Comparative Cost-utility Analysis Between Aprepitant- and Fosaprepitant-containing Regimens To Prevent Chemotherapy-induced Nausea and Vomiting in Patients Receiving Highly Emetogenic Chemotherapy in Japan

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ABSTRACT

Purpose: Clinical trials have shown that the addition of aprepitant (APR) or a phosphorylated prodrug of aprepitant, fosaprepitant (FosAPR) as prophylactic antiemetic therapy consisting of a 5-hydrotryptamine-3 receptor antagonist and dexamethasone is effective in patients receiving highly emetogenic chemotherapy. These combination therapies have been commonly used in Japan. In the present study, we performed a cost-utility analysis of APR and FosAPR in the context of the Japanese medical insurance system, and economic efficiency was compared.

Methods: Data from randomized controlled trials that examined the efficacy of APR and FosAPR in the Japanese population were used. A decision tree was constructed to estimate the effectiveness of chemotherapy for 5 days from the day of the treatment and the cost associated with outpatient chemotherapy from the perspective of a payer. Health outcome was expressed in quality-adjusted life-years (QALYs), and costs were estimated based on medical fees and drug prices from 2018. An incremental cost-effectiveness ratio (ICER) was calculated for each regimen containing either APR or FosAPR. The robustness of the model was assessed using 1-way and probabilistic sensitivity analysis.

Findings: The base-case analysis estimated that the addition of APR or FosAPR would have incremental effects of 0.00166 and 0.00143 QALY and incremental costs of 8305 and 11,348 JPY (74 and 101 USD [1 USD = 112.17 JPY]), resulting in ICERs of 4,992,172 and 7,955,560 JPY/QALY (44,505 and 70,924 USD/QALY), respectively. Sensitivity analysis revealed that the probability of a complete response for delayed chemotherapy-induced nausea and vomiting had the most influence on the ICERs. Reductions in the drug costs of APR and FosAPR also had an effect on the ICERs. According to the probabilistic sensitivity analysis, APR and FosAPR were dominant in terms of cost-effectiveness in 48.7% and 8.55% of cases, respectively.

Implications: The ICER of outpatient prophylactic antiemetic therapy in patients receiving highly emetogenic chemotherapy was calculated in the context of the Japanese medical insurance system. Assuming the willingness-to-pay of 5,000,000 JPY/QALY based on the calculated ICER, our findings suggest that although the addition of APR is cost-effective, FosAPR is not cost-effective. (*Clin Ther*. 2019;41:929–942) © 2019 Published by Elsevier Inc.

Keywords: antiemetic, aprepitant, chemotherapy, cost-effectiveness, emesis, fosaprepitant, pharmacoeconomics.

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INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is a common adverse reaction to the administration of anticancer chemotherapy, and occurs in varying frequencies depending on the type of chemotherapy administered. Various guidelines, including those from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the Japanese Society of Clinical Oncology (JSCO), suggest that antiemetic therapy be administered according to the emetogenic risk with chemotherapy, which is classified, based on the level of emetogenicity, as being high (>90%), moderate (30%−90%), low (10%−30%), or minimal (<10%).[1−3] CINV occurs not only on the day of chemotherapy treatment but also on the days after treatment, and is one factor that influences the quality of life (QoL) of a patient and the ability of a patient to continue with chemotherapy.[4]

Aprepitant (APR) acts by inhibiting the effect of substance P on the neurokinin-1 receptor in the vomiting center of the brain. Triple combination therapy with APR added to a conventional regimen consisting of a 5-hydrotryptamine-3 receptor antagonist and dexamethasone (5-HT$_3$ RA + DEX) has been shown to be effective in suppressing delayed CINV in patients with moderate to high emetogenic risk. Fosaprepitant (FosAPR) is a phosphorylated prodrug of APR, and is rapidly metabolized into APR by endogenous phosphatase, with an onset of action on intravenous administration. Because FosAPR is administered as an intravenous infusion, it can be easily administered via the same intravenous route as anticancer drugs, making it convenient for patients who are already receiving intravenous chemotherapy. Studies have shown that APR and FosAPR have similar efficacy.[5] In the clinical practice guideline on antiemetics, the American Society of Clinical Oncology recommends the addition of either APR or FosAPR to the combination of 5-HT$_3$ RA + DEX in patients receiving chemotherapy,[1] including highly emetogenic chemotherapy (HEC). JSCO's clinical practice guideline on antiemesis in oncology[3] also recommends the prophylactic administration of 5-HT$_3$ RA + DEX + APR or FosAPR in patients undergoing HEC.

Both efficacy and efficiency should be evaluated for any medical technology. Cost-utility evaluation is a measure used for such a purpose in the economic evaluation of medical technologies. Studies have been conducted in various countries to evaluate the cost-effectiveness of prophylactic antiemetic regimens that include APR; however, there are variations in the results.[6−12] Economic analyses of aprepitant have been reported from 7 countries, including Japan. Six of them showed favorable results with aprepitant. Moore et al[6] in the United States reported that aprepitant had little cost-utility benefit. In Japan, Tsukiyama et al[12] evaluated the cost-effectiveness of APR and reported its usefulness in outpatient chemotherapy. These findings suggest that the cost-effectiveness of a medical technology may vary by country due to differences in health care settings. Although FosAPR has a higher drug price than does APR and there is concern about its economic efficiency, investigation of the cost-effectiveness of FosAPR has not yet been conducted. It is meaningful to examine a comparison of the cost-effectiveness of APR and FosAPR that is recommended with the same position in the guidelines. In this study, ICERs of both APR and FosAPR were calculated in the context of the Japanese health care system by the performance of a cost-utility analysis. ICERs were then compared to the willingness-to-pay (WTP) threshold to evaluate the cost-effectiveness of these regimens.

MATERIALS AND METHODS

Modeling

A decision tree was constructed that showed the acute phase and the delayed phase according to methods described previously[7,9,10,12] to estimate and compare the health outcome and cost of antiemetic therapy containing APR or FosAPR (Fig. 1).

Clinical outcomes were defined as *complete response* (CR), with no emesis and no rescue antiemetic therapy, and *incomplete response,* with some emesis or some use of rescue antiemetic therapy. CR was subdivided into 2 mutually exclusive health outcomes: *complete protection,)* which was defined as no emesis, no use of rescue antiemetic therapy, and no significant nausea, or *complete response at best* (CRB), which describes those who achieved CR but not complete protection.

Patients who received outpatient chemotherapy were included in the analysis, and the data collection

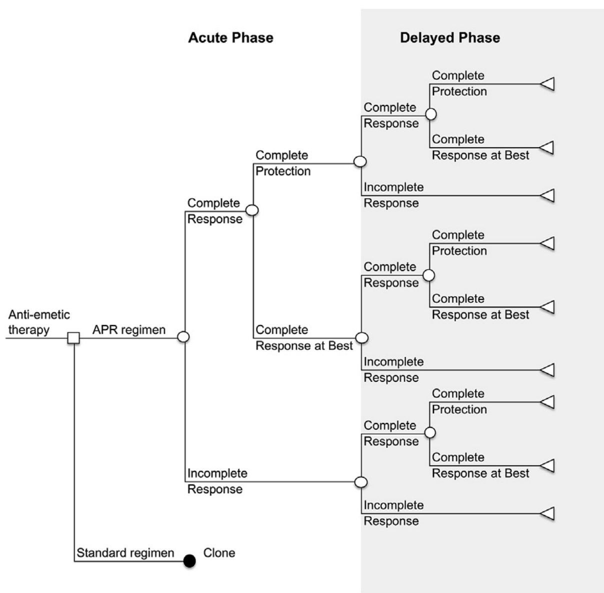

Fig. 1. Decision tree for cost-effectiveness analysis.

period was defined as the first 5 days after the administration of anticancer chemotherapy.

Clinical Data

Two randomized, controlled studies, the Phase II clinical trial of APR (ONO-7436-01)[13] and the Phase III clinical trial of FosAPR (ONO-7847-01),[14] both performed in the Japanese population, were used as the data sources (Table I). The patient eligibility criteria and outcomes measures were the same in these trials. Specifically, patients with cancer were included if they were Japanese, were aged ≥20 years, were administered ≥70 mg/m^2 of cisplatin as HEC, had a life expectancy of at least 3 months, and had an Eastern Cooperative Oncology Group performance status score between 0 and 2. Both trials had a male/female ratio of ~3:1, and the mean dose of cisplatin was ~76 mg/m^2. Among the patients, 70% had a tumor in the respiratory organs, 17% had a tumor in the urogenital organs, and the remaining had a tumor in other organs such as the digestive organs and head and neck.

In ONO-7436-01, a total of 453 patients were randomized into 1 of the following 3 groups: (1) the standard regimen (described subsequently) plus 125/80 mg APR* (oral administration of a dose of 125 mg on day 1 and a dose of 80 mg on days 2–5); (2) the standard regimen plus 40/25 mg APR (oral administration of a dose of 40 mg on day 1 and a dose of 25 mg PO on days 2–5); or (3) the standard regimen alone. From this study, we extracted data from 146 patients who received the 125/80 mg APR regimen and from 149 patients who received the standard regimen to determine the efficacy of these regimens.

In ONO-7847-01, a total of 347 patients were randomized into 1 of 2 groups: (1) the standard regimen (described subsequently); or (2) the standard

Table I. CINV-related health state probabilities from the clinical trials ONO-7436-01 and ONO-7847-01. Data are given as %.

Response	ONO-7436-01				ONO-7847-01			
	Standard Regimen		APR Regimen		Standard Regimen		FosAPR Regimen	
	Acute Phase (n = 149)	Delayed Phase (n = 149)	Acute Phase (n = 146)	Delayed Phase (n = 146)	Acute Phase (n = 173)	Delayed Phase (n = 167)	Acute Phase (n = 173)	Delayed Phase (n = 167)
Complete protection	82.0	44.3	83.6	65.1	77.2	45.8	89.6	58.4
Complete response at best	1.3	7.4	3.4	7.5	3.6	3.0	4.0	6.3
Incomplete response	16.7	48.3	13.0	27.4	19.2	51.2	6.4	35.3

APR = aprepitant; CINV = chemotherapy-induced nausea and vomiting.

regimen plus FosAPR 150-mg infusion. To determine the efficacy of these regimens, we extracted the data from 173 patients who received the FosAPR regimen and 167 patients who received the standard regimen. Patients' daily symptom diaries were used to examine the degree of nausea and vomiting and any rescue medications used for up to 120 h after the administration of chemotherapy.

The primary outcome was the percentage of patients who achieved CR, which was evaluated for the entire follow-up period (0–120 h), during the acute phase (0–24 h), and during the delayed phase (>24–120 h).

Treatment Strategy

The following 3 prophylactic antiemetic therapy regimens were included in the present study: (1) the combination of an intravenous infusion of granisetron[‡] (3 mg/100 mL bag) and dexamethasone phosphate[§] injection (1.65 mg/0.5 mL) (GRA + DEX; standard regimen); (2) the combination of GRA + DEX + APR; or (3) GRA + DEX + FosAPR (Table II). In the analysis of ONO-7436-01, the APR regimen included 3 agents, APR, GRA, and DEX. The standard regimen not including APR was a combination of GRA + DEX. In ONO-7436-01, APR was administered for 5 days from the day of chemotherapy according to the Phase II trial in the United States.[15] However, because other Phase III studies[16,17] later demonstrated that APR was effective when administered for 3 days, this latter regimen has been used for APR capsules (125 and 80 mg) in Japan. Thus, we examined this 3-day regimen with APR capsules in the present study. In the analysis of ONO-7847-01, the FosAPR regimen included 3 agents, FosAPR (150 mg), GRA, and DEX. The standard regimen not containing FosAPR was a combination of GRA + DEX. APR and FosAPR are cytochrome P-450 3A4 inhibitors and are known to increase the blood concentration of DEX. Thus, the dose of DEX was reduced by 50% when APR or FosAPR was administered. According to the Japanese Society of Nephrology, the standard height and weight of the Japanese population are 170 cm and 63 kg, respectively.[18] Given that GRA was administered at 40 μg/kg, the standard dose of GRA was 2.52 mg per patient. As a 3-mg/100 mL GRA IV

Table II. Antiemetic regimens for the prevention of CINV used in the model.

Clinical Trial/ Antiemetic Regimen/Drug	Day1	Day2	Day3
ONO-7436-01			
Standard regimen			
Dexamethasone	12 mg IV	8 mg PO	8 mg PO
Granisetron IV	40 μg/kg	—	—
APR regimen			
Aprepitant PO	125 mg	80 mg	80 mg
Dexamethasone	6 mg IV	4 mg PO	4 mg PO
Granisetron IV	40 μg/kg	—	—
ONO-7847-01			
Standard regimen			
Dexamethasone	20 mg IV	8 mg PO	8 mg PO
Granisetron IV	40 μg/kg	—	—
FosAPR regimen			
FosAPR IV	150 mg	—	—
Dexamethasone	10 mg IV	4 mg PO	8 mg PO
Granisetron IV	40 μg/kg	—	—

APR = aprepitant; CINV = chemotherapy-induced nausea and vomiting; FosAPR = fosaprepitant.

bag was used in the present study, 1 bag would be used even if the amount was 2.52 mg per patient, as the remaining amount would have to be discarded. Thus, the cost of 1 bag of GRA per patient was considered in the analysis. The JSCO clinical practice guideline on antiemesis in oncology[3] recommends the administration of DEX from days 2–4 when APR or FosAPR is added in patients at high emetogenic risk (eg, from cisplatin) receiving chemotherapy. Nonetheless, we analyzed the dose and administration period that were determined according to the regimens in the clinical trials. For outpatient chemotherapy, DEX for oral use was prescribed on and after the second day.

Cost Analysis

Cost analysis was performed from the perspective of the payer, and direct medical costs associated with CINV prevention and additional medical fees associated with CINV were estimated. Cost was calculated based on the Drug Price Standard revised in 2018[19] and Medical Fee Points.[20] For rescue medication, the costs associated with follow-up visits, medical examinations (biochemical blood test [≥10 items], C-reactive protein, venous blood collection), medications (prescription, preparation, and basic dispensing fee if prepared at a hospital), and intravenous infusions were calculated. We assumed that the cost associated with the administration of chemotherapy would be equivalent in all groups; thus the costs associated with therapy other than antiemetic therapy were not included in the calculation. Patients with an incomplete response during the acute or delayed phase were administered rescue treatment with additional drugs and infusions. The JSCO 2010 clinical practice guideline on antiemesis in oncology suggests that dopamine receptor antagonists, corticosteroids, and 5-HT$_3$ RAs are effective as additional therapy in patients with breakthrough nausea and vomiting. The recommended 5-HT$_3$ RAs for rescue medication are different from those recommended as prophylactics. Ramosetron was selected for the analysis because its price is similar to the median of all 5-HT$_3$ RAs. Additional drugs were administered via the oral route during the acute phase. In the delayed phase, patients revisited a medical institution to receive an examination, prescription, and treatment with infusion by a physician, and infusions were prepared by a pharmacist at a hospital pharmacy. Rescue medications were determined based on studies by Oshima et al[21] and Yamanishi et al,[22] who examined cost-effectiveness of DEX and palonosetron as prophylactic antiemetic therapy. Specifically, the following prescriptions were included as rescue medications: metoclopramide tablets (1 tablet 3 times daily for 5 days), DEX 4-mg tablets (1 tablet twice daily for 5 days), and 5-HT 3 RA ramosetron tablets (1 tablet once daily for 5 days). In addition, 500 mL of BFluid injection (MIMS Japan, Tokyo, Japan) was administered once daily at each patient visit. The drug cost of APR was used to calculate the cost of each capsule set (1 set of 125-mg capsules and 2 sets of 80-mg capsules) sold in Japan. APR is administered orally and FosAPR is intravenously administered, but there is no additional prescription or additional cost for drip on the day of chemotherapy from the perspective of the payer, and these differences were not set. Regarding the cost of hospitalization at the time of CINV occurrence, Tsukiyama et al[12] estimated rehospitalization expenses in the expenses survey of their facilities, but they are not estimated in this survey because the clinical trials of APR and FosAPR have not clarified the extension of hospital stay and rehospitalization.

ONO-7847-01 demonstrated that vascular pain was significantly more frequent in patients who received the FosAPR regimen compared with those who received the standard regimen (23.6% vs 12.4%); however, they reported that none of the patients developed serious symptoms. Thus, the costs of side effects associated with antiemetic therapy were not included in the present analysis. The costs calculated in Japanese yen (JPY) were converted to US dollars (USD) using the exchange rate of 2017 announced by organisation for economic co-operation and development (OECD) (1 USD = 112.17 JPY).[23]

Utility Analysis

The utility value of the health state of CINV in Japan has not been reported in clinical trials, and there is no publicly available information. In the present study, utility values used in published CINV literature were used. Sun et al[24] reported QoL evaluation using a visual analog scale according to the presence or absence of CINV. The following utility values were defined: 0.9 for complete protection with no significant symptoms of nausea and vomiting, 0.2 for incomplete response with nausea and vomiting, and 0.7 for CRB. Health state in the acute period was set as 1 day (24 h), health condition of delay period as 4 days (96 h). The sum of the 5-day quality-adjusted life-year (QALY) of survival was calculated using the following formula: QALY = ([Utility value (acute phase) × 1 day] + [Utility value (delayed phase) × 4 days])/365 days (Table III). Since information available for estimating the utility value of CINV is insufficient, sensitivity analysis was performed to examine the influence of these changes on the results. Because there was no report on the difference in QoL between APR and FosAPR, the same utility values were set for both regimens.

Cost-effectiveness Analysis

The study was performed in accordance with the guideline on the economic evaluation of health care technologies in Japan[25] and the consolidated health economic evaluation reporting standards (CHEERS) statement.[26] For cost-effectiveness, the base-case incremental cost-effectiveness ratio (ICER) was calculated by determining the cost of antiemetic therapy and rescue medications as well as the health outcomes in the first 5 days after the administration

Table III. Costs set and Base case QALYs for CINV outcomes.

Acute Phase (Day 1)	Delayed Phase (Days 2–5)	Costs Set for Analysis	Base-case QALYs* (Days 1–5)
CP	CP	Antiemetic regimen	0.0123
	CRB	Antiemetic regimen	0.0101
	IR	Antiemetic regimen	0.0047
		Outpatient reexamination fee	
		Blood test	
		Pharmacy cost	
		Internal medicine	
		Infusion therapy	
CRB	CP	Antiemetic regimen	0.0118
	CRB	Antiemetic regimen	0.0096
	IR	Antiemetic regimen	0.0041
		Outpatient reexamination fee	
		Blood test	
		Pharmacy cost	
		Internal medicine	
		Infusion therapy	
IR	CP	Antiemetic regimen	0.0104
	CRB	Antiemetic regimen	0.0082
	IR	Antiemetic regimen	0.0027
		Outpatient reexamination fee	
		Blood test	
		Pharmacy cost	
		Internal medicine	
		Infusion therapy	

CINV = chemotherapy-induced nausea and vomiting; CP = complete protection; CRB = complete response at best; IR = incomplete response; QALYs = quality-adjusted life-years.

* Base-case QALYs (days 1–5) = ([Utility value (acute phase) × 1 d] + [Utility value (delayed phase) × 4 d])/365 d. CP, CRB, and IR were assigned utility values 0.9, 0.7, and 0.2, respectively.

of chemotherapy. Base-case analysis incorporating baseline parameters was performed. In this study, discounts were not applied during the 5-day short-term observation period. The WTP threshold used 5,000,000 JPY (44,575 USD/QALY) defined by Shiroiwa et al.[23] TreeAge Pro 2016 (TreeAge Software Inc, Williamstown, Massachusetts) was used for the analysis.

Sensitivity Analysis

In the study, we created a simulation model for clinical decision analysis and calculated ICERs by defining many assumptions for various variables, including transition probability, utility values, and cost. One-way sensitivity analysis was performed to assess the influence of the uncertainty of parameters on ICERs. Efficacy of antiemetic therapy was analyzed within the 95% CIs of the efficacy values reported in ONO-7436-01 and ONO-7847-01. Variations in the utility values and cost were examined within the ranges of ±0.1 and ± 25%, respectively. Drug expenses of APR and FosAPR are unlikely to increase with future drug price revisions, and only the lower limit is considered because only the possibility of declining is considered.

To determine the effect on ICER, a probabilistic sensitivity analysis was performed to examine the variation in data, including the uncertainly of the base case, and to determine the robustness of the results. A Monte Carlo simulation with 10,000 samples was performed by using the following distributions: uniform distribution for the number of outpatient visit days on and after the second day, β distribution for transition probability and utility value, and γ distribution for cost. Using the cost-effectiveness acceptability curve, the probability of ICER being lower than WTP was calculated.

RESULTS

Estimated Costs

The expected costs of drugs for antiemetic treatment in each regimen for 5 days after chemotherapy were calculated. The drug costs per course of standard antiemetic therapy (GRA + DEX) in ONO-7436-01 and ONO-7847-01 were estimated to be 3587 and 3983 JPY (31.98 and 35.51 USD), respectively. Similarly, the drug costs per course of 3 agents combined (GRA + DEX + APR or FosAPR) in the APR or FosAPR regimen were estimated to be 14,928 and 17,835 JPY (133.09 and 159.00 USD), respectively

Table IV. Estimated costs of antiemetic regimen over 5 days after cycle 1 of chemotherapy. Data are given as JPY (USD) (exchange rate, 1 USD = 112.17 JPY).

Antiemetic Drug*	Unit Cost	ONO-7436-01		ONO-7847-01	
		Standard Regimen	APR Regimen	Standard Regimen	FosAPR Regimen
Fosaprepitant 150 mg IV	14,545 (129.67)	—	—	—	14,545 (129.67)
Aprepitant capsule set† PO	11,638.2 (103.76)	—	11,638.2 (103.76)	—	—
Granisetron 3 mg IV	2,993 (26.68)	2,993 (26.68)	2,993 (26.68)	2,993 (26.68)	2,993 (26.68)
Dexamethasone 2 mg IV	99 (0.88)	594 (5.30)	297 (2.65)	990 (8.83)	297 (2.65)
Dexamethasone 4 mg PO	33.6 (0.30)	134.4 (1.20)	67.2 (0.60)	134.4 (1.20)	100.8 (0.90)
Subtotal	—	3,587 (31.98)	14,928.2 (133.09)	3983 (35.51)	17,835 (159.00)

CINV = chemotherapy-induced nausea and vomiting; JPY = Japanese yen.
* Japanese National Health Insurance Drug Price Standard listed in 2018.
† Aprepitant capsule set consists of one 125mg capsule and two 80 mg capsules.

(Table IV). Health care costs associated with rescue medications were estimated to be 6547 JPY (58.37 USD) during the acute phase, with pharmacy costs and oral medicine costs of 10,221 JPY (91.12 USD) during the delayed phase, and additional costs of reexamination, blood testing, nutrient infusion, and an additional nutrient infusion were estimated to be 2094 JPY (18.67 USD) (Table V).

Base-Case Results

Results over 5 days after cycle 1 of chemotherapy from the base case are shown in Table VI. In a given patient, the APR regimen had an incremental effect of 0.00166 QALY, an incremental cost of 8305 JPY (74.04 USD), and an ICER of 4,992,172 JPY/QALY (44,505 USD/QALY). Similarly, the FosAPR regimen had an incremental effect of 0.00143 QALY, an incremental cost of 11,348 JPY (101.17 USD), and an ICER of 7,955,560 JPY/QALY (70,924 USD/QALY).

Sensitivity

Tornado diagrams of 1-way sensitivity analyses illustrate the effect of uncertainty on each parameter of ICER (Fig. 2). The probability of a CR in the delayed phase in the APR and standard regimens had the most influence on the increase in ICER with APR, with the maximum ICER being ~7,170,000 JPY/QALY (63,921 USD/QALY). The cost of APR had the greatest effect on the reduction in ICER, which was reduced to ~3,240,000 JPY/QALY (29,000 USD/QALY). Variations in ICER due to other parameters were within 5,900,000 JPY/QALY (53,000 USD/QALY). Similarly, the probability of a CR in the delayed phase had the greatest influence on the increase in ICER with FosAPR, with the maximum ICER being ~12,000,000 JPY/QALY (107,000 USD/QALY). The cost of FosAPR had the greatest effect on the reduction in ICER, which was reduced to ~5,400,000 JPY/QALY (48,000 USD/QALY).

Table V. Estimated costs of rescue medication for CINV. Data are given as JPY (USD) (exchange rate, 1 USD = 112.17 JPY).

Cost Type	Unit Cost	Acute CINV	Delayed CINV	Additional Nutrient Infusion
Outpatient reexamination fee	720 (6.42)	–	720 (6.42)	720 (6.42)
Blood test*				
Peripheral blood test diagnostic fee	1120 (9.98)	–	1120 (9.98)	–
Plasma protein immunologic test	160 (1.43)	–	160 (1.43)	–
Blood drawing fee	300 (2.67)	–	300 (2.67)	–
Pharmacy*				
Prescription fee	420 (3.74)	420 (3.74)	420 (3.74)	–
Dispensing fee	90 (0.80)	90 (0.80)	90 (0.80)	–
Dispensing technology basic fee	80 (0.71)	80 (0.71)	80 (0.71)	–
Internal medicine†				
Metoclopramide, dexamethasone, ramosetron	5957 (53.11)	5957 (53.11)	5957 (53.11)	–
Infusion therapy				
Infusion fee*	970 (8.65)		970 (8.65)	970 (8.65)
BFluid†	404 (3.60)		404 (3.60)	404 (3.60)
Total		6547 (58.37)	10,221 (91.12)	2094 (18.67)

CINV = chemotherapy-induced nausea and vomiting; JPY = Japanese yen.
Exchange rate, 1 USD = 112.17 JPY.
* Japanese National Health Insurance Price listed in 2018.
† Japanese National Health Insurance Drug Price Standard listed in 2018.

Table VI. Base-case results over 5 days after cycle 1 of chemotherapy. Data are given as JPY (USD) (exchange rate, 1 USD = 112.17 JPY).

Clinical Trial/Strategy	Costs		QALYs		ICER (JP/US)
	5-Day	Incremental	5-Day	Incremental	
ONO-7436-01					
Standard regimen	11,200 (99.85)	—	0.00813	—	—
APR regimen	19,506 (173.89)	8,305 (74.04)	0.00979	0.00166	4,992,172 (44,505)
ONO-7847-01					
Standard regimen	12,081 (107.70)	—	0.00793	—	—
FosAPR regimen	23,429 (208.87)	11,348 (101.17)	0.00936	0.00143	7,955,560 (70,924)

APR = aprepitant; FosAPR = fosaprepitant; ICER = incremental cost-effectiveness ratio; JPY = Japanese yen; QALYs = quality-adjusted life-years.

A cost-effectiveness plane and a cost-effectiveness acceptability curve were generated based on the results of probabilistic sensitivity analysis (Figures 3 and 4). Many points in both analyses existed in the upper right-hand quadrant (ie, more effective and more expensive). According to the results of the APR regimen, points were distributed around the diagonal showing WTP of 5,000,000 JPY per QALY. In FosAPR results, many points existed above the diagonal line of WTP. At a WTP threshold of 5,000,000 JPY, APR and FosAPR had probabilities of cost-effectiveness of 48.7% and 8.55%. The FosAPR regimen became less cost-effective than the APR regimen.

DISCUSSION

In the present study, we performed a cost-utility analysis of prophylactic antiemetic therapy with HEC from the perspective of the payer. Specifically, we examined the cost-utility of antiemetic therapy consisting of the addition of a neurokinin-1 receptor inhibitor, APR or FosAPR, and calculated an ICER

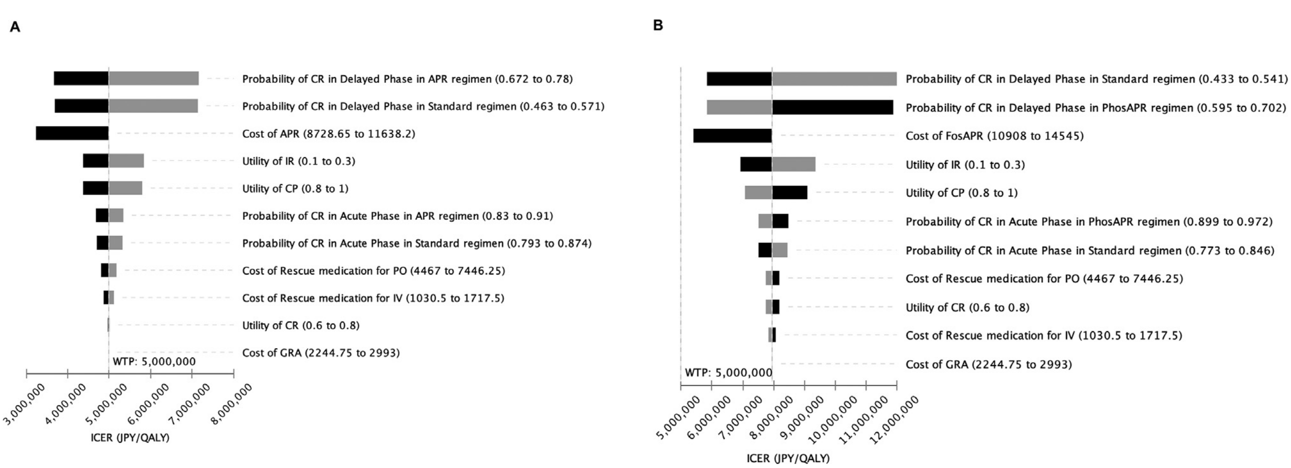

Fig. 2. One-way sensitivity analyses of aprepitant (APR) (A) and phosphorylated (Fos)-APR (B) regimens versus standard regimen. CR = complete response; GRA = granisetron; ICER = incremental cost-effectiveness ratio; IR = incomplete response; WTP = willingness to pay.

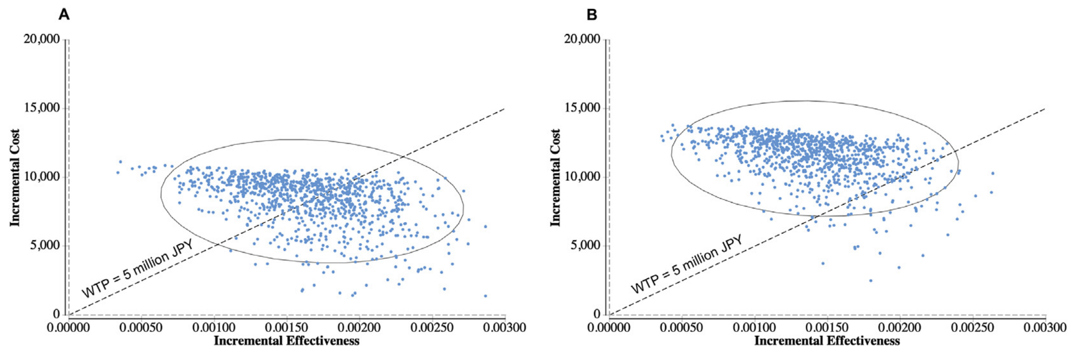

Fig. 3. Cost-effectiveness planes for probabilistic sensitivity analyses of aprepitant (APR) (A) and phosphorylated (Fos)-APR (B) regimens versus standard regimen. JPY = Japanese yen; WTP = willingness to pay.

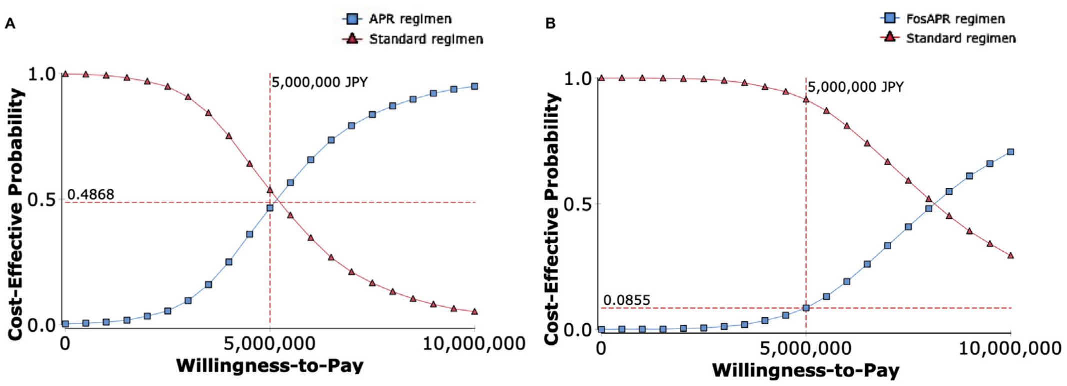

Fig. 4. Cost-effectiveness acceptability curve for probabilistic sensitivity analyses of aprepitant (APR) (A) and phosphorylated (Fos)-APR (B) regimens versus standard regimen.

using QALYs. Compared to the combination of GRA + DEX, the addition of APR resulted in an ICER of 4,990,000 JPY/QALY (44,500 USD/QALY), and the addition of FosAPR resulted in an ICER of 7,960,000 JPY/QALY (70,900 USD/QALY). This finding suggests that although prophylactic antiemetic therapy with addition of APR is cost-effective, FosAPR is not cost-effective in Japan.

The data were derived from regimens used in randomized, controlled trials performed in Japan. Given that the cost of APR and FosAPR is 4-fold more than that of GRA, the estimated additional cost per treatment with the APR regimen was ~11,000 JPY (98 USD) and per treatment with the FosAPR regimen was 14,000 JPY (125 USD) compared with the standard regimen. Our results demonstrated that the additional expected cost per patient was estimated to be ~8000 JPY (71 USD) with the APR regimen and 11,000 JPY (98 USD) with the FosAPR regimen. This finding suggests that the addition of APR or FosAPR leads to a reduction in nausea and vomiting that is not adequately responsive to combination therapy with GRA + DEX alone, resulting in a cost-savings for additional therapy that may be required. However, the economic value of APR and FosAPR cannot be evaluated properly based on the expected cost alone. In addition to prolonging survival, QoL is an important indicator to consider regarding treatments for major life-threatening diseases such as cancer and heart disease. QALY is used in many countries to assess the efficiency of medical care, including prophylactic antiemetic therapy in patients undergoing chemotherapy for cancer. CINV is a serious issue in patients because it may influence the ability of a patient to continue chemotherapy. We demonstrated that in a given patient, the incremental effects of the APR and FosAPR regimens were 0.00166 and 0.00143 QALY, respectively. This result suggests that the addition of APR or FosAPR leads to a reduction in nausea and vomiting that is not adequately responsive to combination therapy with GRA + DEX alone, resulting in improved QoL. We demonstrated that the APR regimen was cost-effective, assuming the base-case ICER of ~4,990,000 JPY/QALY (44,500 USD/QALY) and a WTP of 5,000,000 JPY (44,575 USD). On the other hand, the ICER of the FosAPR regimen was ~7,950,000 JPY/QALY (70,900 USD/QALY), indicating that the FosAPR regimen is inferior in terms of cost-effectiveness.

In the 1-way sensitivity analyses, we demonstrated that the probability of a CR in the delayed phase had the most influence on the ICER. This finding could have been attributed to the reduced QoL in patients and to the additional costs of rescue medications, including those of follow-up visits, medical examinations, and medications for CINV in the delayed phase. The ICER was below the WTP threshold due to a 25% reduction in the price of APR, but the ICER with FosAPR did not fall below WTP even at a drug price reduction of 25%. To improve the cost-effectiveness of FosAPR, it is indicated that future drug price revision or the appearance of generic drugs will require a further reduction in drug costs.

Assuming the WTP of 5,000,000 JPY, the probabilistic sensitivity analysis demonstrated that the APR regimen would be superior in terms of cost-effectiveness in 48.7% of cases. This result indicates that although the APR recommended by JSCO from the viewpoint of effectiveness in HEC is somewhat cost-effective, the estimation of its cost-effectiveness can be changed by the uncertainty of various parameters. There was no report comparing the economic evaluation of these regimens. However, we demonstrated that addition of the FosAPR regimen would be superior in terms of cost-effectiveness in only 8.55% of cases, suggesting that it is not cost-effective.

Given our results, we compared our findings to those of previous studies on the economic evaluation of APR administered outside of Japan.[7,9–12] Tsukiyama et al[12] analyzed the cost model in their facility and analyzed it in the same model as in this study and reported that APR is advantageous for cost-effectiveness in outpatient chemotherapy. They reported that the ICER of APR was 3,906,698 JPY (35,910 USD) in the outpatient setting. In this study, the rescue treatment used in other published reports was set as a reference. Differences from this research were found to be due to the difference in this estimate. A study from the United States[6] examined the cost-effectiveness of APR in comparison to that of a control regimen of DEX + ondansetron in patients undergoing 5 courses of chemotherapy, using a Markov model, and demonstrated that the ICER (97,429 USD, ~11,200,000 JPY) exceeded the common threshold (50,000 USD). A study from Belgium[8] constructed a decision tree based on the 801 trial[27] and demonstrated that APR was dominant (ie, more effective and less expensive) compared with a control regimen of DEX + ondansetron in patients undergoing 6 courses of chemotherapy. Studies from Germany, the United Kingdom, and Hong Kong used the same decision tree that was used in the present study. Based on the 052[16] and 054[17] trials, the study in Germany[9] demonstrated that the addition of APR was cost-effective compared with a control regimen of DEX + ondansetron, with an ICER of €28,891 (~3,800,000 JPY). The UK study[7] also demonstrated that the addition of APR was cost-effective, with an ICER of £10,847 (~1,610,000 JPY) compared with a control regimen of DEX + ondansetron in patients with breast cancer. Based on the 052, 054, 801, and 130[25] trials, studies from Hong Kong[10] and Singapore[11] demonstrated that the addition of APR was cost-effective compared with a regimen of 5-HT_3 RA + DEX, with ICERs of 440,950 HKD (~6,000,000 JPY) and 40,600 USD (~4,550,000 JPY). The discrepancies in ICER may be explained by the difference in the analytical model, the clinical trials used as the data source, the use of the combination therapy with DEX and ondansetron as the comparative standard therapy, and the differences in drug prices and the health insurance systems across these countries. To our knowledge, our study is the first report on the cost-effectiveness of FosAPR. We demonstrate that FosAPR was less cost-effective, given that FosAPR is more expensive than APR in Japan. However, unlike APR, FosAPR does not need to be re-administered on and after the second day. Thus, its usefulness in elderly patients and patients who have difficulties taking medications should be recognized. The economic evaluation of pharmaceuticals should be performed using appropriate models and parameters that reflect the evidence and health care settings of various countries. Our results may effectively serve as an index of future economic evaluations.

There were limitations to the present study. First, the utility values incorporated in the analysis model were derived from previous studies using data obtained from countries other than Japan. Some differences in health care systems among various countries or regions are likely; however, we assumed that the pattern of utility values in Japan is similar to that of other countries, as it is difficult to measure the difference in utility values among countries. Although the 1-way sensitivity analysis showed that the variation in utility values did not have a significant impact on the results, it is still important to measure utility weights in the Japanese population. If the data on utility values for CINV are available from the Japanese population, the results of our current model can be updated. Second, although we included only outpatient chemotherapy in our analysis, the administration of HEC regimens is not limited to outpatients. The administration of HEC regimens is performed in outpatients, particularly with the recent incorporation of short hydration with cisplatin.[26] However, HEC regimens are also administered to inpatients, and many hospitals that administer chemotherapy to inpatients use the diagnosis procedure combination. However, because the diagnosis procedure combination does not reflect the difference in the cost of antiemetic therapy, outcomes measures such as reduced length of stay and rates of re-examination should be examined to determine the cost difference from the perspective of a payer. As currently there is little evidence on these outcomes available, future studies using these outcomes to evaluate the cost-effectiveness of prophylactic antiemetic therapy in inpatients are warranted.

In the present study, we used QALYs to determine the ICER of prophylactic antiemetic therapy in patients receiving cancer chemotherapy. Our findings lay the groundwork for future studies to compare the analyses used in the economic evaluation of pharmaceuticals and to evaluate the influence on QoL. The Ministry of Health, Labour and Welfare is expected to introduce a system within the Japanese medical insurance system in the future, in which drug prices are adjusted based on the cost-effectiveness of drugs and medical devices. Our findings provide important insights that should be considered in the discussion of this system.

CONCLUSIONS

In the context of the Japanese medical insurance system, addition of APR to prophylactic antiemetic therapy for outpatient HEC was cost-effective, although the addition of FosAPR is not cost- effective.

AUTHORS' CONTRIBUTIONS

MK designed the study, and wrote the initial draft of the manuscript. RM contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests with regard to the content of this article.

REFERENCES

1. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American society of clinical oncology clinical practice guideline update. *J Clin Oncol*. 2017;35:3240–3261. https://doi.org/10.1200/JCO.2017.74.4789.

2. Berger MJ, Ettinger DS, Aston J, et al. NCCN guidelines insights: antiemesis, version 2.2017. *J Natl Compr Canc Netw*. 2017;15:883–893. https://doi.org/10.6004/jnccn.2017.0117.
3. Takeuchi H, Saeki T, Aiba K, et al. Japanese Society of Clinical Oncology clinical practice guidelines 2010 for antiemesis in oncology: executive summary. *Int J Clin Oncol*. 2015;21:1–12. https://doi.org/10.1007/s10147-015-0852-1.
4. Oo TH, Hesketh PJ. Drug Insight: new antiemetics in the management of chemotherapy-induced nausea and vomiting. *Nat Clin Prac Oncol*. 2005;2:196–201. https://doi.org/10.1038/ncponc0132.
5. Grunberg S, Chua D, Maru A, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with cisplatin therapy: randomized, double-blind study protocol—EASE. *J Clin Oncol*. 2011;29:1495–1501. https://doi.org/10.1200/JCO.2010.31.7859.
6. Moore S, Tumeh J, Wojtanowski S, Flowers C. Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. *Value Health*. 2007;10:23–31. https://doi.org/10.1111/j.1524-4733.2006.00141.x.
7. Humphreys S, Pellissier Jones A. Cost-effectiveness of an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer in the UK. *Cancer Manag Res*. 2013;5:215–224. https://doi.org/10.2147/CMAR.S44539.
8. Annemans L, Strens D, Lox E, Petit C, Malonne H. Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. *Support Care Cancer*. 2007;16:905–915. https://doi.org/10.1007/s00520-007-0349-1.
9. Lordick F, Ehlken B, Ihbe-Heffinger A, et al. Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. *Eur J Cancer*. 2007;43:299–307. https://doi.org/10.1016/j.ejca.2006.09.019.
10. Chan SL, Jen J, Burke T, Pellissier J. Economic analysis of aprepitant-containing regimen to prevent chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy in Hong Kong. *Asia-pac J Clin Oncol*. 2014;10:80–91. https://doi.org/10.1111/ajco.12170.
11. Lopes G, Burke T, Pellissier J, Zhang XH, Dedhiya S, Chan A. Aprepitant for patients receiving highly emetogenic chemotherapy: an economic analysis for Singapore. *Value Health Res Issues*. 2012;1:66–74. https://doi.org/10.1016/j.vhri.2012.03.002.
12. Tsukiyama I, Hasegawa S, Ikeda Y, et al. Cost-effectiveness of aprepitant in Japanese patients treated with cisplatin-containing highly emetogenic chemotherapy. *Cancer Sci*. 2018;109:2881–2888. https://doi.org/10.1111/cas.13736.
13. Takahashi T, Hoshi E, Takagi M, Katsumata N, Kawahara M, Eguchi K. Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. *Cancer Sci*. 2010;101:2455–2461. https://doi.org/10.1111/j.1349-7006.2010.01689.x.
14. Saito H, Yoshizawa H, Yoshimori K, et al. Efficacy and tolerability of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Ann Oncol*. 2012;24:1067–1073. https://doi.org/10.1093/annonc/mds541.
15. Chawla SP, Grunberg SM, Gralla RJ, et al. Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer*. 2003;97:2290–2300. https://doi.org/10.1002/cncr.11320.
16. Hesketh PJ, Grunberg SM, Gralla RJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol*. 2003;21:4112–4119. https://doi.org/10.1200/JCO.2003.01.095.
17. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. *Cancer*. 2003;97:3090–3098. https://doi.org/10.1002/cncr.11433.
18. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012 [in Japanese]. *Nihon Jinzo Gakkai Shi*. 2012;54:1034–1191.
19. *National Health Insurance Drug Price Standard*. Tokyo, Japan: Jiho, Inc; 2018.
20. *Reimbursement Schedule of Social Insurance*. Tokyo, Japan: Social Insurance Research Laboratory; 2018.
21. Oshima Y, Ban A, Hisada T, Gocho S, Saito H, et al. Pharmacoeconomic evaluation of low dose steroids for delayed nausea due to anticancer chemotherapy. *J Jpn Soc Hosp Pharm*. 2009;45:365–368.
22. Yamanishi Y, Tajima H, Ikeda S, Yamada H, Inoue T, Takeda H. Cost-effectiveness analysis of 5-HT_3 receptor antagonist drug: palonosetron in cancer

chemotherapy. *Jpn J Pharm Palliat Care Sci*. 2014:37–43.
23. Shiroiwa T, Sung Y-K, Fukuda T, Lang H-C, Bae S-C, Tsutani K. International survey on willingness to pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ*. 2010;19:422–437. https://doi.org/10.1002/hec.1481.
24. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer*. 2004;13:219–227. https://doi.org/10.1007/s00520-004-0710-6.
25. Rapoport BL, Jordan K, Boice JA, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer*. 2009;18:423–431. https://doi.org/10.1007/s00520-009-0680-9.
26. Sakaida E, Iwasawa S, Kurimoto R, et al. Tolerability of a short hydration method for cisplatin administration in comparison with a conventional method—a retrospective study. *Jpn J Clin Oncol*. 2016;46:370–377. https://doi.org/10.1093/jjco/hyv203.
27. Schmoll HJ, Aapro MS, Poli-Bigelli S, et al. Comparison of an aprepitant regimen with a multiple-day ondansetron regimen, both with dexamethasone, for antiemetic efficacy in high-dose cisplatin treatment. *Ann Oncol*. 2006;17:1000–1006. https://doi.org/10.1093/annonc/mdl019.

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