Note

Evaluation of Antiemetic Therapy for Hepatic Transcatheter Arterial Infusion Chemotherapy with Cisplatin

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Antiemetic prophylaxis with aprepitant, a 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist and dexamethasone is recommended for patients receiving intravenous cisplatin chemotherapy. Whether the same antiemetic regime is superior for hepatic transcatheter arterial infusion chemotherapy with cisplatin (CDDP-TAI) is unknown. We conducted a retrospective study of antiemetic prophylaxis protection against chemotherapy-induced nausea and vomiting (CINV) in CDDP-TAI at Nagasaki University Hospital. The rate of complete response (CR) to antiemetics in the acute (<24h) and delayed phases (24–120h) was measured. Twenty-four patients were treated with a 5-HT₃ receptor antagonist (granisetron or azasetron) and dexamethasone on the day of chemotherapy (day 1 only). There was a significant difference between the CR rates in the acute and delayed phases, 91.6, and 69.7%, respectively. Combination of a 5-HT₃ antagonist and dexamethasone on day 1 is effective against acute CINV, but not delayed CINV during CDDP-TAI. These results may help guide the management of nausea and vomiting during CDDP-TAI to achieve better tolerance and compliance for fewer interventions and increased favorable therapeutic outcomes.

Key words antiemetic; cisplatin; 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist; transcatheter infusion chemotherapy

Chemotherapy-induced nausea and vomiting (CINV) is an adverse event that can last for days following therapy and can significantly impair a patient's quality of life. Patients developing CINV may occasionally be forced to discontinue or postpone their chemotherapy.¹⁾ Thus, it is crucial to provide appropriate supportive care for the continuity of chemotherapy. CINV is classified into acute CINV (occurring within 24h of chemotherapy) and delayed CINV (occurring more than 24h after chemotherapy).

cis-Diamminedichloroplatinum(II) (CDDP; cisplatin) possesses a high risk of inducing CINV according to the emetogenic classification schema. CDDP is administered intravenously or intra-arterially. The antiemetic guidelines of the Multinational Association for Supportive Care in Cancer (MASCC),²⁾ the National Comprehensive Cancer Network (NCCN),³⁾ the American Society of Clinical Oncology (ASCO)⁴⁾ and the Japanese Society of Clinical Oncology (JSCO)⁵⁾ recommend a three-drug combination with aprepitant (days 1–3), a 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist (5-HT₃ antagonist) (day 1) and dexamethasone (days 1–3 or 1–4). However, intra-arterial administration of CDDP appears to be more effective than intravenous (i.v.) administration for the treatment of hepatocellular carcinoma. The concentration of CDDP in hepatocyte of intra-arterial administration is higher than i.v. administration.⁶⁾ Thus, intra-arterial administration of CDDP is thought to have fewer systemic adverse effects than i.v. administration.⁷⁾ However, Louvet *et al.* reported that CINV was observed immediately following a high-dose, CDDP liver arterial injection.⁸⁾ Furthermore, despite receiving 5-HT₃ receptor antagonist prophylaxis, patients in a phase II study of transcatheter arterial infusion chemotherapy with CDDP (CDDP-TAI) experienced anorexia and vomiting at rates of 82.5 and 40.0%, respectively.⁹⁾ Thus, a

5-HT₃ receptor antagonist alone may be insufficient antiemetic prophylaxis for CDDP-TAI. More research is required to establish antiemetic prophylaxis guidelines for CDDP-TAI.

In the present study, we retrospectively investigated the effectiveness of antiemetic therapy regimes for CDDP-TAI across acute and delayed phases of CINV.

PATIENTS AND METHODS

Patients This study was carried out in accordance with the Declaration of Helsinki (Fourth revision: Somerset West, South Africa, 1996) and under approval by the Nagasaki University Ethics Committee (No. 14052666). Subjects comprised 33 patients who received a first course of CDDP-TAI for hepatocellular cancer at the Nagasaki University Hospital from April 2009 to September 2013. Patients were excluded from

Table 1. Patients Characteristics

Patients (n=33)	
Sex (male/female)	26/7
History of alcohol intake (yes/no)	9/24
History of CINV (yes/no)	3/30
Combination of anticancer agents (yes/no)	18/15
Median (range)	
Age (years)	61 (31–84)
Weight (kg)	59.0 (40.6–88.9)
Body surface area (m ²)	1.63 (1.31–2.01)
Dose of intra-arterial of cisplatin (mg/m ²)	55.9 (34.0–76.3)
Serum creatinine (mg/dL)	0.73 (0.48–1.27)
Creatinine clearance ^{a)} (mL/min)	77.6 (48.2–174.6)

a) Cockcroft–Galut calculation.

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this study because of either complications that induced nausea and/or vomiting (e.g. symptomatic brain metastases, opioid dose change within 120h following chemotherapy), or the use of corticosteroids for reasons other than antiemesis. Baseline characteristics of included patients are presented in Table 1.

Treatment Schedule The fine-powder formation of CDDP was completely dissolved in 70mL saline and heated to 50°C. A catheter was introduced into the hepatic artery under angiographic guidance, and CDDP was administrated at a dose of 40–65mg/m² by infusion into the artery. Adequate hydration was administrated before and after CDDP-TAI by an i.v. infusion of 1000–2000mL to prevent kidney damage. Some patients were received antiemetic prophylaxis before CDDP-TAI on day 1. When patients were received antiemetic prophylaxis on days 2 and 3, aprepitant or dexamethasone was orally administrated in the morning.

Data Collection and Assessment All data were retrospectively collected from the electronic medical record system. They included age, sex, weight, body surface area, history of alcohol intake, dose of CDDP, history and episodes of CINV, and whether other anticancer agents and antiemetic agents were also used. The primary measured endpoint was determined as the achievement of a complete response (CR) to antiemetics in which there were no emetic episodes and no administration of rescue therapy within 120h after the start of chemotherapy.²⁾ This endpoint was further classified into an acute phase (within the first 24h) and a delayed phase (24–120h).

Statistical Analysis McNemar's test was used to compare the CR rates between the acute phase, delayed phase and overall phase. Comparisons of CR rates among 5-HT₃ receptor antagonists were analyzed using the Yates' chi-squared test. Data were analyzed using Microsoft Excel 2010, and a *p* value of <0.05 was considered statistically significant.

RESULTS

Antiemetic Therapies for CDDP-TAI CINV The antiemetic therapy regimes used for CINV during this study are detailed in Table 2. Three patients were not treated with any antiemetic and two patients were treated with i.v. granisetron

3mg (day 1 only). Twenty-four patients were treated with an i.v. 5-HT₃ receptor antagonist and dexamethasone 8mg on day 1 only. 5-HT₃ receptor antagonists included azasetron 10mg (*n*=7), granisetron 1mg (*n*=10) and granisetron 3mg (*n*=7). Three patients were treated with i.v. granisetron 1 or 3mg, and dexamethasone 8 or 13.2mg on day 1, followed by oral dexamethasone 4 or 8mg on days 2 and 3. One patient was given oral aprepitant 125mg, i.v. palonosetron 0.75mg and dexamethasone 4mg on day 1, followed by oral aprepitant 80mg on days 2 and 3.

Efficacy CR rates in the acute phase and delayed phase for all patients were 87.9 and 69.7%, respectively (Fig. 1). Further, the CR rate in the delayed phase was significantly lower than that in the acute phase for all patients (*p*=0.031). CR rates in the acute phase and delayed phase for twenty-four patients, received with a 5-HT₃ receptor antagonist and dexamethasone 8mg on day 1 only, were 91.7 and 66.7%, respectively. Similarly, the CR rate in the delayed phase was significantly lower than that in the acute phase (*p*=0.031). Further, the CR rates in the acute phase for azasetron 10mg, granisetron 1mg, and granisetron 3mg were 100, 85.7, and 90.0%, respectively, and in the delayed phase were 71.4, 57.1, and 70.0%, respectively. There were no significant differences between the CR rates in the acute phase and in the delayed phase between azasetron 10mg, granisetron 1mg and granisetron 3mg (Table 3). Both CR rates in the acute phase and the delayed phase for the three patients who were not treated with any antiemetic were 33.3%. Both CR rates in the acute phase and the delayed phase for three patients treated with granisetron 1 or 3mg, and dexamethasone 8 or 13.2mg on day 1, followed by dexamethasone 4 or 8mg on days 2 and 3, were 100%. A similar CR rate was seen for one patient was given aprepitant 125mg, palonosetron 0.75mg and dexamethasone 4mg on day 1, followed by oral aprepitant 80mg on days 2 and 3. The CR rates in the acute and delayed phase for two patients receiving granisetron 3mg on day 1 only were also 100.0% (data not shown).

DISCUSSION

Since the first-generation 5-HT₃ receptor antagonist granis-

Table 2. Antiemetic Regimes

	Patients no.
Nothing	3
5-HT ₃ antagonist (day 1)	2
Granisetron 3mg (day 1)	2
5-HT ₃ antagonist (day 1)+Dexamethasone (day 1)	24
Azastron 10mg (day 1)+Dexamethasone 8mg (day 1)	7
Granisetron 1mg (day 1)+Dexamethasone 8mg (day 1)	10
Granisetron 3mg (day 1)+Dexamethasone 8mg (day 1)	7
5-HT ₃ antagonist (day 1)+Dexamethasone (days 1–3)	3
Granisetron 3mg (day 1)+Dexamethasone 8mg (day 1), 4mg (days 2, 3)	2
Granisetron 1mg (day 1)+Dexamethasone 13.2mg (day 1), 8mg (days 2, 3)	1
Aprepitant (days 1–3)+5-HT ₃ antagonist (day 1)+Dexamethasone (day 1)	1
Aprepitant 125mg (day 1), 80mg (days 2, 3)+Palonosetron 0.75mg (day 1)+Dexamethasone 4mg (day 1)	1

Fig. 1. Complete Response Rates Sorted According to Antiemetic Regime and Acute, Delayed or Combined Phases
Statistical differences determined using McNemar's test.

Table 3. Comparison of Complete Response Rates of Azasetron 10mg, Granisetron 1mg and Granisetron 3mg

	Complete response						<i>p</i> Value
	Azasetron 10mg		Granisetron 3 mg		Granisetron 1 mg		
	Rate	Individuals (CR/overall)	Rate	Individuals (CR/overall)	Rate	Individuals (CR/overall)	
Acute phase	100.0	7/7	85.7	6/7	90.0	9/10	0.918
Delayed phase	71.4	5/7	57.1	4/7	70.0	7/10	0.976
All phases	71.4	5/7	57.1	4/7	70.0	7/10	0.976

etron was marketed in the early 1990s, this pharmacological class has played a central role in the antiemetic therapy for CINV. While granisetron was shown to mitigate acute CINV, its efficacy for delayed CINV is limited.¹⁰ Conversely, the more recently developed aprepitant, a selective neurokinin-1 receptor antagonist,^{11–13} and palonosetron, a long-acting second-generation 5-HT₃ receptor antagonist,¹⁴ have demonstrated promising outcomes in the control of delayed CINV. While antiemetic guidelines published in Japan, U.S.A. and Europe should be used to determine the risk of emesis in CINV,^{2–5} the guidelines were not written for CDDP-TAI CINV prophylaxis. To address this problem, we have investigated antiemetic therapies for CDDP-TAI.

The important finding was that the CR rate in the delayed phase was significantly lower than in the acute phase for the group receiving a 5-HT₃ receptor antagonist and dexamethasone on day 1 only. However, there were no significant differences amongst the different 5-HT₃ receptor antagonist treatments (namely, azasetron 10mg, granisetron 1mg and granisetron 3mg) (Table 3). This result is in accord with other reports that azasetron is not inferior to granisetron,¹⁵ and that there are no significant differences between 1- and 3-mg granisetron.^{16–18} Matsumura *et al.* reported that patients treated with granisetron 40μg/kg and dexamethasone 8mg before CDDP-TAI experienced reduced food intake from days 1 to 8 and a loss of appetite from days 1 to 2.¹⁹ From this

observation, and from the results in the present study, the delayed phase of CINV following CDDP-TAI does not appear to be adequately controlled by a 5-HT₃ receptor antagonist and 8-mg dexamethasone on day 1 only.

Aprepitant and palonosetron have demonstrated promising outcomes in the control of acute and delayed CINV according to previous studies.^{11–14} Also, the increased dexamethasone has been previously found to be effective in both acute and delayed phases.^{5,10} Aprepitant, palonosetron, or extended dexamethasone may be effective to control the delayed CINV of CDDP-TAI. Despite our limited number of patients, patients receiving aprepitant and palonosetron, or dexamethasone on days 1 and 3 in our study were well controlled in both acute and delayed phases CINV (data not shown). A prospective, controlled trial is needed to clarify CDDP-TAI CINV prophylaxis. CDDP has relatively high emetogenicity, and is listed as high risk in emetogenic classification schema. Antiemetic prophylaxis with the i.v. administration of CDDP recommended is a three-drug combination with aprepitant, a 5-HT₃ antagonist and dexamethasone. However, three-drug combination may be not necessary to the intra-arterial administration of CDDP since the intra-arterial administration is thought to have fewer systemic adverse effects than i.v. administration. If patients received extended dexamethasone, it is worth keeping in mind that up to 15% of hepatocellular cancer patients are infected with Hepatitis B virus (HBV). Considering that Mochida

described how corticosteroids managed to reactivate HBV, it may be necessary therefore to screen for existing HBV infections prior to undertaking an antiemetic prophylaxis regime that involved extended dexamethasone use.²⁰⁾ The monitoring of HBV reactivation could be managed according to established guidelines.²¹⁾

In conclusion, the present study confirms that administration of a 5-HT₃ receptor antagonist and dexamethasone only on day 1 is effective for acute phase, but not delayed phase, CINV in CDDP-TAI. The development of better antiemetic prophylaxis guidelines will lead to improved treatment compliance and therapeutic outcomes.

Conflict of Interest The authors declare no conflict of interest.

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