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ORIGINAL ARTICLE

Cost-utility analysis of aprepitant for patients who truly need it in Japan

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Abstract

Purpose Neurokinin-1 receptor antagonist (NK_1RA) is recommended to prevent chemotherapy-induced nausea and vomiting (CINV) in patients who receive highly or moderately emetogenic chemotherapy (HEC or MEC, respectively). We previously reported that aprepitant, an NK_1RA, was needed to control CINV in 43% and 12% of patients who received HEC and MEC, respectively (*Support Care Cancer* 23:905–912, 2015). To elucidate the cost-effectiveness of aprepitant in these patients, a cost-utility analysis according to the necessity of aprepitant was performed.

Methods A decision-analytic model was developed according to the necessity of aprepitant and CINV responses in both acute and delayed phases of chemotherapy. Probabilities of health states and medical costs were derived from the results of the abovementioned trial.

Result In patients who received HEC and needed aprepitant, the incremental cost-effectiveness ratio (ICER) with aprepitant, relative to the regimen with no aprepitant, was 7912 US dollars (USD) per quality-adjusted life year (QALY) gained, which was far below the commonly accepted threshold of 50,000 USD/QALY. The ICER was 27,457 USD/QALY in patients who received MEC and needed aprepitant. In contrast, in patients who received HEC or MEC but did not need aprepitant, the ICER was 175,959 or 478,844 USD/QALY, respectively.

Conclusion Regardless of whether a patient received HEC or MEC, aprepitant use was highly cost-effective for patients who truly needed it. These results warrant further research to predict the necessity of NK_1RA treatment before initiating emetogenic chemotherapies.

Keywords Aprepitant · Neurokinin-1 receptor antagonist (NK_1RA) · Cost-effectiveness · Highly emetogenic chemotherapy (HEC) · Moderately emetogenic chemotherapy (MEC) · Incremental cost-effectiveness ratio (ICER)

Introduction

Chemotherapy-induced nausea and vomiting (CINV) reduces oral intake and decreases the patient's willingness to continue chemotherapy, which may lead to discontinuation or failure of cancer treatment [1]. While CINV remains a common adverse event in patients who receive highly or moderately emetogenic chemotherapy (HEC or MEC, respectively), a new strategy for antiemetic therapy including neurokinin-1 receptor antagonists (NK_1RAs) has brought better control of CINV. Aprepitant, one of the NK_1RAs, penetrates the blood-brain barrier [2] and inhibits emesis signaling by blocking substance P binding to neurokinin-1 receptors [3]. Aprepitant has been shown to be effective for delayed emesis, as well as acute emesis, in several phase III clinical trials for patients who received HEC containing cisplatin [4–6] and MEC containing anthracycline and cyclophosphamide [7–9]. Aprepitant was approved in Japan in 2009, based on this

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evidence and the results of a Japanese phase II clinical trial on patients who received cisplatin-based HEC [10]. Antiemetic guidelines in many countries, including Japan, recommend uniform use of aprepitant in combination with a 5-hydroxytryptamine receptor antagonist (5-HT_3RA) and a corticosteroid for patients who received HEC or some MEC [11–14]. However, increasing medical costs due to uniform use of NK_1RAs is a concern. Gomez et al. [15] reported low adherence to antiemetic guidelines in a recent population-based study. They showed that adherence rates for the use of NK_1RAs were less than 10% for patients who received cisplatin-based chemotherapy, while that with a 5-HT_3RA and dexamethasone was 60–90%. They also pointed out that economics was one of the factors for a lower adherence rate on a predictive factor analysis.

To date, the cost-effectiveness of aprepitant has been reported from seven countries. Lordick et al. [16] reported that an aprepitant-containing regimen was cost-effective compared with a conventional two-drug regimen, analyzed by a decision-analytic model based on protocol 052/054 from the German legal health insurance perspective. In contrast, Moore et al. [17] reported that aprepitant provides only modest incremental benefit compared with conventional treatment, using a Markov model in 5 cycles of cisplatin-based chemotherapy from the United States insurance payer perspective. They also stated that aprepitant was cost-effective only when the frequent delayed CINV required costly rescue medications. Other studies from Belgium, the UK, Hong Kong, and Singapore consistently concluded that aprepitant was cost-effective, using the decision-analytic model based on phase III trials of aprepitant [16, 18–21]. We also recently reported that the cost-effectiveness of aprepitant was limited in the outpatient care setting, based on a randomized phase II trial of aprepitant in Japan [22].

In these trials, the conventional two-drug regimen could control CINV in 40–50% of patients who received HEC, and the addition of aprepitant increased the complete response rate of CINV to 60–90%. We previously investigated the efficacy of aprepitant for patients with thoracic malignancy who needed it and who did not need it. A patient who needed aprepitant was defined as a patient who experienced CINV without aprepitant and received it for therapeutic and/or prophylactic intent. The results showed that patients who needed aprepitant for HEC and MEC were 43% and 12%, respectively. Other patients who did not need aprepitant maintained a good quality of life through the study period [23]. Based on these results, we considered that aprepitant would be highly cost-effective for patients who truly need it. The purpose of this study was to evaluate the cost-effectiveness of aprepitant according to its necessity for patients who received HEC or MEC under Japanese health economic conditions.

Methods

Model and design

The cost-effectiveness of the aprepitant-containing regimen (prophylactic aprepitant (PA) regimen) was analyzed by comparing it with that of the regimen without aprepitant (no prophylactic aprepitant (NPA) regimen) in patients who received HEC or MEC. A decision-analytic model was developed based on a previous report by Humphreys et al. [18] (Fig. 1). The PA meets current Japanese, European, and American antiemetic guidelines for cisplatin-containing chemotherapy. The PA consisted of granisetron (1 mg IV), dexamethasone (6.6 mg IV), and aprepitant (125 mg PO) on day 1, and dexamethasone (6.6 mg IV) and aprepitant (80 mg PO) on days 2 and 3. The NPA consisted of granisetron (1 mg IV) and dexamethasone (6.6 mg IV) on day 1, and dexamethasone (6.6 mg IV) on days 2 and 3. Patients who were enrolled in our previous study were divided into those who needed aprepitant and those who did not need aprepitant in each of the groups of those who received HEC or MEC. HEC included cisplatin-containing doublet chemotherapy and/or bevacizumab or radiotherapy. MEC included carboplatin-based doublet chemotherapy and/or bevacizumab or radiotherapy, or amrubicin single agent. The demography of patients was described in detail previously [23]. A patient who needed aprepitant was defined as a patient who experienced CINV and received aprepitant for therapeutic intent in the first course of chemotherapy and/or prophylactic intent in the subsequent courses of chemotherapy, as described in our previous report [23]. A patient who did not need aprepitant meant a patient who did not use aprepitant throughout the study period in the previous study. Cost-utility analyses for PA against NPA were conducted in four patterns of patients as follows: (1) patients who needed aprepitant and received HEC, (2) patients who did not need aprepitant and received HEC, (3) patients who needed aprepitant and received MEC, and (4) patients who did not need aprepitant and received MEC. These cost-utility analyses were performed from the perspective of payers of the Japanese National Health Insurance system.

Health state outcomes

Health state outcomes were evaluated using quality-adjusted life years (QALYs), calculated for health conditions according to a decision-analytic model for days 1–5 on chemotherapy (Table 1). The 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 for each health state was assigned according to the previous reports [18]: a utility value of 0.79 for complete protection (CP) (no emesis, requiring no rescue medication and numerical rating scale (NRS) of nausea less than 2.5), 0.594 for complete response

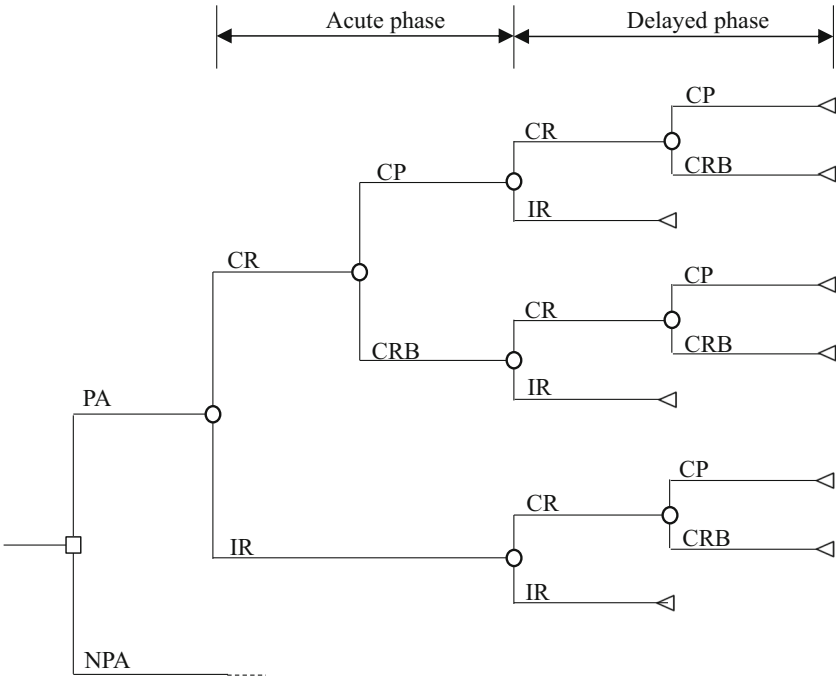

Fig. 1 The model decision tree. Nine health states are included in the model and represent all possible pairings of three clinical outcomes in the acute and delayed phases of CINV. The model decision tree depicts nine possible health states, marked by a triangle, to compare costs and clinical outcomes associated with an aprepitant-containing antiemetic regimen versus no aprepitant regimen. PA, prophylactic aprepitant regimen; NPA, no prophylactic aprepitant regimen; CP, complete protection; CRB, complete response at best; IR, incomplete response

at best (CRB) (no emesis, requiring no rescue medication and NRS of nausea over 2.5) [24], and 0.27 for incomplete response (IR) (any emesis, NRS of nausea over 2.5, or requiring any rescue medication) [25]. The calculated results of utility values of acute and delayed emesis are shown in Table 2.

Cost variables

Drug costs for prophylactic antiemetic therapies and rescue treatments for CINV in each treatment group were determined according to the probability of the health state in the acute phase and in the delayed phase based on our previous research [18]. Ethics approval for the research was obtained in advance from the institutional review board. All costs for medicines were assigned from the Japanese National Health Insurance (NHI) drug price standard listed in 2016 (Table 3). Costs for additional visits to outpatient clinics or re-hospitalization were not included, because all patients received chemotherapy as inpatients during the study period. The medical fee for rescue prescription was not considered, because it was included in the bundled payment system for inpatient care in the NHI system in 2016. The costs calculated in Japanese yen (JPY) were converted to the United States dollars (USD) using the exchange rate reported by the Organization for Economic Cooperation and Development (OECD) in 2016 (1 USD = 108.79 JPY) [26].

Table 1 Utility values for chemotherapy-induced nausea and vomiting (CINV) outcomes

Health state	Utility weight		
	Base case	Lower bound	Upper bound
Complete protection	0.790	0.594	0.900
Complete response at best	0.594	0.416	0.772
Incomplete response	0.270	0.189	0.350

Valuing outcomes

The incremental cost-effectiveness ratio (ICER) was calculated to verify the cost-effectiveness of the aprepitant-containing antiemetic regimen. ICER was calculated as follows:

ICER = (cost with PA − cost with NPA) / (QALY with PA − QALY with NPA).

The average medical cost of each group was used for calculation of the ICER of the base case. A discount was not applied to this analysis because the values of drug costs and medical treatment were assumed not to change in the only 5-day observational period in this study. A willingness-to-pay (WTP) threshold of 5 million Japanese yen (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. [27].

Sensitivity analyses

Deterministic and probabilistic sensitivity analyses were performed to assess the 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 the Monte Carlo simulation. In the sensitivity analysis,

Table 2 Utility values for CINV outcomes during the acute and delayed phases

Health state during the acute phase (day 1)	Delayed phase (days 2–5)	5-day QALY		
		Base case	Lower bound	Upper bound
CP	CP	0.011	0.008	0.012
	CRB	0.009	0.006	0.011
	IR	0.005	0.004	0.006
CRB	CP	0.010	0.008	0.012
	CRB	0.008	0.006	0.011
	IR	0.005	0.003	0.006
IR	CP	0.009	0.007	0.011
	CRB	0.007	0.005	0.009
	IR	0.004	0.003	0.005

The 5-day QALY was calculated as follows: utility weight / 365 × 5

CP complete protection, *CRB* complete response at best, *IR* incomplete response

the ranges of parameters varied were 20% for drug costs and for probability. The utilities assigned to CRB and IR were varied by ± 30%, and that assigned to CP was varied between the lower bound equivalent of the CRB health state of 0.594 and the upper bound equivalent of 0.90 (Table 1), as reported by Sun et al. [28].

Cost-utility analyses in this study were conducted using TreeAge® Pro 2014 (TreeAge Software, Inc., Williamstown, MA, USA).

Results

Cost-utility outcomes

The probability of each health state in the 5 days from the onset of chemotherapy is shown in Table 4. In patients who needed aprepitant but did not receive prophylactic aprepitant, the complete response (CR) (i.e., the sum of CP and CRB) rate was 0% in both HEC and MEC. The CR rates of patients were higher in

Table 3 Costs of medical resources

Brand name	Generic name	Cost (USD)
Emend® capsules set 125 mg and 80 mg	Aprepitant	108.36
Nauzerin® tablet 10 mg	Domperidone	0.10
Gasmotin® tablet 5 mg	Mosapride citrate hydrate	0.17
Primperan® injection 10 mg	Metoclopramide hydrochloride	0.52
Novamin® tablet 5 mg	Prochlorperazine maleate	0.09
Decadron® tablet 0.5 mg	Dexamethasone	0.05
Decadron® phosphate injection 3.3 mg	Dexamethasone sodium phosphate	1.73
Aloxi® IV injection 0.75 mg	Palonosetron hydrochloride	137.30
Granisetron injection 1 mg [NK]	Granisetron hydrochloride	11.51
Nasea® OD tablet 0.1 mg	Ramosetron hydrochloride	12.11
Serotone® tablet 10 mg	Azasetron hydrochloride	12.91
Gaster® D tablet 20 mg	Famotidine	0.43
Gaster® injection 20 mg	Famotidine	2.33
Omepral® injection 20 mg	Omeprazole sodium hydrate	4.29
Takepron® OD tablet 15 mg	Lansoprazol	0.82
Atarax®-P solution injection (25 mg/mL)	Hydroxyzine hydrochloride	0.51
Wypax® tablet 0.5 mg	Lorazepam	0.06
Solita®-T No. 1 injection 500 mL	Maintenance IV solution No. 1	1.57
Solita®-T No. 3 injection 200 mL	Maintenance infusion	1.31
Solita®-T No. 3G injection 500 mL	Maintenance infusion (7.5% glucose)	1.43
Lactec® injection 500 mL	Lactated Ringer's solution	1.42
BFluid® injection 500 mL	Vitamin B1, glucose, electrolyte, amino acids	4.34

Source for the medicines: National Health Insurance drug price 2016 in Japan

Table 4 CINV-related health state probabilities

Health state outcome (acute–delayed)	HEC patients ($n = 28$) who				MEC patients ($n = 49$) who			
	Need aprepitant ($n = 12$)		Do not need aprepitant ($n = 16$)		Need aprepitant ($n = 6$)		Do not need aprepitant ($n = 43$)	
	NPA (%)	PA (%)	NPA (%)	PA (%)	NPA (%)	PA (%)	NPA (%)	PA (%)
CP-CP	0	8.3	43.8	50.0	0	33.3	58.1	60.5
CP-CRB	0	25.0	12.5	18.8	0	0	9.3	11.6
CP-IR	41.7	41.7	43.8	31.3	83.3	33.3	30.2	25.6
CRB-CP	0	0	0	0	0	0	0	0
CRB-CRB	0	8.3	0	0	0	16.7	0	0
CRB-IR	33.3	0	0	0	0	16.7	0	0
IR-CP	0	0	0	0	0	0	0	0
IR-CRB	0	0	0	0	0	0	0	0
IR-IR	25.0	16.7	0	0	16.7	0	2.3	2.3
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

The numbers are actual probabilities observed in our previous study [23]

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy, *PA* prophylactic aprepitant, *NPA* no prophylactic aprepitant, *CP* complete protection, *CRB* complete response at best, *IR* incomplete response, *CP-CRB* CP in acute phase and CRB in delayed phase

MEC than in HEC using prophylactic aprepitant (50% and 42%, respectively). In patients who did not need aprepitant, a modest increase in the CR rate by adding prophylactic aprepitant was observed in both HEC and MEC (from 56% to 69% and from 67% to 72%, respectively). The same tendency was observed in variations of quality-adjusted life days (QALDs) (Table 5). QALDs in patients who needed aprepitant were increased more by using prophylactic aprepitant in HEC than in MEC (from 1.67 to 2.37 and from 1.78 to 2.71, respectively). In patients who did not need aprepitant, QALDs were originally higher compared with those who needed aprepitant, and the increments in QALDs by prophylactic aprepitant were small in both HEC and MEC (from 2.94 to 3.15 and from 3.19 to 3.27, respectively).

In patients who needed aprepitant, the ICER was below the WTP threshold in both HEC and MEC (7912 USD/QALY and 27,457 USD/QALY, respectively). In patients who did not need aprepitant, the ICERs were far over the WTP threshold. These results indicate that PA is highly cost-effective when used for patients who need aprepitant.

Sensitivity analysis

Deterministic sensitivity analysis showed that the cost for PA was a major parameter that impacted the cost-effectiveness of aprepitant in patients who need aprepitant, while the probability of the acute CR and that of acute CP to delayed CR

Table 5 Summary of health state outcomes and costs during days 1–5 of chemotherapy

	HEC patients ($n = 28$) who				MEC patients ($n = 49$) who			
	Need aprepitant ($n = 12$)		Do not need aprepitant ($n = 16$)		Need aprepitant ($n = 6$)		Do not need aprepitant ($n = 43$)	
	No PA	PA	No PA	PA	No PA	PA	No PA	PA
Health outcome measure								
Mean number of emetic events	1.75	0	0.25	–	1.00	0.33	0.18	–
Complete response (%)	0	41.7	56.3	68.8	0	50.0	67.4	72.1
Quality-adjusted life days	1.67	2.37	2.94	3.15	1.78	2.71	3.19	3.27
Health care resource measure (USD)								
Antiemetic regimen	37.4	135.4	37.4	135.4	37.4	135.4	37.4	135.4
Rescue medication	91.8	8.5	10.4	10.8	36.0	5.6	3.5	5.1
Total cost	129.2	143.9	47.9	146.2	73.5	141.0	41.0	140.6
Incremental cost-effectiveness ratio (USD/QALY)	7912		175,959		27,457		478,844	

HEC highly emetogenic chemotherapy, *MEC* moderately emetogenic chemotherapy, *PA* prophylactic aprepitant, *QALY* quality-adjusted life year

(CP-CR) after PA were the main parameters that affected the results in those who did not need aprepitant (Fig. 2a). The results of the probabilistic sensitivity analysis showed that PA provided benefit in 98% and 95% of patients who needed aprepitant and received HEC and MEC, respectively (Fig. 2b). On the other hand, in patients who did not need aprepitant, nearly 100% of patients who received HEC and MEC did not obtain benefit from PA (99.4% and 99.6%, respectively). The results of the bi-dimensional analysis of the scatter plots showed that all dots were distributed in the area of increment in effectiveness on the horizontal axis, regardless of the necessity of aprepitant and of HEC or MEC, while the distance from the intersection was different in the groups (Fig. 2c). The distribution of patient scatter plots from the line of the WTP threshold also differed. Most dots of patients who needed aprepitant were distributed under the line of the WTP threshold, while those of patients who did not need aprepitant were over the WTP threshold line. These results indicated that aprepitant was more effective against the increment in cost for patients who needed it, but it was too costly with little increment in effectiveness for patients who did not need aprepitant.

Discussion

This is the first report of a cost-utility analysis of an aprepitant-containing antiemetic regimen focusing on the necessity of aprepitant for patients from the Japanese National Health Insurance payer perspective, within the scope of our literature search.

The results of this study suggest that aprepitant was cost-effective for patients who needed it and not for patients who did not need it, regardless of whether patients received HEC or MEC. Aprepitant was also more cost-effective for patients who received HEC than for those who received MEC. The results of this study partly support previous reports of the cost-effectiveness of aprepitant by Lordick et al. [16] in Germany, Humphreys et al. [18] in the UK, Annemans et al. [19] in Belgium, Lopes et al. [21] in Singapore, and Chan et al. [20] in Hong Kong. These reports all concluded that aprepitant showed superior cost-effectiveness in analyses using a decision-analytic model similar to that of the present study. In contrast, Moore et al. [17] reported only modest incremental benefits of aprepitant and pointed out that the cost-effectiveness of aprepitant would be obtained only when the

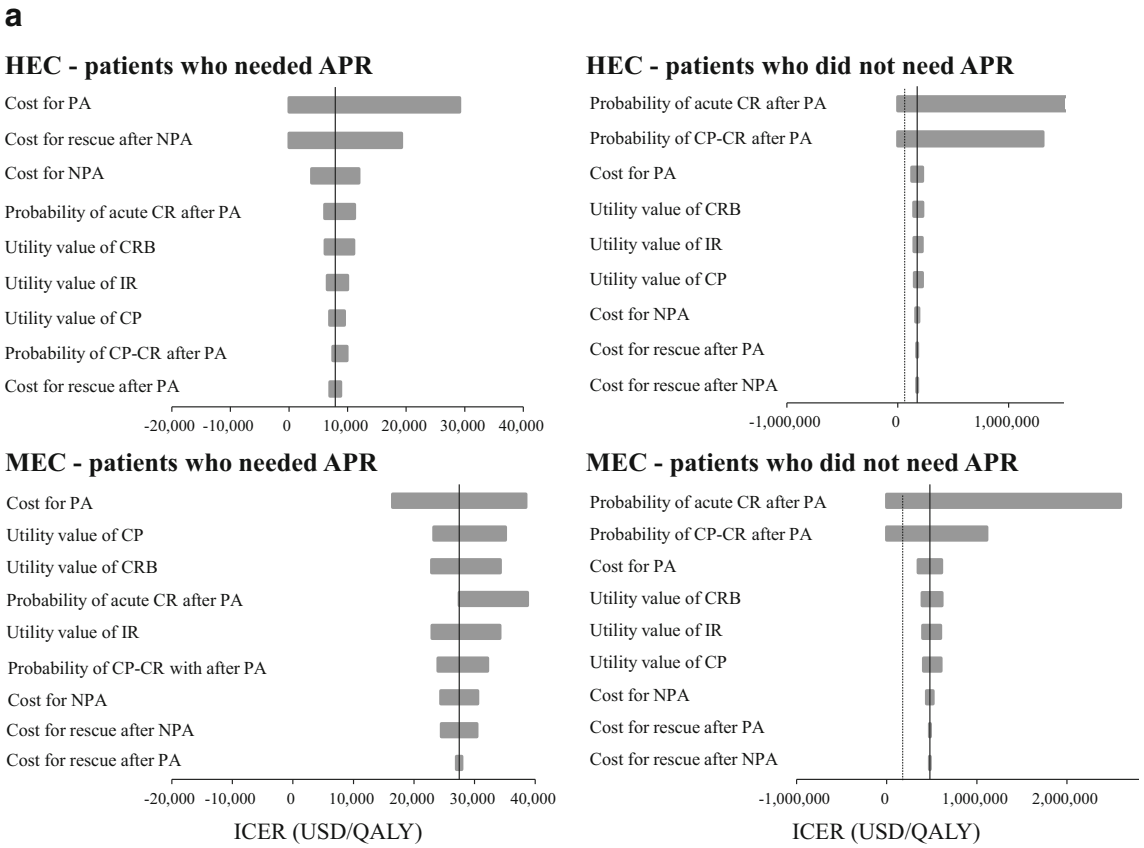

Fig. 2 The results of sensitivity analyses by deterministic analysis using the tornado method (**a**) and probabilistic analyses by the Monte Carlo simulation for the cost-effectiveness acceptability (**b**) and for the incremental cost-effectiveness ratio (**c**). HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; CP, complete protection; CRB, complete response at best; IR, incomplete response; CP-CR, acute phase CP and delayed phase CP or CRB; QALY, quality-adjusted life year; USD, United States dollar; WTP, willingness to pay

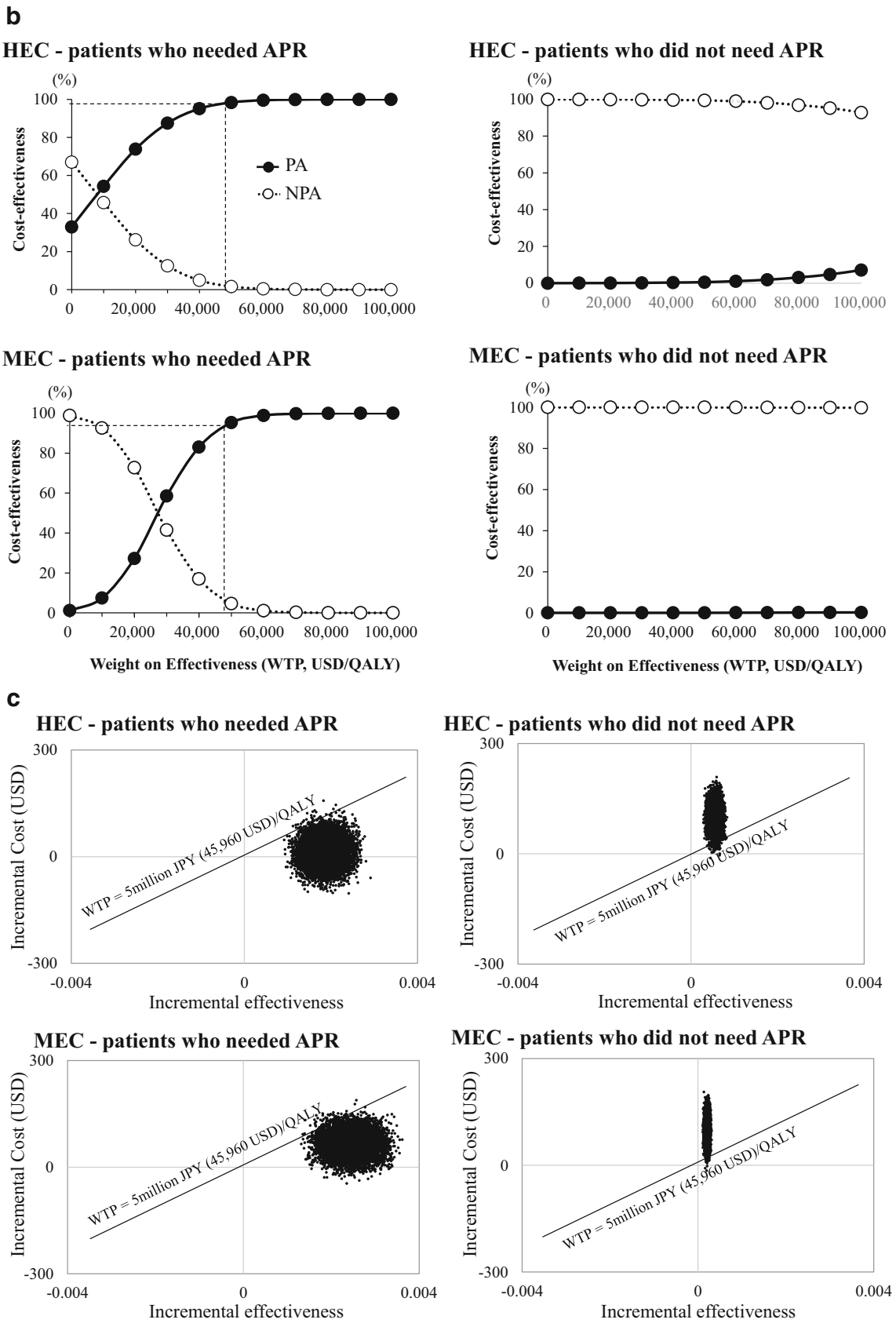

Fig. 2 (continued)

frequent delayed CINV required costly rescue medications. In the present study, patients who obtained the benefit of aprepitant were those who needed aprepitant, and they required costly rescue treatment when they did not receive prophylactic aprepitant. This analysis did not include health care costs of CINV and additional outpatient visits, ER visits, and re-hospitalizations, because all patients in this study were inpatients during the study period, and the health care costs of CINV were included in the bundled payment system in the Japanese NHI system. If the analysis included these health care costs as outpatient setting, the total medical costs for patients who did not use PA and needed aprepitant would become much larger. Thus, the incremental cost (cost with PA − cost with NPA) and ICER would become smaller, making the trend of the results of this study more significant.

A meta-analysis that integrated 17 clinical trials indicated that the use of aprepitant caused an increase in the risk of infection [29]. Aprepitant should ideally be used for patients who truly need it, considering this disadvantage. In our previous study referenced in this analysis, benzodiazepine use was the only negative demographic factor for the necessity of aprepitant [23]. Further detailed subgroup analysis showed that patients who had two of the three factors, no use of benzodiazepine, no regular intake of alcohol, and no daily bowel movements needed aprepitant more frequently (data not shown). Other than these factors, younger age and female sex have been constantly reported as risk factors for CINV [30–35]. Dranitsaris et al. [36] developed a prediction tool to identify cancer patients at high risk of CINV, scoring predictive risk factors. Among these, CINV in the prior cycle of chemotherapy and using non-prescribed antiemetics at home were patient factors with the highest odds ratio for developing CINV. Genetic polymorphisms in genes relating to individual risks of CINV have been described. Mukoyama et al. [37] reported that polymorphisms in the genes coding dopamine D_2 receptor, serotonin 5-HT_3C receptor, and catechol-*O*-methyltransferase were associated with the frequency of CINV. Variants in a gene coding for 5-HT_3RAs, drug transporter ATP-binding cassette B1 protein, one of the multi-drug-resistant transporter protein, were shown to be associated with severe acute nausea [38]. However, these risk factors have not yet been established as criteria to definite the need for aprepitant. Currently, we have no effective screening methods to identify high-risk patients for CINV before chemotherapy, and we agree to follow the current antiemetic guidelines recommending the uniform use of aprepitant. Further studies are warranted for more accurate risk assessment of CINV to identify these patients before starting chemotherapy. This will also promote the optimal use of aprepitant in terms of medical economy as well.

The model analysis in the current study has several limitations. First, the fixed utility values in each health condition were derived from reports on European and American patients [18, 24, 25]. Potential biases from using these values from different races cannot be excluded. Second, probabilities of each health state were estimated based on our previous study with a small sample size of patients in a single institute [23]. To deal with the uncertainties associated with these potential biases, deterministic and probabilistic sensitivity analyses were performed, and the effects of utility values on the results were modest in patients who needed aprepitant. Although we did not analyze in this study, other way to estimate the uncertainty around the patient clinical outcomes, including the bootstrap method, might also be considered [39].

In conclusion, regardless of HEC or MEC, an antiemetic regimen containing aprepitant was cost-effective for patients who needed aprepitant but not for patients who did not need it. These result warrant further studies for selecting patients before chemotherapy who truly need NK_1RAs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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