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Aprepitant, palonosetron, with dexamethasone to prevent nausea and vomiting induced by cisplatin-based chemotherapy for hepatocellular carcinoma

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Objective: We examined the antiemetic efficacy and safety of aprepitant, palonosetron, and dexamethasone (APD) combination therapy in advanced hepatocellular carcinoma (HCC) patients.
Methods: This study was conducted at four hospitals on patients who were not suitable for resection, local ablation therapy, or were not responsive to TACE (transcatheter arterial chemoembolization), who received APD combination therapy (oral aprepitant 125 mg on day 1 and 80 mg on days 2 and 3, intravenous palonosetron 0.75 mg on day 1, and intravenous dexamethasone 9.9 mg on day 1, and oral dexamethasone 8 mg on days 2－4). The primary endpoint was complete response (CR), defined as no vomiting and no rescue medication in the first cycle.
Results: There were 39 patients registered in this study from April 2012 through October 2014. However, 2 patients were excluded from the analyses because their self-reported questionnaires were incomplete. CR in the overall period was achieved in 34 patients (91.9%), and the CR rates in the acute and delayed phases were 94.6% and 91.9%, respectively. Moreover, complete control of the nausea rates, defined as rates of no nausea, no vomiting, and no rescue medication in the acute and delayed phases, were 86.5% and 78.3%, respectively.
Conclusion: The APD combination therapy was excellent in advanced HCC patients receiving cisplatin-based chemotherapy.

Key words: aprepitant, palonosetron, nausea, vomiting, cisplatin

Introduction

Hepatocellular carcinoma (HCC) is a major cause of mortality in patients with cirrhosis.[1] In Japan, almost 30,000 people die annually because of HCC, and 47,000 people were estimated to suffer from this type of cancer in 2010.[2] Treatment options, such as resection, local ablation, transcatheter arterial chemoembolization (TACE), and liver transplantation have been performed in patients with HCC.[3-9] Sorafenib has also been established as the standard treatment for advanced HCC; however, the survival rate and safety remain unsatisfactory.[10,11]

In Japan, hepatic arterial infusion chemotherapy (HAIC) is used to induce tumor shrinkage or regression of vascular invasion after sorafenib administration. However, HAIC is not commonly used worldwide because of a lack of evidence for the survival benefit and the complicated management including the side effects of chemotherapy. In HAIC, cisplatin is the key drug in the chemotherapy for HCC. However, cancer chemotherapy-induced nausea and vomiting (CINV) are the most common side effects of the cisplatin-based chemotherapy.[12,13]

The current standard prophylactic antiemetic therapy for patients with HCC receiving single-day cisplatin-

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based chemotherapy is a two-drug combination of a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist and dexamethasone.[14] However, the complete response (CR) rate, defined as no vomiting and no rescue medication in the first cycle was 60%－80%.[14,15] Therefore, more effective antiemetic therapy is needed to achieve adequate control of CINV.

Aprepitant (neurokinin-1 receptor antagonist) and palonosetron (5-HT3 receptor antagonist) are newer antiemetic agents with demonstrated efficacy for both acute and delayed CINV.[16] Antiemetic guidelines recommend that aprepitant should be added to a 5-HT_3 receptor antagonist and dexamethasone in patients receiving highly emetogenic single-day chemotherapy.[17] However, to our knowledge, there are no clinical studies that have examined antiemetic therapy for HCC including these new drugs in single-day cisplatin-based chemotherapy. Therefore, we examined the antiemetic efficacy and safety of a combination therapy of aprepitant, palonosetron, and dexamethasone (APD) combination therapy in advanced HCC patients receiving this chemotherapy.

Patients and Methods

This open-label, single-arm study was conducted at four hospitals in Japan. The inclusion criteria was for patients aged ≥20 years old, HCC confirmed histologically from a biopsy, or by radiographic findings on dynamic computed tomography (CT). None of the patients were suitable for resection, local ablation therapy, or were not responsive to TACE based on the "Refractory to TACE" definition used by the consensus guidelines of the Japan Society of Hepatology (2010).[18] An ECOG (Eastern Cooperative Oncology Group) Performance Status of 0 or 1, Child-Pugh liver function class A or B, adequate hematologic findings (defined as a neutrophils ≥1,500/ml, platelet count ≥50,000/ml, hemoglobin ≥8.5 g/dl, adequate hepatic function [total bilirubin ≤2 mg/dl, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤5 times the upper limit of the normal range, and adequate renal function (creatine clearance ≥60 ml/min/body)]). The exclusion criteria were patients with metastasis in the brain or intestine; nausea, vomiting, and retching within 24 hours before chemotherapy; use of drugs with antiemetic activity, including benzodiazepines, within 48 hours before the chemotherapy; and use of drugs with possible effects on metabolism of the study drugs within 2 weeks before the chemotherapy.

Written informed consent was obtained from all the patients. The protocol of the study was approved by the Kitasato University School of Medicine Ethics Committee and the ethical review board at each hospital. The study was conducted following the principles of the Declaration of Helsinki and the Ethical Guidelines for Clinical Research in Japan. This study is registered with the UMIN-Clinical Trials Registry in Japan (UMIN000007265).

Chemotherapy

The Seldinger method was used to introduce the catheter into the right femoral artery, and a microcatheter was placed for chemoinfusion in the proper hepatic artery. A fine powder formation of cisplatin (IA-call; Nippon Kayaku, Tokyo) was dissolved in saline solution that had been heated to 50℃. This solution was then administered at a dose of >65 mg/m^2 over a period of about 30 minutes. This treatment was repeated at intervals of 4 to 6 weeks if no intolerable side effects appeared or the disease progression was ruled out using an imaging-based diagnostic modality.

Antiemetic therapy

The antiemetic therapy consisted of intravenous palonosetron 0.75 mg on day 1, oral aprepitant 125 mg on day 1 and 80 mg on days 2 and 3, and intravenous dexamethasone 9.9 mg (12 mg of dexamethasone sodium phosphate) on day 1, and oral dexamethasone 8 mg (9.6 mg) on days 2 to 4. All antiemetics were administered approximately 1 hour before the administration of cisplatin on the chemotherapy day or at the same time on days 2 to 4.

Assessment

Data were collected using case report forms and patient diaries in the overall period, from 0 to 120 hours after the start of chemotherapy. The acute and delayed phases were defined as 0 to 24 hours and >24 to 120 hours, respectively. The case report form included recording of a daily assessment of the severities of nausea and vomiting based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0,[19] antiemetics added to the test antiemetic therapy, and adverse drug reactions considered to have a causal relationship with the drugs in the present study. Patients were asked to record the severity of nausea scored on a 3-point scale (Grade 0, none; Grade 1, slight; Grade 2, moderate; 3, worst) and the number of vomiting episodes in the patient's diary.

The primary endpoint was CR defined as no vomiting and no rescue medication in the first cycle. The secondary endpoints were: CRs in the acute and delayed phases in

the first cycle; frequency of rescue medication; complete control of the nausea rate, defined as no nausea, no vomiting, and no rescue medication in the first cycle; incidence and severity of nausea, based on CTCAE and the subjective rating scale completed by the patients; and safety, based on the types, incidences, and severity of adverse drug reactions.

Statistical analyses

Analyses were based on the per-protocol analysis and the full analysis set. Descriptive statistics, such as mean, standard deviation, and percentage, were calculated to summarize and evaluate the data. The predictive significance of continuous variables for CR was assessed in univariate analyses and then estimated in multivariate analyses using a logistic regression model to identify independent predictors of CR. The impact of the clinical variables on CR was estimated by calculating the odds ratios (OR) and the 95% confidence intervals (CIs) using logistic regression analyses. Cumulative probability of time to survival was estimated using the Kaplan-Meier method. Analyses were performed using the statistical package, SPSS Base 17.0 J for Windows (SPSS, Chicago, IL, USA).

Results

From April 2012 through October 2014, 39 patients were registered in this study. However, 2 patients were excluded from the analysis because their self-reported questionnaires were incomplete. The baseline characteristics are shown in Table 1. Seventy-seven percent of the patients were male with a median age of 70 years.

Table 1. Patient baseline clinical characteristics

Variable	Value	
Sex, male/female	30/9	
Age, years, mean (range)	70.2	(54－85)
Etiology		
HCV/HBV/Alcohol/other/unknown	24/6/5/4	
Body surface area, mean (range)	1.62	(1.2－2.07)
Laboratory data, mean (range)		
Neutrophils/mm^3	3,558	(1,241－12,367)
Hemoglobin g/dl	12.1	(8.5－15)
Platelet count/mm^3	156,700	(9,300－32,900)
Aspartate aminotransferase	73.3	(19－305)
Alanine aminotransferase	47.8	(13－151)
Total bilirubin mg/dl	1.0	(0.1－3.7)
Albumin g/dl	3.5	(1.4－5.0)
Prothrombin time (%)	76.9	(26－121)
Creatinine (mg/dl)	0.77	(0.47－1.10)
Alpha-fetoprotein (ng/ml)	5,152	(0.5－83,000)
DCP (ng/ml)	12,629	(14－492,565)
Child-Pugh score	6.2	(5－11)
Ascites (Yes/No)	5/34	
History of encephalopathy (Yes/No)	1/38	
Stage II/III/IVa/IVb	2/17/15/5	
Vascular invasion (Yes/No)	17/22	
Distant metastasis (Yes/No)	6/33	

HCV, hepatitis C virus; HBV, hepatitis B virus; DCP, des-gamma-carboxyprothrombin

Table 2. Complete response rate

Hours	0－24	24－48	48－72	72－96	96－120	24－120
%	94.6	97.3	100	97.3	97.3	91.9

Table 3. Complete control of the nausea rates

Hours	0－24	24－48	48－72	72－96	96－120	24－120
Grade 2 (n)		1				1
Grade 1 (n)	5	4	3	2	1	7
Grade 0 (n)	32	32	34	35	36	29
Grade 0 (%)	86.5	86.5	91.9	94.6	97.3	78.3

Grade 0, none; Grade 1, slight; Grade 2, moderate; 3, worst

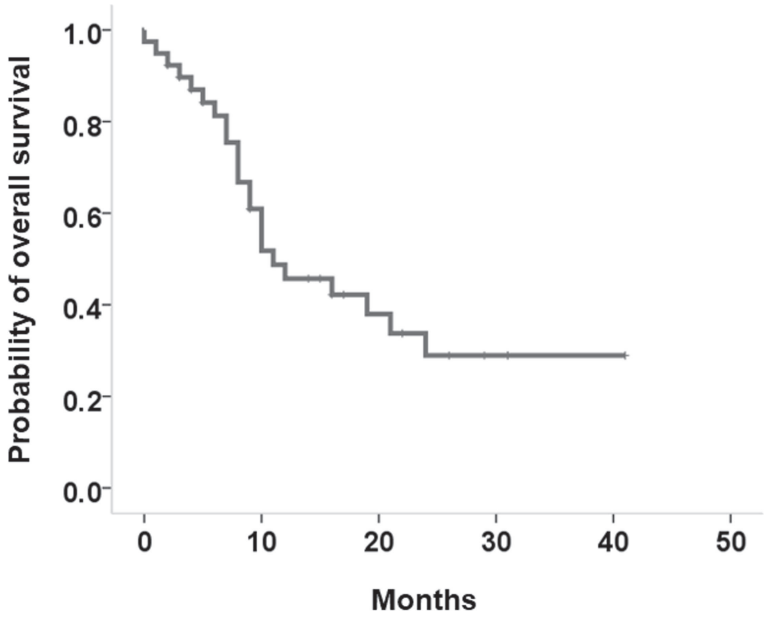

Figure 1. Kaplan-Meier curve for survival. The median overall survival of all the patients was 11.0 months (95% CI, 4.8－17.2).

Table 4. Incidence of adverse events and adverse drug reactions

Toxicity	Grade 1/2	Grade 3/4
Fever	0/0	0/0
Abdominal pain	0/2	0/0
Diarrhea	0/1	0/0
Constipation	0/4	0/0
Encephalopathy	0/0	0/1
Neutropenia	1/0	0/0
Anemia	9/2	0/0
Thrombocytopenia	2/0	0/0
Blood bilirubin increased	2/6	1/0
AST increased	11/8	5/1
ALT increased	11/6	5/0
Creatinine increased	2/0	0/0

AST, aspartate aminotransferase; ALT, alanine aminotransferase

Antiemetic efficacy

CR in the overall period was achieved in 34 patients (91.9%), and CR rates in the acute and delayed phases were 94.6% and 91.9%, respectively (Table 2). Furthermore, complete control of nausea rates in the acute and delayed phases were 86.5% and 78.3%, respectively, and there were 24 episodes (8 episodes with the use of rescue medication; 16 episodes without the use of rescue medication) in 8 patients (Table 3).

Antitumor efficacy

Overall, 8 patients (20.5%) had a partial response, and 10 (25.6%) achieved a stable disease according to the mRECIST (Modified Response Evaluation Criteria in Solid Tumors).[20] Twenty patients (51.3%) died during the observation period. The median overall survival of all patients was 11.0 months (95% CI, 4.8－17.2 months) (Figure 1).

Adverse events

Adverse events of more than grade 3 occurred during the first cycle: blood bilirubin increase (3%), AST increase (16%), and ALT increase (14%) (Table 4). No study drug-related deaths occurred. All the manifestations of toxicity returned to their basal levels within 1 month after treatment. However, 1 patient had flapping tremor, mild altered consciousness, with confusion, and hyperammonemia (99 μg/dl; normal range 30－80 μg/dl). Initially, we had diagnosed that patient as having suffered hepatic encephalopathy after chemotherapy; therefore, we infused a large volume of intravenous extracellular fluid. However, the patient was losing consciousness. Therefore, we performed a head CT and magnetic resonance imaging, and diagnosed the patient as having extra-pontine myelinolysis caused by rapid correction of hyponatremia. The patient recovered completely after 1 week treated with steroids and Solu-Medrol infusions ([methylprednisolone] 1,000 mg × 3 days). The patient received treatment for 2 weeks and was discharged.

Predictive factors for CR

We evaluated the correlation between baseline characteristics and CR according to a logistic regression model. There were no significant predictors of CR in the univariate analyses.

Discussion

To our knowledge, this is the first study evaluating antiemetic efficacy and safety of an APD combination therapy in advanced HCC patients receiving 65 mg/m^2 or more cisplatin-based arterial chemotherapy. We showed that the antiemetic efficacy was 91.9% in patients receiving this chemotherapy. Generally, more than 50 mg/m^2 of cisplatin-based chemotherapy is associated with a very high risk of nausea and vomiting, and is classified as highly emetogenic chemotherapy.[12,13] However, the CR rate of an advent 5-HT3 with dexamethasone is 60%－80%; moreover, delayed vomiting is still not adequately controlled.[14,15] Therefore, it is noteworthy that CR rates in the delayed phases were also 91.9% in this APD combination therapy.

Recently, Suzuki et al.[21] reported that they performed a prospective multicenter randomized study to investigate the efficacy and safety of APD combination therapy for malignant tumors without HCC (lung cancer, gastric cancer, esophagus cancer, cervical cancer, endometrial cancer, head and neck cancer, etc.) In their study,[21] the CR rate was obtained during the acute phase and the delayed phase in 91.8% and 59.1% of the patients, respectively. The CR rate in the acute phase was nearly the same as that in the present study; however, the CR rate in the delayed phase was much lower than that in the present study (91.9%), because the Suzuki et al. study[21] included patients with gastric and esophageal cancer who had symptoms caused by strictures or gastrointestinal symptoms such as anorexia and/or nausea. Indeed, there were no patients who complained of nausea before the HAIC treatment in the present study. On the other hand, Takeshima et al.[22] reported that in gynecological cancer, the CR rate in the delayed phase of APD combination therapy was only 56.3%. However, the differences of the chemotherapy regimens between those studies and that in the present study should be considered. Therefore, further studies are warranted to determine the antiemetic efficacy in the delayed phase of APD combination therapy in patients with HCC.

While HAIC is used to induce tumor shrinkage or regression of vascular invasion after sorafenib administration in Japan, there is very little evidence for the complicated management including the side effects of chemotherapy in patients with advanced HCC. Kondo et al.[23] reported that HAIC treatment with cisplatin (65 mg/m^2) for HCC with portal vein tumor thrombosis demonstrated a non-anorexia rate (68.4%) and a non-nausea rate (73.3%) in an antiemetic therapy by only administering 5-HT3 (granisetron). On the other hand, we showed the antiemetic efficacy in HAIC treatment: the CR rate (acute and delayed: 94.6% and 91.9%, respectively) and complete control of the nausea rate (acute and delayed: 86.5% and 78.3%, respectively).

However, we could not directly compare the two groups because their antiemetic evaluation was quite different from that in the present study. Therefore, it is important for these patients treated with HAIC to obtain more effective antiemetic combination therapy by performing randomized controlled studies that administer or do not administer palonosetron.

Remarkably, in the present study, AST and ALT levels increased 16% and 14%, respectively. Kondo et al.[23] reported that Grade 3 or 4 of AST and/or ALT level elevation was 19.3% in their HAIC treatment with cisplatin. Therefore, we presume that this liver damage was caused by cisplatin administration but not the combination therapy of APD.

The medical cost of this combination therapy of APD (JPY27,000 per session) is considerably higher than that of a 5-HT3 with dexamethasone (JPY15,000 per session). However, a safer treatment is required, especially for patients with esophageal varices who may have life-threatening bleeding events, because the medical cost markedly increases when a life-threatening event occurs.

The limitations in the present study were that it was conducted on a relatively small population and was a single-arm study. To our knowledge, this is the first study on the antiemetic efficacy and safety of a combination therapy of APD in advanced HCC patients. In the near future, based on the results from this sample, we will perform a new prospective randomized trial that focuses on the antiemetic efficacy in the delayed phase of aprepitant and dexamethasone combination therapy to compare palonosetron to granisetron.

The antiemetic efficacy and safety of APD combination therapy was excellent in advanced HCC patients receiving cisplatin-based chemotherapy. In the future, based on this data, we will attempt to discover other new treatments to achieve antiemetic efficacy in advanced HCC patients receiving cisplatin-based chemotherapy.

Conflicts of Interest

None

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