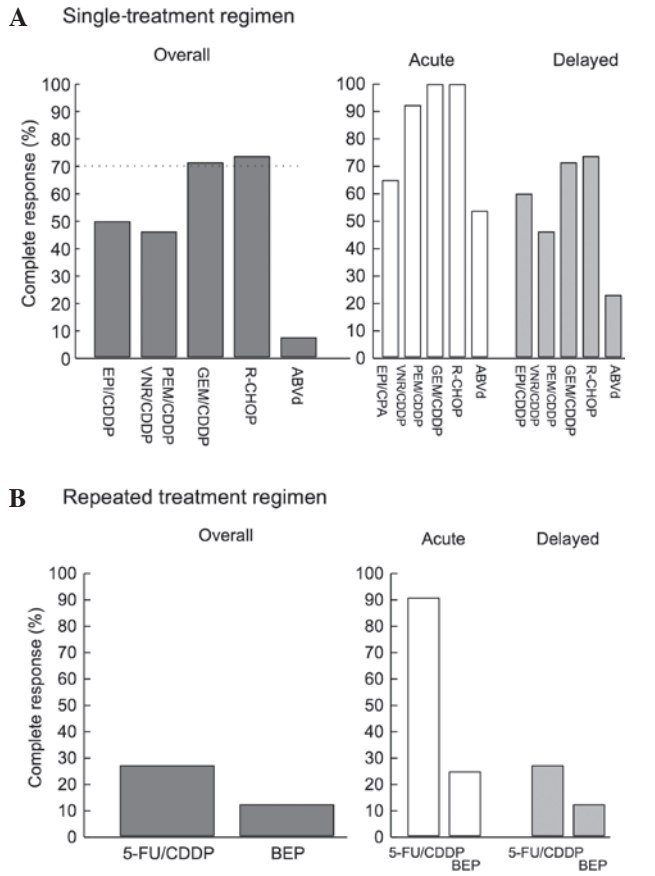

Figure 1. Comparison of the rates of emetic control response by a combination of granisetron and DEX among various HEC regimens. Chemotherapy regimens included: (A) 5 single-treatment regimens such as EPI/CPA (n=20), PEM or VNR/CDDP (n=13), GEM/CDDP (n=14), ABVd (n=13) and R-CHOP21 (n=19), and (B) 2 multiple-day chemotherapy regimens, including 5-FU/CDDP (n=11) and BEP (n=16). All patients, except for those receiving R-CHOP21, were administered intravenous granisetron and DEX (20 mg) on day 1 prior to chemotherapy, followed by oral DEX (8 mg) on days 2-4 for the prevention of CINV. In patients receiving R-CHOP21, only granisetron was injected on day 1.

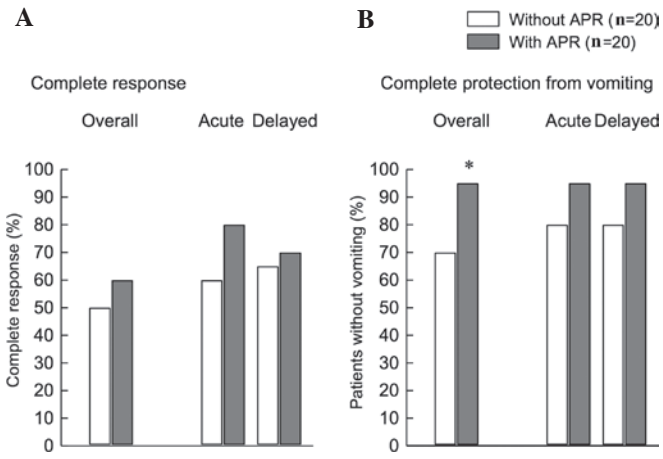

Figure 2. Effect of a triple antiemetic treatment using APR, granisetron and DEX on the (A) control response and (B) complete protection from vomiting in patients receiving the first course of EPI/CPA regimen. Patients were all administered intravenous granisetron (3 mg) and DEX (12 mg) and oral APR (125 mg) on day 1 prior to chemotherapy, followed by oral DEX (8 mg) on days 2-4 and APR (80 mg) on days 2 and 3. The rate of complete response or complete protection from vomiting was assessed during acute (day 1), delayed (days 2-5) and overall periods (days 1-5). *P<0.05 by Fisher's exact probability test.

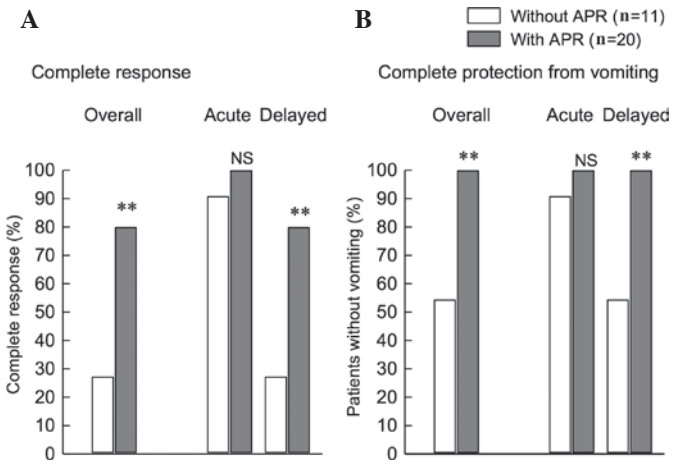

Figure 3. Effect of a triple combination therapy using APR, granisetron and DEX on (A) the control response and (B) complete protection from vomiting in patients receiving the first course of 5-FU/CDDP regimen. In the APR-treated group, intravenous granisetron (3 mg) and DEX (12 mg) and oral APR (125 mg) were administered prior to chemotherapy, followed by oral DEX (8 mg) on days 2-5 and APR (80 mg) on days 2-3 or 2-5, while in the control group, intravenous granisetron (3 mg) and DEX (20 mg) were injected prior to chemotherapy, and oral DEX (8 mg) was administered on days 2-5. The rate of complete response or complete protection from vomiting was assessed during the acute (day 1), delayed (days 2-5) and overall periods (days 1-5). **P<0.01 by Fisher's exact probability test.

during acute, delayed and overall periods was improved by 20 (P=0.301), 5 (P=1.000) and 10% (P=0.751), respectively, although the complete protection from vomiting during the overall period was significantly (P<0.05) improved from 70.0 to 95.0% (Fig. 2B).

By contrast, the complete response and complete protection from vomiting during the overall (days 1-5) period were significantly improved in the 5-FU/CDDP regimen (from 27.3 to 80.0%, P<0.01, for complete response; from 54.5 to 100%, P<0.01, for complete protection from vomiting), in which the relative risk for overall complete response was 2.933 [95% confidence intervals (CI)], 1.090-7.891) (Fig. 3).

However, the control of CINV decreased on days 6 and 7 in patients administered with APR for 3 days (Fig. 4A), resulting in a marked impairment of the overall complete response (Fig. 4C), when the observation period was extended to 7 days (40.0% during the 7-day period vs. 60.0% during the 5-day period). The administration of APR (80 mg/day) for the remaining 2 days (days 2-5) completely eradicated the incidence of vomiting (Fig. 4B), in which the complete protection from vomiting was increased, although this increase (P=0.0526), from 60.0 to 100% (Fig. 4D), was not significant. The overall (days 1-7) complete response showed an improvement from 40.0 to 66.7% (P=0.347) (Fig. 4C).

Discussion

HEC regimens examined in the present study consisted of cisplatin-based chemotherapy, dacarbazine-based chemotherapy and a combination chemotherapy of anthracycline and cyclophosphamide such as EPI/CPA and R-CHOP21. The antiemetic effect of a combination therapy using granisetron and DEX markedly varied among chemotherapy regimens. A good overall complete response was observed in the GEM/CDDP

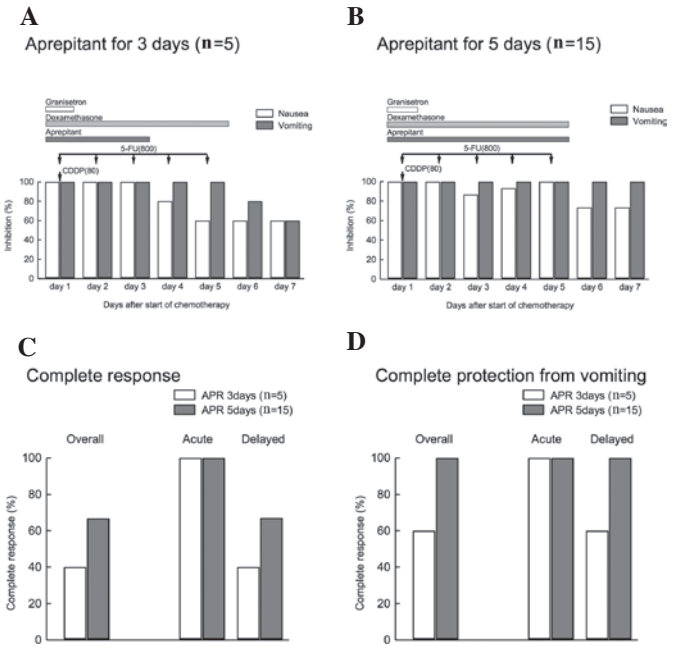

Figure 4. Comparison of time course in the complete protection from nausea and vomiting following the administration of APR for (A) 3 or (B) 5 days after the initiation of chemotherapy. Comparison of the effects of 3-and 5-day APR treatment schedule on the (C) complete response and (D) complete protection from vomiting in patients receiving the first course of 5-FU/CDDP regimen for head-and-neck cancer (C). APR was administered at 125 mg on day 1 and at 80 mg on (A, C and D) days 2-3 or (B, C and D) 2-5. Patients were administered intravenous granisetron (3 mg) and DEX (12 mg) and APR (125 mg) on day 1 prior to chemotherapy, followed by DEX (8 mg) on days 2-5 and APR (80 mg) on days 2-3 or 2-5.

(71.4%) and R-CHOP21 (73.7%) regimens, a moderate response was evident in EPI/CPA (50.0%), PEM/CDDP or VNR/CDDP (46.2%) and 5-FU/CDDP (27.3%) regimens, but the response was extremely poor in BEP (12.5%) and ABVd (7.7%) regimens. Our data on the complete response in the R-CHOP21 regimen were generally consistent with the data reported by Vitolo *et al* (21). In that study, most of the patients (79%) exhibited no gastrointestinal adverse reactions, including CINV. By contrast, the rate of complete response in the GEM/CDDP regimen observed in the present study was much higher than that reported by Dogliotti e*t al* (22), in which the incidence of CINV was 74.5%, indicating that the complete protection from CINV was assumed to be 25.5%. Although we were not able to elucidate the difference between findings of that study and those of this study, the discrepancy may be due to the fact that CINV was monitored only in the first course of the chemotherapy in our study, whereas up to six courses of chemotherapy were examined in the study by Dogliotti e*t al* (22).

Although several clinical practice guidelines for the prevention of CINV documented by MASCC (5), ASCO (6), and NCCN (7) recommend the use of a triple combination such as NK_1 antagonist, 5-HT_3 antagonist and DEX for the prevention of CINV associated with HEC regimens, a combination of two drugs such as 5-HT_3 antagonist and DEX was considered to be satisfactory for the prophylaxis of CINV in GEM/CDDP for bladder cancer and R-CHOP21 for malignant B-cell lymphoma on the first course of chemotherapy. However, the addition of APR should be considered to prevent CINV effectively in other chemotherapy regimens, including EPI/CPA for breast cancer, PEM or VNR/CDDP for lung cancer, 5-FU/CDDP for head-and-neck cancer, BEP for testicular tumor and ABVd for Hodgkin's lymphoma.

Therefore, we evaluated the efficacy of triple combination antiemetic medication, including APR, granisetron and DEX, in a single-day HEC regimen such as EPI/CPA and multiple-day chemotherapy regimens such as 5-FU/CDDP. APR caused a slight, but not significant, increase in the complete response rate in breast cancer patients receiving EPI/CPA, although the rate of complete protection from vomiting was significantly ($P<0.05$) elevated, after APR was added, from 70.0 to 95.0% (relative risk, 1.357; 95% CI, 1.001-1.839). A slight but significant preventive antiemetic effect of APR has also been reported by Warr *et al* (23) in breast cancer patients receiving anthracycline/cyclophosphamide combination chemotherapy. Those authors showed that the overall complete response is enhanced by 8.3% (from 42.5 to 50.8%) following the addition of APR to the combination therapy of ondansetron and DEX.

In contrast to these findings, APR resulted in a marked and significant ($P<0.01$) improvement of the overall complete response from 27.3 to 80.0% in the 5-FU/CDDP regimen, when the observation period was set to 5 days. The incidence of vomiting 5 days after chemotherapy was completely blocked by the administration of APR for 3 or 5 days ($P<0.01$). Adding APR to a combination antiemetic therapy has been proven to improve the complete response by approximately 15-20% in patients receiving cisplatin-based chemotherapy (8,10,24). Chawla *et al* (25) reported a more marked improvement of the overall complete response, in which the rate is elevated from 43.7 to 71.0% after the addition of APR to a combination therapy in patients receiving cisplatin ($\geq$70 mg/m^2)-based chemotherapy.

However, the control of nausea and vomiting was impaired at 6 and 7 days after chemotherapy, resulting in a reduction of the overall complete response (40.0%), when the observation period was extended to 7 days. It was notable that the addition of APR for an additional 2 days (days 1-5) completely blocked the incidence of vomiting during the 7-day period of time and the overall (days 1-7) complete response was improved, though not significantly ($P=0.347$), to 66.7% as compared to the 3-day APR treatment regimen (40.0%). Therefore, it is likely that an extended administration of APR is required for the prevention of CINV in patients receiving the 5-FU/CDDP regimen for head-and-neck cancer. The safety and efficacy of extended APR treatment in the multiple-day HEC and MEC regimens were also reported by Jordan *et al* (26), although those authors did not compare the complete response between the multiple-day APR and the standard 3-day APR treatment regimens.

In conclusion, the present data on the differences in the rates of emetic control by a combination therapy using 5-HT_3 antagonist and DEX suggest that APR is not required for an initial course of a few HEC regimens such as GEM/CDDP and R-CHOP21. However, administration of APR for 5 days, instead of for 3 days, was more effective in preventing CINV in a multiple-day chemotherapy regimen such as 5-FU/CDDP. Therefore, appropriate use of APR should be carried out depending on the emetogenicity of each HEC regimen.

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