Received: 7 May 2018 | Accepted: 7 July 2018

DOI: 10.1111/cas.13736

ORIGINAL ARTICLE

WILEY Cancer Science

Cost-effectiveness of aprepitant in Japanese patients treated with cisplatin-containing highly emetogenic chemotherapy

Ikuto Tsukiyama[1,2] | Shiori Hasegawa[3] | Yoshiaki Ikeda[3] | Masayuki Takeuchi[2] | Sumiyo Tsukiyama[2] | Yusuke Kurose[2] | Masayuki Ejiri[2] | Masaki Sakuma[2] | Hiroko Saito[2] | Ichiro Arakawa[4] | Tadao Inoue[5] | Etsuro Yamaguchi[6] | Akihito Kubo[6]

[1]Faculty of Pharmacy, Meijo University, Nagoya, Japan

[2]Department of Pharmacy, Aichi Medical University School of Medicine, Nagakute, Japan

[3]School of Pharmacy, Kinjo Gakuin University, Nagoya, Japan

[4]Faculty of Pharmacy, Teikyo Heisei University, Chiba, Japan

[5]Faculty of Pharmacy, Ohu University, Koriyama, Japan

[6]Department of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, Nagakute, Japan

Correspondence: Akihito Kubo, Department of Respiratory Medicine and Allergology, Aichi Medical University School of Medicine, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan (kuboa@aichi-med-u.ac.jp).

Chemotherapy-induced nausea and vomiting (CINV) remains a major adverse event in cancer chemotherapy. Although aprepitant is effective in preventing CINV, an increment in financial burden for uniform use of aprepitant is a concern. The aim of the present study was to define the cost-effectiveness of aprepitant from the perspective of the Japanese National Health Insurance system. Based on the results of a randomized phase II trial comparing an aprepitant-containing regimen versus a nonaprepitant regimen in Japanese patients who received cisplatin-containing highly emetogenic chemotherapy, a decision analytic model was developed. The incremental cost-effectiveness ratio (ICER) was calculated both in the outpatient care setting (OCS) and in the inpatient care setting (ICS). The use of the aprepitant-containing regimen was associated with improved quality of life compared with the nonaprepitant regimen, with an increment in quality-adjusted life years (QALY) of 0.0016. The incremental total medical costs associated with the use of the aprepitant regimen were lower in the OCS than in the ICS, 6192 JPY (56.92 USD) and 9820 JPY (90.27 USD), respectively. The ICER was calculated as 3 906 698 JPY (35 910 USD) per QALY gained in the OCS and 6 195 781 JPY (56 952 USD) per QALY gained in the ICS. Cost-effectiveness of the aprepitant-containing antiemetic therapy was limited to the OCS, considering the threshold of willingness-to-pay commonly accepted (5 million JPY [45 960 USD] in Japan and 50 000 USD in the USA). The efficacy of aprepitant offsets the costs for revisiting clinics or rehospitalization added with rescue medications in the OCS.

KEYWORDS

chemotherapy-induced nausea and vomiting, cost-effectiveness, highly emetogenic chemotherapy, quality-adjusted life year incremental cost-effectiveness ratio

1 | INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) remains one of the distressing events for patients who receive cancer chemotherapy. It causes reduced oral intake[1] and has negative impacts on quality of life (QOL).[2,3] It may even reduce patients' willingness to continue anticancer treatment.[4] Clinical practice guidelines on antiemetics in Japan Society of Clinical Oncology[5] classified cisplatin-based chemotherapies as highly emetogenic chemotherapies (HEC) and recommend aprepitant-containing 3-drug regimens,

including a 5-hydroxytryptamine 3 receptor antagonist (5-HT_3RA) and dexamethasone, the same as those of major international organizations, the National Comprehensive Cancer Network (NCCN),[6] the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO),[7] and the American Society of Clinical Oncology (ASCO).[8] Aprepitant, a selective neurokinin-1 receptor antagonist (NK_1RA), inhibits nausea and vomiting signals by blocking the interaction of substance P with the NK-1 receptor.[9-11] The efficacy of aprepitant for CINV was confirmed in clinical trials globally[12-14] and in Japan,[15] and it was approved by the FDA in the USA in 2003 and by the Ministry of Health, Labor, and Welfare in Japan in 2009. Although optimal antiemetic prophylaxis according to emetogenic risk of chemotherapy is important for patients to continue their cancer treatment, the increased financial burden is a concern for aprepitant, which is a costly antiemetic agent. Gomez et al[16] reported that socioeconomic barriers associated with NK_1RA therapy affected suboptimal adherence to guideline recommendations for antiemetic prophylaxis. Cost-effectiveness analyses of aprepitant have been reported from 6 countries. Five of them showed a positive result with aprepitant,[17-21] whereas Moore et al[22] from the USA reported that aprepitant provides only modest benefits. However, as far as we could ascertain, there are no reports on the cost-effectiveness of aprepitant in Japan. The objective of the present study was to define, from the Japanese National Health Insurance payer perspective, the cost-effectiveness of aprepitant for preventing CINV in patients who received cisplatin-based HEC.

2 | METHODS

2.1 | Model building

The cost-effectiveness of the aprepitant-containing antiemetic regimen was analyzed by comparison with the regimen without aprepitant in patients who received cisplatin-based HEC. A decision analytic model was developed based on the phase II clinical trial, which verified the effect of aprepitant on CINV for Japanese patients who received cisplatin-based chemotherapy, as a company sponsored trial for the new drug application in Japan with compliance with Good Clinical Practice.[15] Patients who were enrolled in the cited trial were planned to receive chemotherapy including cisplatin ($\geq$70 mg/m^2). The aprepitant regimen consisted of the 3-drug combination of aprepitant, a 5-HT_3RA and dexamethasone (Table 1), which corresponded to antiemetic regimens recommended in current major antiemetic guidelines. The antiemetic regimen without aprepitant consisted of the 2-drug combination of a 5-HT_3RA and dexamethasone. The decision analytic model was designed to track health outcomes and costs related to episodes of nausea and vomiting. Nine health states were applied in the model and represent all possible pairings from 3 clinical outcomes in the acute and delayed phases of CINV (Figure 1). The clinical outcomes used to classify patients in the model were defined as: complete response (CR) with no emesis and no rescue antiemetic therapy, and incomplete response (IR) with some emesis or use of rescue therapy. CR was further subdivided into 2 mutually exclusive health outcomes: (a) complete protection (CP) with no emesis, no rescue therapy and no significant nausea; (b) complete response at best (CRB) with no emesis and no rescue therapy excluding CP.[17-21]

The probabilities of predicting the outcomes from one health state to another were determined using the data from the clinical trial results (Table 2).[15] Duration of aprepitant administration was assumed to be 3 days according to the common practical use of aprepitant derived from Protocol 052.[13] The dose of dexamethasone in the aprepitant-containing regimen was assumed to be half of that in the nonaprepitant regimen considering the area under the blood concentration-time curve (AUC) of dexamethasone, increasing to 2.2-fold higher as a result of the inhibition of cytochrome P450 (CYP) 3A4 by aprepitant.[23] The cost-effectiveness of the aprepitant-containing antiemetic regimen compared with that of the nonaprepitant regimen was assessed using the incremental cost-effectiveness ratio (ICER) at a time horizon of 5 days according to the cited trial[15] and duration of CINV.[24,25] The analysis was conducted both in the outpatient care setting (OCS) and in the inpatient care setting (ICS) from the Japanese National Health Insurance system payer perspective.

2.2 | Health state outcomes

Health state outcomes were evaluated using quality-adjusted life years (QALY), calculated for 9 patterns of health conditions according to an established decision analytic model for days 1-5 on chemotherapy (Table 3). QALY in each treatment group was integrated according to the probability of the health state in the acute phase and in the delayed phase. A utility value of each health state was assigned according to the previous reports,[17-20] and utility values of 0.9, 0.7 and 0.2 were assigned to CP, CRB, and IR, respectively.

2.3 | Cost variables

Drug costs for prophylactic antiemetic therapies and rescue treatments for CINV in each treatment group were determined according

TABLE 1 Antiemetic regimens for prevention of CINV used in the model, based on the Japanese phase II trial of aprepitant[15] and clinical practice

Antiemetic regimen	Drugs	Day 1	Day 2	Day 3
Aprepitant regimen	Aprepitant p.o.	125 mg	80 mg	80 mg
	Granisetron i.v.	40 μg/kg	NA	NA
	Dexamethasone i.v.	6 mg	4 mg	4 mg
Nonaprepitant regimen	Granisetron i.v.	40 μg/kg	NA	NA
	Dexamethasone i.v.	12 mg	8 mg	8 mg

CINV, chemotherapy-induced nausea and vomiting; i.v., intravenous; p.o., oral; NA, not applicable.

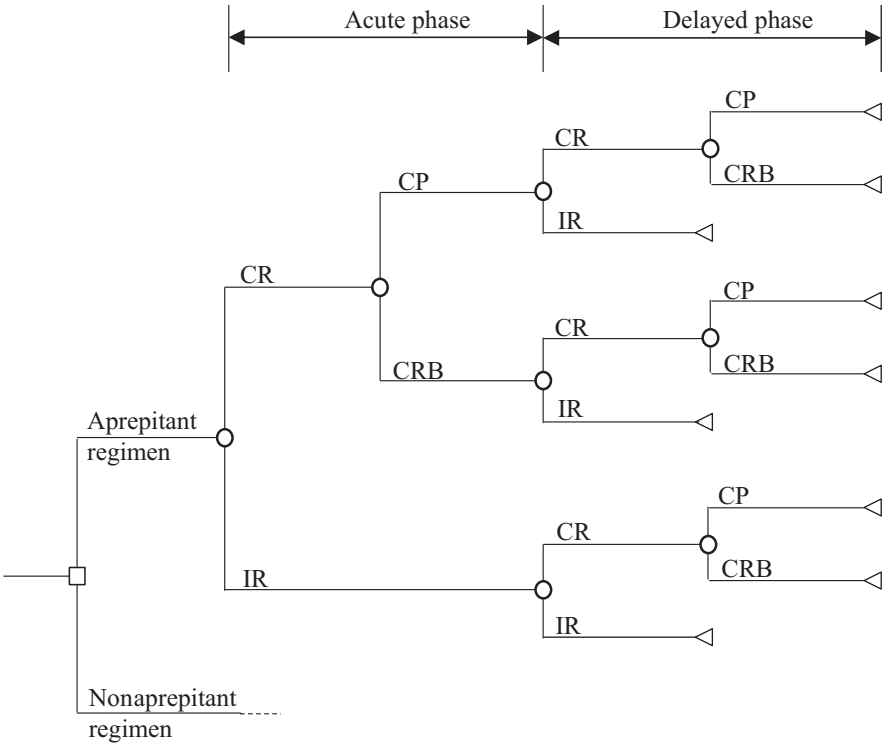

FIGURE 1 Decision analytic model. The model decision tree depicts 9 possible health states, marked by a triangle, to compare costs and clinical outcomes associated with an aprepitant-containing antiemetic regimen vs a no aprepitant regimen. CP, complete protection; CR, complete response; CRB, complete response at best; IR, incomplete response

TABLE 2 Health state probabilities used in the model, based on the Japanese phase II trial of aprepitant[15]

Health state outcomes by phase		Aprepitant regimen (n = 146)	Nonaprepitant regimen (n = 149)
Acute phase (day 1)	Delayed phase (days 2-5)	%	%
CP	CP	61.6	43.0
	CRB	5.5	6.0
	IR	16.4	32.9
CRB	CP	2.1	1.3
	CRB	1.4	0
	IR	0	0
IR	CP	1.4	0
	CRB	0	1.3
	IR	11.0	15.4

CP, complete protection; CRB, complete response at best; IR, incomplete response.

TABLE 3 Utility values for CINV outcomes

Health state outcomes by phase		5-d QALY		
Acute phase (day 1)	Delayed phase (days 2-5)	Base case	Lower bound	Upper bound
CP	CP	0.0123	0.0096	0.0137
	CRB	0.0101	0.0073	0.0126
	IR	0.0047	0.0035	0.0056
CRB	CP	0.0118	0.0090	0.0134
	CRB	0.0096	0.0067	0.0123
	IR	0.0041	0.0029	0.0053
IR	CP	0.0104	0.0081	0.0117
	CRB	0.0082	0.0058	0.0106
	IR	0.0027	0.0019	0.0036

5-d QALY = ([utility value (acute phase) × 1 d] + [utility value (delayed phase) × 4 d])/365 d. The utility values of 0.9, 0.7 and 0.2 were assigned to CP, CRB, and IR, respectively.
CINV, chemotherapy-induced nausea and vomiting; CP, complete protection; CRB, complete response at best; IR, incomplete response; QALY, quality-adjusted life years.

to the probability of the health state in the acute phase and in the delayed phase.

Costs for rescue treatments were assessed based on the retrospective review of consumed medical resources from clinical records of patients in Aichi Medical University Hospital who received cisplatin-containing HEC and a prophylactic antiemetic regimen with or without aprepitant (Table 4). The extracted clinical records were in the time period between the approval of aprepitant by the Japanese government and general use of aprepitant in the oncology clinic of this hospital. During that period, some oncologists were prescribing aprepitant and some were not, and clinical records for both an antiemetic regimen with aprepitant and that without aprepitant were

available. Ethics approval for the survey was obtained in advance from the institutional review board.

In Japan, patients are covered by the national health insurance (NHI) system, and copayment of a patient is 10%-30% of the total medical cost according to his/her age. Ministry of Health, Labor, and Welfare determines prescribing drug prices and expenses for medical treatment and care and registers them into the NHI standard list to which national insurance is applicable. All costs for drugs in this study were assigned from the NHI Drug Price Standard listed in 2016. Diagnosis Procedure Combination (DPC) system is a diagnosis group classification and the medical fee associated with any particular hospitalization is determined based on DPC assigned to that hospitalization.[26] The current analysis was, however, carried out without considering the DPC system and copayment of a patient, which was to assess the interaction of health outcomes and total medical costs, focusing on the consumed medical resources.

The medical fees for revisiting the outpatient clinic, rehospitalization and drug prescriptions were assigned from the NHI price listed in 2016. The costs calculated in Japanese yen (JPY) were converted to US dollars (USD) using the exchange rate reported by the Organization for Economic Cooperation and Development (OECD) in 2016; 1 USD = 108.79 JPY.[27]

2.4 | Valuing outcomes

The incremental cost-effectiveness ratio (ICER) was calculated to verify the cost-effectiveness of the aprepitant-containing antiemetic regimen. A discount was not applied to this analysis because the values of drug costs and medical treatment were assumed not to change in the short 5-day observational period in this study. A willingness-to-pay (WTP) threshold of 5 million JPY (45 960 USD/QALY) was used to define strategies that provide cost-effective utilization of resources in the Japanese health-care system, as defined by Shiroiwa et al.[28]

2.5 | Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were carried out to assess uncertainty and robustness of this model by evaluating the effects of differing model parameters. Probabilistic sensitivity analysis was conducted by 10 000 iterations of an automatic multiple random numbering method using Monte Carlo simulation. In the sensitivity analysis, the ranges of parameters varied were 95% confidence intervals for probability and ±30% for utility weights and drug costs.

TABLE 4 Estimated costs of medical resources

	Costs JPY (USD)	Min JPY (USD)	Max JPY (USD)
Drug[a]			
Aprepitant 125 mg (p.o.)	4972.7 (45.71)	NA	NA
Aprepitant 80 mg (p.o.)	3393 (31.19)	NA	NA
Dexamethasone 1.65 mg (i.v.)	103 (0.95)	NA	NA
Dexamethasone 3.3 mg (i.v.)	181 (1.66)	NA	NA
Dexamethasone 6.6 mg (i.v.)	335 (3.08)	NA	NA
Granisetron 1 mg (i.v.)	1485 (13.65)	NA	NA
Aprepitant regimen[b]	15 631.7 (145.24)	10 492.2 (101.67)	20 321.2 (188.81)
Nonaprepitant regimen[b]	4516 (42.12)	3161.2 (29.48)	5870.8 (54.75)
Rescue medication[b]			
Aprepitant group	849.8 (7.81)	594.9 (5.47)	1104.7 (10.15)
Nonaprepitant group	2145.2 (19.72)	1501.6 (13.80)	2788.8 (25.63)
Medical fees[c]			
Costs for hospitalization	25 210 (231.73)	17 647 (162.21)	32 773 (301.25)
Costs for revisit outpatient	720 (6.62)	504 (4.63)	936 (8.60)
Costs for drug prescription (p.o., no more than 6 drugs)	420 (3.86)	294 (2.70)	546 (5.02)

Exchange rate, 1 USD = 108.79 JPY, based on the Organization for Economic Cooperation and Development (OECD) 2016.[27]

i.v., intravenous; p.o., oral; NA, not applicable.

[a]Japanese National Health Insurance Drug Price Standard listed in 2016.

[b]Average costs estimated from the clinical practice in our institution.

[c]Japanese National Health Insurance Price listed in 2016.

All analyses in this study were conducted using TreeAge PRO 2014 (TreeAge Software, Inc., Williamstown, MA, USA).

3 | RESULTS

3.1 | Health state outcomes

Use of the aprepitant-containing regimen was associated with improved QOL compared with the nonaprepitant regimen for CINV caused by cisplatin-based highly emetogenic chemotherapy. The estimated gain in QALY with the aprepitant regimen was 0.00159 (Table 5).

3.2 | Cost variables

Total medical costs associated with the use of the aprepitant regimen were higher than those of the nonaprepitant regimen both in the OCS and in the ICS. Estimated increment in total medical costs with the aprepitant regimen was lower in the OCS than in the ICS, 6192 JPY (56.92 USD) versus 9820 JPY (90.27 USD), respectively.

3.3 | Outcomes in cost-effectiveness

In the OCS, we calculated the ICER to be 3 906 698 JPY (converted to 35 910 USD) per QALY gained, indicating that the aprepitant regimen was more cost-effective in the OCS. In contrast, in the ICS, the ICER was calculated as 6 195 781 JPY (converted to 56 952 USD) per QALY, which was over the WTP threshold (5 million JPY [45 960 USD] in Japan and 50 000 USD in the USA).

3.4 | Sensitivity analysis

Univariate sensitivity analyses showed that factors that mainly affected these results were cost of the aprepitant regimen, CR rate of the delayed phase, utility weight of CP, and CR rate of the acute phase (Figure 2A,B). Costs for rescue treatment had less effect than those for rehospitalization. The probability that the aprepitant regimen was cost-effective was higher in the OCS than in the ICS, 65% versus 35%, respectively (Figure 2C). In the incremental cost-effectiveness scatterplot, the presence of a dot in the first quadrant means that the aprepitant regimen is both costlier and more effective than the nonaprepitant regimen. In the OCS, the first quadrant contained 85% of the samples, 60% of which had an ICER of <5 million JPY (45 960 USD)/QALY. In the ICS, the first quadrant contained 97% of the samples, 35% of which had an ICER of <5 million JPY/QALY. These results mean that more samples were included in the cost-effective area in the OCS than in the ICS (Figure 2D).

4 | DISCUSSION

This study showed the cost-effectiveness of an aprepitant-containing prophylactic antiemetic regimen for CINV in patients who received cisplatin-based chemotherapy from the Japanese National Health insurance system payer perspective. Results of this study suggested that the cost-effectiveness of aprepitant was higher in the OCS than in the ICS. Lordick et al[17] showed the beneficial cost-effectiveness of the aprepitant-containing therapy for CINV in high-dose cisplatin-based chemotherapy based on protocols 052/054 from the German legal health insurance perspective. Humphreys et al[18] showed that aprepitant was cost-effective in anthracycline-cyclophosphamide-based chemotherapy from the British National Health Service (NHS) perspective. Annemans et al in Belgium, Chan et al in Hong Kong, and Lopes et al in Singapore reported consistently better results, with aprepitant cost-effective in both cisplatin and anthracycline-cyclophosphamide-based chemotherapy in each national health system.[19-21] Reports from Germany and Hong Kong noted that the analyses were conducted in the OCS.[17,20] Other reports from the UK, Belgium and Singapore[21] did not clearly describe the setting, but it was implied that it was the OCS as they considered costs for reconsultation, rehospitalization, and visits of a home doctor or other health-care professionals when adverse events as a result of chemotherapy occurred.[18,19,21] These reports all concluded that aprepitant was superior in cost-effectiveness in analyses using a decision analytic model similar to that of the present study. The results of the present study that aprepitant was superior in cost-effectiveness in the OCS support these reports. One of the reasons why there was no cost-effectiveness in the ICS would include the difference in costs related to rescue treatment as compared with that in the OCS. Prevention of CINV with aprepitant would reduce rescue treatment, and this would decrease opportunities for revisiting the hospital and rehospitalization in the OCS.

The aprepitant regimen not only had a positive impact on health outcomes and QOL for patients receiving cisplatin-based chemotherapy, but also counterbalanced incremental total medical costs including indirect costs that would be wasted by CINV without it.[29] However, the ICER slightly exceeded the WTP threshold in the ICS (6 195 781 JPY (56 952 USD)/QALY), but this does not negate the

TABLE 5 Results of cost-utility analysis

	Setting	Aprepitant regimen	Nonaprepitant regimen	Difference	ICER JPY/QALY (USD/QALY)
QALY	–	0.00948	0.00789	0.00159	–
Costs JPY (USD)	Outpatient setting	19 542 (179.63)	13 349 (122.71)	6192 (56.92)	3 906 698 (35 910)
	Inpatient setting	16 482 (151.50)	6661 (61.23)	9820 (90.27)	6 195 781 (56 952)

QALY, quality-adjusted life years shown in Table 3 footnote; ICER, incremental cost-effectiveness ratio = ([cost for aprepitant regimen] – [cost for nonaprepitant regimen])/([QALY of aprepitant regimen] – [QALY of nonaprepitant regimen]).
Exchange rate, 1 USD = 108.79 JPY, based on the OECD 2016.[27]

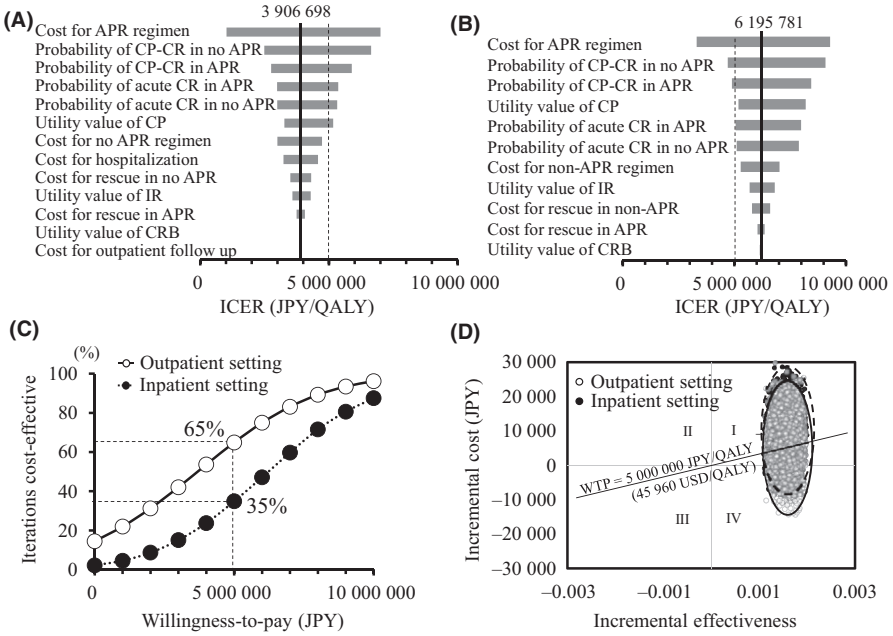

FIGURE 2 Sensitivity analysis. Tornado diagrams show the results of one-way sensitivity analyses in the (A) outpatient care setting and (B) inpatient care setting. (C) Cost-effectiveness acceptability curve and (D) scatter plot show the results of probabilistic sensitivity analysis by Monte Carlo simulation; the outpatient care setting is shown by white circles, and the inpatient care setting is shown by closed circles. In the scatter plot, dots in the outpatient setting are joined with a solid line, and those in the inpatient setting are joined with a broken line. APR, aprepitant; CP-CR, complete protection in acute phase and complete response in delayed phase; CRB complete response at best; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness-to-pay which was assumed to be 5 million JPY as validated by Shiroiwa et al;[28] Exchange rate, 1 USD = 108.79 JPY, based on the OECD 2016[27]

efficacy of aprepitant itself. Univariate sensitivity analysis indicated that factors that mainly affected these results included cost of aprepitant and CR rate. Recently, short hydration was shown to improve QOL for patients who received cisplatin-based chemotherapy.[30-32] Furthermore, aprepitant was used in an antiemetic regimen to prevent CINV in those studies. NK_1RA and other newer generation antiemetics have markedly improved gastrointestinal toxicity induced by cisplatin,[12-15,33-35] which may enable oral hydration. Moreover, the clinical use of aprepitant in the OCS may provide patients with better cost-effectiveness.

Patients without nausea and vomiting in the acute phase are at reduced risk of nausea and vomiting in the delayed phase,[36] and the success of CINV control in the first chemotherapy cycle is associated with a decrease in CINV in the subsequent chemotherapy cycles.[37,38] Considering the importance of CINV control in early phases of chemotherapy, aprepitant should be used from the onset of the first chemotherapy in accordance with antiemetic guidelines. In subsequent chemotherapy cycles, adjustment of antiemetic therapy may be considered depending on each patient's condition and taking into account the medical economic aspect.

This model analysis has some limitations. Parameters used in this model were estimates drawn from published sources. Although the probabilities of each health condition were estimated from the results of a domestic phase II study,[15] the fixed utility values in each health condition were derived from reports on European and American patients.[39-41] Biases arising from using utility values from different races and single clinical trial data cannot be excluded. To deal with the uncertainties associated with these potential biases, deterministic and probabilistic sensitivity analyses were carried out, and the effects of utility values on the results were modest. Health state probabilities in the present study were data from Japanese patients. Emetogenicity may differ depending on age, gender, alcohol consumption or other patient characteristics.[42,43] However, these factors were not considered in the current analysis, and our results may not directly be extrapolated to other HEC.

In conclusion, the aprepitant-containing prophylactic antiemetic therapy was cost-effective in the OCS, but not in the ICS, in Japanese patients who received cisplatin-based HEC.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest for this article.

ORCID

Ikuto Tsukiyama http://orcid.org/0000-0001-9861-9730

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How to cite this article: 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