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Original Article

Cost-effective use of aprepitant in multiple-day chemotherapy regimens

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Abstract: Background: Aprepitant is a highly effective but expensive antiemetic drug. Repeated treatment with aprepitant is required to control emesis in multiple-day chemotherapy. In the present study, cost-effectiveness analysis was carried out for the use of aprepitant in multiple-day chemotherapy, including FP (5-fluorouracil, cisplatin) for head and neck cancer and BEP (bleomycin, etoposide, cisplatin) for germ cell carcinoma. Patients and Methods: A single center, retrospective study was carried out in 46 patients receiving multiple-day chemotherapy. Standard antiemetic medication included aprepitant for 3 days for FP and for 5 days for BEP, in combination with 5-HT_3 receptor antagonist and dexamethasone. In the multiple aprepitant treatment groups, aprepitant was added to the standard medication for another 2 days (FP) or 3 days (BEP). Complete protection (CP: no vomiting, no significant nausea and no rescue) was assessed during 7 days for FP or 9 days for BEP as the primary endpoint. Health states were assessed by quality-adjusted life-year (QALY) using the published utility weights. For cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) was calculated, where the difference in the QALY was used. Results: The rate of CP was improved by multiple aprepitant treatment both in FP (54% *versus* 20%) and BEP (54% *versus* 0%). The ICERs calculated for FP and BEP were USD 17,167 or GBP 11,135/QALY gained, and USD 38,543 or GBP 25,001/QALY gained, respectively, both of which were within the threshold values configured in the UK or US. Conclusions: Repeated administration of aprepitant was found to be cost-effective for the multiple-day chemotherapy.

Keywords: Multiple-day chemotherapy, complete protection, aprepitant, quality-adjusted life year, incremental cost-effectiveness ratio

Introduction

Chemotherapy-induced nausea and vomiting (CINV) still restrict patients' activities of daily living and decrease quality of life (QOL) [1-3]. Appropriate antiemetic medication during cancer chemotherapy is required not only to improve patients' QOL but also to maintain the dose-intensity of chemotherapy. Several clinical practice guidelines for prevention of CINV have been advocated from the Multinational Association of Supportive Care in Cancer (MASCC) [4], the American Society of Clinical Oncology (ASCO) [5], the National Comprehensive Cancer Network (NCCN) [6], and the Japanese Society of Clinical Oncology (JSCO) [7], in which chemotherapy is classified into four categories based on the emetogenicity, including high emetic risk chemotherapy (HEC), moderate emetic risk chemotherapy (MEC), low emetic risk chemotherapy, and minimal emetic risk chemotherapy. The guidelines recommend several antiemetic medications according to the emetic risk category of chemotherapy used primarily as the single-day regimen.

Although the guideline-consistent antiemetic medication has been reported to yield better control of CINV than guideline-inconsistent medication for the single-day chemotherapy regimen [8-10], it is still difficult to control CINV associated with multiple-day chemotherapy regimens such as the combination of cisplatin with bleomycin and etoposide (BEP) or with etoposide (EP) for germ cell tumor [11-13] and the combination chemotherapy with cisplatin and 5-fluorouracil (FP) for head and neck cancer [14, 15].

Table 1. Anti-emetic and each regimen costs

Costs	Cost (JPY)
Anti-emetic costs	
Aprepitant 125 mg tab	4985.2
Aprepitant 80 mg tab	3402.3
Granisetron 3 mg IV	4214.0
Dexamethasone 6.6 mg IV	182.0
Regimen costs	
Standard regimen for FP	17096.0
Standard regimen for BEP	41120.0
Mulitiple aprepitant treatment regimen for FP	23900.0
Mulitiple aprepitant treatment regimen for BEP	47925.0
Rescue treatment	1300.0

We previously reported in head and neck cancer patients receiving FP (cisplatin 80 mg/m^2, day 1; 5-fluorouracil 800 mg/m^2, days 1-5) that the additional treatment with aprepitant on days 4-5 of the chemotherapy to the standard antiemetic medication (granisetron, aprepitant and dexamethasone on day 1, aprepitant and dexamethasone on days 2-3, and dexamethasone on days 4-5) showed a better overall complete response (67% *versus* 40%) or overall complete protection from vomiting (100% *versus* 60%) [15].

On the other hand, Albany et al [11] reported in patients receiving BEP for testicular cancer that administration of aprepitant for 5 days (days 3-7 of chemotherapy) significantly improves the rate of complete response as compared with aprepitant non-treatment group (42% versus 13%, P<0.001).

Aprepitant is a highly effective antiemetic drug that blocks neurokin in NK_1 receptor [16, 17] but is more expensive than other antiemetic drugs. Humphreys et al [18] reported the cost-effectiveness of aprepitant in breast cancer patients receiving single-day MEC, including anthracycline and cyclophosphamide combination chemotherapy. They showed that aprepitant causes a predicted gain of 0.0048 quality-adjusted life years (QALYs) as compared with the standard antiemetic regimen without aprepitant, and that the incremental cost effectiveness ratio (ICER) is GBP 10,847/QALY gained, which is below the threshold commonly accepted in the UK (GBP 20,000-30,000/QALY).

In the present study, we evaluated the cost-effectiveness of aprepitant in multiple-day regimens such as FP and BEP.

Patients and methods

Study setting and patients

The present study was carried out in accordance with the guidelines for the care for human study adopted by the Ethics Committee of the Gifu Graduate School of Medicine (approved no.27-33 of the Institutional Review Board).

Thirty one patients who received the first cycle of FP (5-FU 800 mg/m^2, days 1-5; cisplatin 80 mg/m^2, day 1) for head and neck cancer during October 2010 and December 2011, and 15 patients receiving the first cycle of BEP (bleomycin 30 mg/body, days 1, 8 and 15; etoposide 100 mg/m^2, days 1-5; cisplatin 20 mg/m^2; days 1-5) for testicular germ cell carcinoma during November 2010 and September 2014 in Gifu University Hospital were the subjects of the present study.

Data collection

Patients' laboratory data and the data on the control of CINV such as the occurrence or grade of nausea and vomiting, presence or absence of rescue treatment with antiemetic drugs were collected from electronic medical record and pharmaceutical care record. The severity of nausea and vomiting was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [19].

Antiemetic medication

In FP, the standard antiemetic medication was the administration of aprepitant (125 mg, oral), granisetron (3 mg, intravenous) and dexamethasone (9.9 mg, intravenous) before chemotherapy, followed by subsequent treatment with aprepitant (80 mg/day, oral, days 2-3) and dexamethasone (6.6 mg, intravenous, days 2-5). In case of BEP, granisetron (3 mg/day, days 1-5), dexamethasone (9.9 mg/day, intravenous, day 1 and 6.6 mg, intravenous, days 2-7) and aprepitant (125 mg, oral, day 1 and 80 mg/day, oral, days 2-5) were treated as the standard antiemetic medication. In the multi-

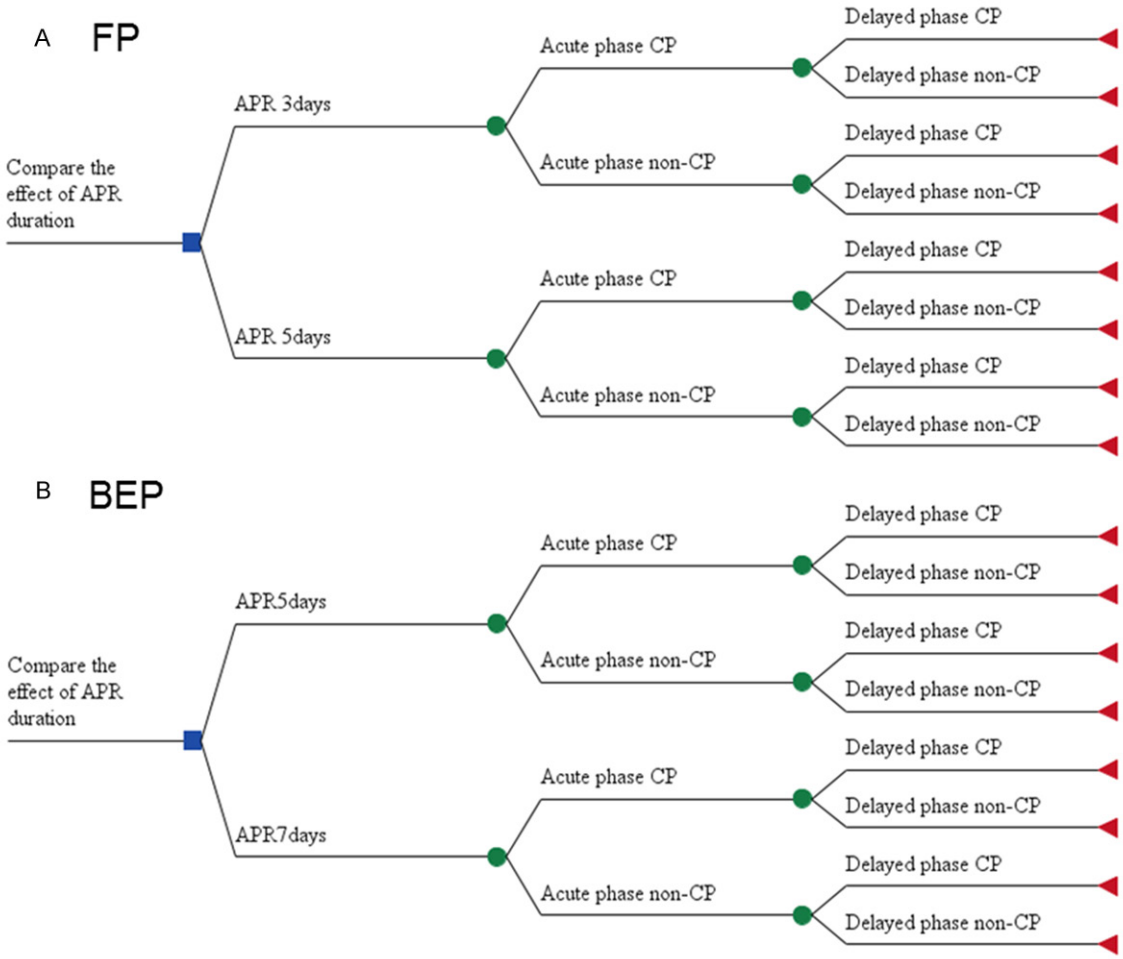

Figure 1. Model decision tree depicting between CP and non-CP in the standard treatment group and multiple-aprepitant treatment group for FP (A) and BEP (B).

ple-aprepitant treatment group, aprepitant (80 mg/day, oral) was added on days 4 and 5 for FP, or days 6-7 for BEP to the standard antiemetic medication.

Evaluation of the control of CINV

The primary endpoint was complete protection (CP: no vomiting, no significant nausea and no rescue). Secondary endpoints were complete response (CR: no vomiting and no rescue), proportion of patients without nausea or vomiting were also assessed during acute (within 24 h after chemotherapy for FP or days 1-5 of chemotherapy for BEP) and delayed (2-5 days of chemotherapy for FP or 6-9 days for BEP) periods. The occurrence of vomiting, significant nausea or addition of rescue during the evaluation period was regarded as incomplete response (IR). The significant nausea was defined as the symptom with grade 2 or higher, as assessed by CTCAE v4.0.

Cost-effectiveness analysis

The cost-effectiveness analysis was carried out according to the method of Humphreys et al [18] with modifications. Briefly, the quality-adjusted life-day (QALD) was assessed from the health states during acute and delayed periods, in which the health states were classified into three states such as CP, CR and IR. The utility weight of each health state was assumed to be 0.79 for CP, 0.594 for CR, and 0.27 for IR, according to the data reported by Humphreys et al [18]. The total QALDs were calculated by summing up QALDs during acute and delayed periods. The QALY was then predicted by dividing the total QALDs by 365 days. The incremental cost-effective ratio (ICER) was used as a

Table 2. Demographics of patients

(A) FP	Standard treatment group	Multiple-aprepitant treatment group	*P*-values
Age (years old)	51.2	61.5	0.013[a)]
Body weight (kg)	52.00±3.98	55.71±1.97	0.448[b)]
Gender (male/female)	2/3	17/9	0.350[c)]
Serum albumin (g/dL)	3.78±0.19	3.79±0.068	0.967[b)]
Aspartate aminotransferase (IU/L)	13.00±3.89	19.31±3.74	0.264[b)]
Creatinine clearence (mL/min)	95.75 mine	86.32±3.65	0.340[b)]
Neutrophil count (/μL)	4204±1091	3584±228	0.606[b)]
Leukocytes count (/μL)	6552±1156	5834±296	0.576[b)]
Hemoglobin (g/dL)	11.62±0.96	13.03±0.294	0.226[b)]
Platelet count (× 10^4/μL)	26.08±1.66	22.25±1.13	0.091[b)]
(B) BEP			
Age (years old)	36.6	27	0.120[a)]
Body weight (kg)	64.90±8.77	66.98±14.10	0.814[b)]
Gender (male/female)	3/0	12/0	1.000[c)]
Metastasis (%)	66.7	91.7	0.371[c)]
Serum albumin (g/dL)	4.30±0.72	4.12±0.61	0.659[b)]
Aspartate aminotransferase (IU/L)	21.33±6.11	20.58±5.32	0.834[b)]
Creatinine clearence (mL/min)	74.07 mine	74.76 mine	0.960[b)]
Total bilirubin (mg/dL)	0.7±0.17	0.64±0.23	0.692[b)]
Neutrophil count (/μL)	5287±2080	3858±1654	0.222[b)]
Leukocytes count (/μL)	7647±1473	7168±2381	0.749[b)]
Hemoglobin (g/dL)	15.70±1.42	14.15±1.76	0.185[b)]
Platelet count (× 10^4/μL)	25.03±5.08	20.97±5.11	0.239[b)]
Amylase (mg/dL)	74.00±1.73	68.72±14.24	0.543[b)]

a) Mann-Whitney U-test, b) t-test, c) Fisher's exact probability test; FP: 5-fluorouracil, cisplatin, BEPbleomycin, etoposide, cisplatin).

measure for the cost-effectiveness of the multiple-aprepitant treatment regimen relative to the standard treatment regimen, and calculated by dividing the difference in the cost for antiemetic medication by the difference in QALDs or QALY between the two groups.

Unit costing

Anti-emetic costs and each regimen costs were shown in **Table 1**. We added mainly olanzapine as a rescue medication to the antiemetic medication. Thus, rescue medication cost was the cost of olanzapine 5 mg/day for 5. The costs of clinic and laboratory based resources except anti-emetics were not included in the present cost-effectiveness analysis.

Sensitivity analysis

As shown in **Figure 1**, the decision tree was prepared between CP and non-CP in the standard treatment group and multiple-aprepitant treatment group for FP and BEP using TreeAge Pro 2014 (TreeAge Software, Inc., MA, USA). Sensitivity analyses were performed to evaluate the uncertainty of the model by fluctuating the rate of CP and additional drug cost stochastically by the method of β distribution and normal distribution, respectively. The acceptability curves were plotted the beneficial probability of the cost-effectiveness in each group by altering the threshold of ICER, and the probability of cost-effectiveness was estimated from the acceptability curves at the upper limit of ICER calculated based on the value used in the UK (GBP 20,000-30,000/QALY or GBP 54.8-82.2/QALD) or US (USD 50,000/QALY or USD 137/QALD). In addition, the beneficial probability of cost-effectiveness was assessed by the sensitivity analyses based on 1,000 times Monte Carlo simulations.

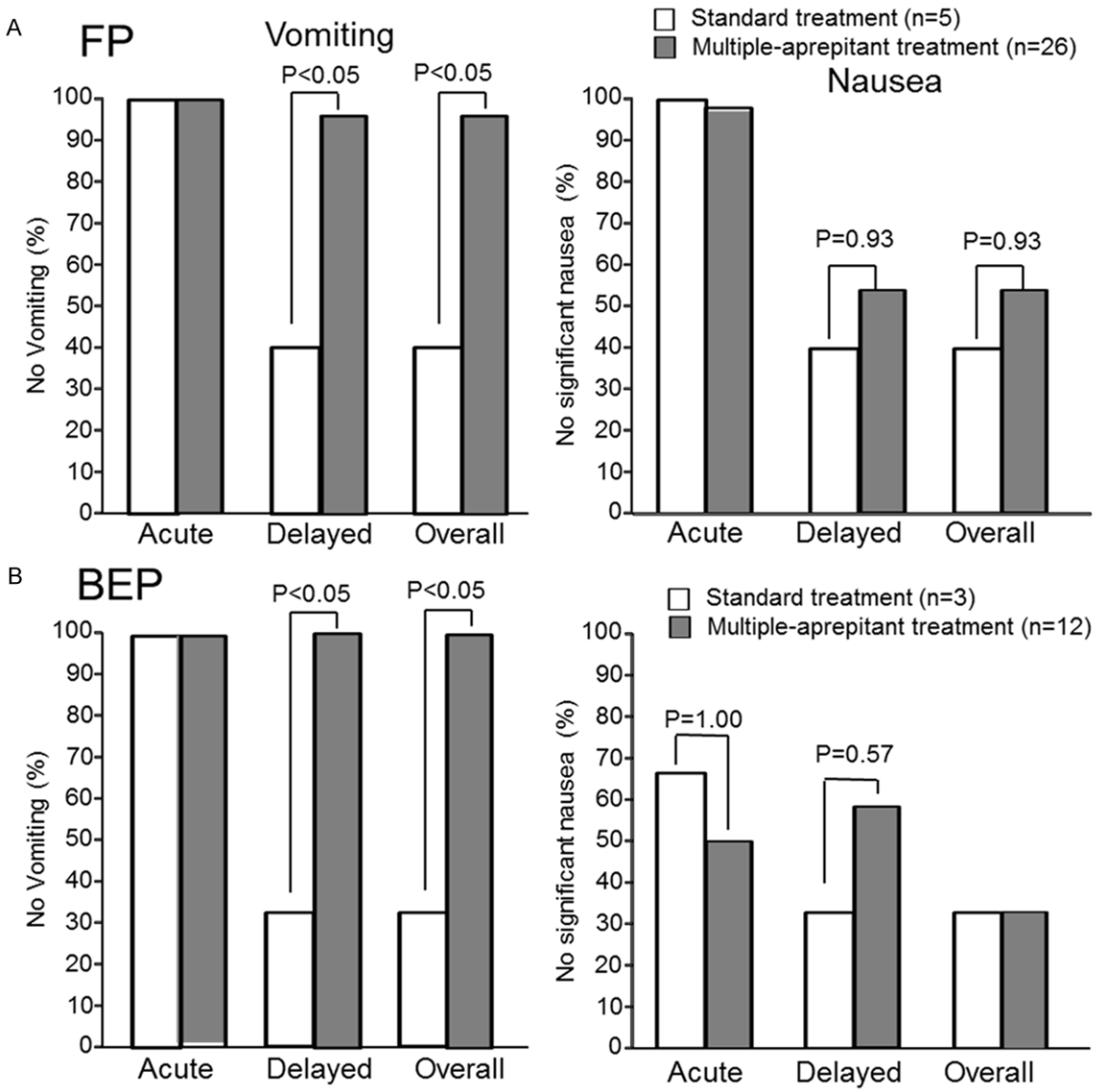

Figure 2. Comparison of antiemetic effects of the standard medication with and without multiple aprepitant treatment in patients receiving FP for head and neck cancer (A) and BEP for testicular germ cell carcinoma (B). The proportion of no vomiting or no significant nausea during acute, delayed and overall periods was assessed. Standard antiemetic medication was a combination of granisetron (3 mg, day 1), dexamethasone (9.9 mg, day 1 and 8 mg, days 2-5) and aprepitant (125 mg, day 1 and 80 mg, days 2-3) for FP, or a combination of granisetron (3 mg, days 1-5), dexamethasone (9.9 mg, day 1 and 8 mg, days 2-7) and aprepitant (125 mg, day 1 and 80 mg, days 2-5) for BEP.

Statistical analyses

Data was analyzed by using IBM SPSS Statistics ver. 21 (IBM Japan Services Co., Ltd., Tokyo, Japan). Parametric variables were analyzed using *t*-test, while nonparametric data were analyzed by the Mann-Whitney U-test or chi-square-test. *P* value of less than 0.05 was considered statistically significant.

Results

Demographics of patients

In patients with head and neck cancer receiving FP, there were no significant differences in the patients' demographics except for age between the standard treatment group and multiple-aprepitant treatment group (**Table 2**).

Table 3. Control of CINV and cost-effectiveness between multiple aprepitant treatment group and standard aprepitant treatment group in patients receiving FP or BEP

	FP regimen				BEP regimen			
	APR for 3 days (n=5)		APR for 5 days (n=26)		APR for 5 days (n=3)		APR for 7 days (n=12)	
	Acute (day 1)	Delayed (days 2-7)	Acute (day 1)	Delayed (days 2-7)	Acute (day 1-5)	Delayed (days 6-9)	Acute (day 1-5)	Delayed (days 6-9)
Complete protection (CP)	100%	20%	100%	54%	67%	0%	50%	58%
Complete response (CR)	0%	0%	0%	8%	33%	33%	25%	25%
Incomplete response (IR)	0%	80%	0%	38%	0%	67%	25%	17%
QALDs	0.79	2.244	0.79	3.45	3.62	1.51	3.06	2.62
QALY	0.0022	0.0061	0.0022	0.0095	0.0099	0.0041	0.0084	0.0072
QALDs gained			1.21				0.54	
QALYs gained			0.0033				0.0015	
Costs	9,563	10,207	9,563	17,012	40,574	546	40,574	7,351
Difference in costs			6,805					6,805
ICER/QALD gained			5,644					12,672
ICER/QALY gained			2,060, 224					4,625, 101

FP: 5-fluorouracil, cisplatin, BEP: bleomycin, etoposide, cisplatin, APR: aprepitant, QALD: quality-adjusted life day, QALY: quality-adjusted life year, ICER: incremental cost-effectiveness ratio.

Moreover, no significant differences in the demographics of patients receiving BEP for testicular germ cell carcinoma between the two groups (**Table 2**).

Control of CINV

In FP regimen, the rates of complete inhibition of acute and delayed vomiting were 100% and 40%, respectively, in the standard treatment group, while the values were 100% and 96.2%, respectively, in the multiple-aprepitant treatment group (**Figure 2A**). There was a significant (P<0.05) difference in the rate of complete inhibition of delayed vomiting between the two groups. The rates of inhibition of acute and delayed nausea were 100% and 40%, respectively, in the standard treatment group, whereas the values were 98.6% and 53.8%, respectively, in the multiple-aprepitant treatment group. However, there were no significant differences in the rates of complete inhibition of nausea between the two groups. The rates of CP were 100% and 20% during acute and delayed periods, respectively, in the standard treatment group, whereas the rates were 100% and 53.8% during acute and delayed periods, respectively, in the multiple-aprepitant treatment group (**Table 2**). The rate of CP tended to be improved, though not significantly, by multiple aprepitant treatment (53.8% *versus* 20%, P=0.18).

On the other hand, in patients receiving BEP, the rates of complete inhibition of acute and delayed vomiting were 100% and 33.3%, respectively, in the standard treatment group, while the values were both 98.6% in the multiple-aprepitant treatment group (**Figure 2B**). There was a significant (P<0.05) difference in the rate of complete inhibition of delayed vomiting between the two groups. On the other hand, there were no significant differences in the rates of complete inhibition of nausea between the two groups (acute nausea: 66.7% *versus* 50%; delayed nausea: 33.3% *versus* 58.3% in the standard treatment group *versus* multiple-aprepitant treatment group, respectively). The rates of CP were 66.7% and 0% during acute and delayed periods, respectively, in the standard treatment group, 50% and 58.3% during acute and delayed periods, respectively, in the multiple-aprepitant treatment group (**Table 2**). The rate of CP tended to be improved, though not significantly, by multiple aprepitant treatment (53.8% *versus* 0%, P=0.20).

Cost-effectiveness of multiple aprepitant treatment in FP

The health states of patients receiving FP were 3.03 QALDs (acute: 0.79 QALDs; delayed: 2.24 QALDs) in the standard treatment group, and 4.24 QALDs (acute: 0.79 QALDs; delayed: 3.45 QALDs) in the multiple-aprepitant treatment group (**Table 3**). Therefore, the multiple aprepitant treatment gained 1.21 QALDs or 0.0033 QALY. Difference in the cost for antiemetic medication between the standard group and multi-

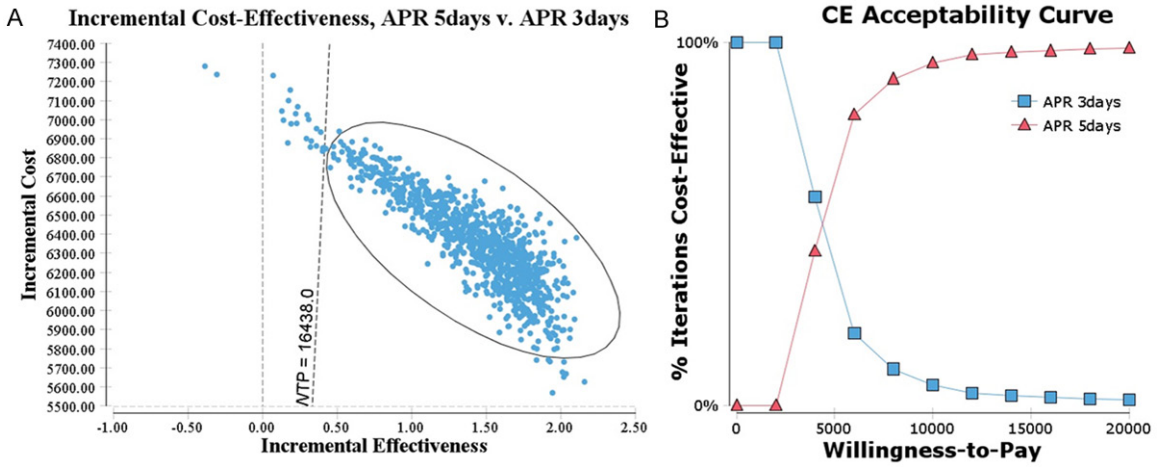

Figure 3. Cost-effectiveness analysis of multiple aprepitant treatment in FP. Distribution of cost-effectiveness ratio based on 1,000 times Monte Carlo simulation (A) if the threshold of ICER was set to JPY16,438 (USD 137)/QALD or JPY 6 milion (USD 50,000/QALY) and the acceptability curve for cost-effectiveness (B).

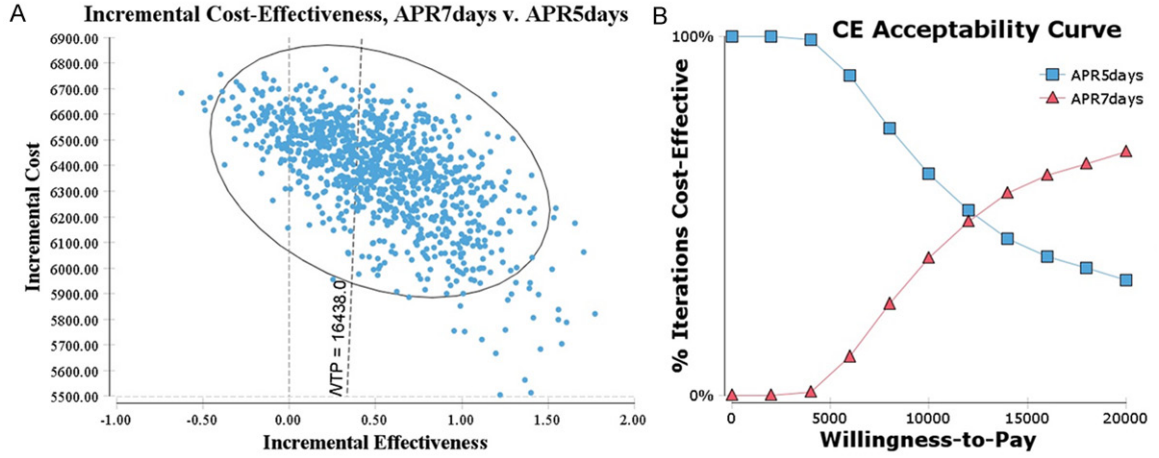

Figure 4. Cost-effectiveness analysis of multiple aprepitant treatment in BEP. Distribution of cost-effectiveness ratio based on 1,000 times Monte Carlo simulation (A) if the threshold of ICER was set to JPY16,438 (USD 137)/QALD or JPY 6 milion (USD 50,000/QALY) and the acceptability curve for cost-effectiveness (B).

ple-aprepitant group was JPY 6,804 (USD 56.7), resulting in the ICER was JPY 5,644 (USD 47.0)/QALD gained or JPY 2,060,042 (USD 17,167)/QALY gained (**Table 3**). The ICER was within a range of threshold ICER value configured in the US (USD 50,000/QALY) or UK (GBP 30,000/QALY). Sensitivity analyses based on 1,000 times Monte Carlo simulations indicated that the beneficial probability of cost-effectiveness was 97.5% in the multiple-aprepitant treatment group, when the threshold of ICER was set to JPY 16,438 (USD 137)/QALD (JPY 6,000,000/QALY or USD 50,000/QALY) (**Figure 3A**). Acceptability curve showed the probability of cost-effectiveness of the multiple-aprepitant treatment was indicated over 95% (**Figure 3B**).

Cost-effectiveness of multiple aprepitant treatment in BEP

The health states of patients receiving BEP were 3.62 QALDs and 1.51 QALDs during acute and delayed periods, respectively, in the standard treatment group, while the values in the multiple-aprepitant treatment group were 3.06 QALDs and 2.62 QALDs during acute and delayed periods, respectively in the multiple-aprepitant treatment group (**Table 3**). Thus, the multiple aprepitant treatment gained 0.54

QALDs or 0.0015 QALY (**Table 3**). The ICER was JPY 12,672 (USD 106/QALD) or JPY 4,625,101 (USD 38,543/QALY) that was within the threshold ICER used in the US (USD 50,000/QALY) or UK (GBP 30,000/QALY). Sensitivity analyses based on 1,000 times Monte Carlo simulations indicated that the beneficial probability of cost-effectiveness was 55.7% in the multiple-aprepitant treatment group, when the threshold of ICER was set to JPY 16,438 (USD 137)/QALD (JPN 6,000,000/QALY or USD 50,000/QALY) (**Figure 4A**). Acceptability curve showed that the probability of cost-effectiveness of the multiple-aprepitant treatment was approximately 60% (**Figure 4B**).

Discussion

FP chemotherapy has been shown as the effective combination chemotherapy for locally advanced squamous cell carcinoma of the head and neck [20], although it causes serious (grade 3-4) adverse events, including nausea and vomiting. FP (cisplatin 80 mg/m^2, day 1; 5-FU 800 mg/m^2, days 1-5) used in the present study is a single-day HEC with multiple-day low risk chemotherapy regimen, in which the emetic risk period was considered to be during 5 days after chemotherapy. On the other hand, BEP (bleomycin 30 mg/body, days 1, 8 and 15; etoposide 100 mg/m^2, days 1-5; cisplatin 20 mg/m^2; days 1-5) for germ cell carcinoma is a multiple-day HEC regimen, in which the emetic risk period was considered to be during 7 days after chemotherapy consisting of acute period for 5 days and following delayed period for 2 days. Therefore, the guideline-recommended standard antiemetic medication for FP is considered to include three drug combination of 5-HT$_3$ receptor antagonist (day 1), dexamethasone (12 mg/day, day 1 and 8 mg/day, days 2-5) and aprepitant (125 mg/day, day 1 and 80 mg/day, days 2-3) before chemotherapy, while that for BEP is three drug combination of 5-HT$_3$ receptor antagonist (days 1-5), dexamethasone (12 mg/day, day 1 and 8 mg/day, days 2-5) and aprepitant (125 mg/day, day 1 and 80 mg/day, days 2-5).

In our previous report, vomiting occurs on days 6-7 in patients receiving FP with the standard antiemetic medication and the addition of aprepitant on days 4 and 5 completely inhibits the incidence of vomiting during 7 days after chemotherapy [15]. In the present study, vomiting occurred in one patient (3.8%) of 26 patients in multiple-aprepitant treatment (5 days) group, which was significantly ($P<0.05$) lower than that (60%, 3 of 5 patients) in the standard antiemetic medication group, although CP had a tendency to be higher in multiple-aprepitant treatment group.

Humphreys et al [18] reported the cost-effectiveness of aprepitant in breast cancer patients, in which the health states were estimated by using the utility weights of 0.79 for CP, 0.594 for CR, and 0.27 for IR. Based on this assumption, the health states during 7 days in patients receiving FP was estimated to be 3.03 QALDs (0.0083 QALYs) in the standard treatment group and 4.24 QALDs (0.0117 QALYs) in the multiple-aprepitant treatment group, thereby suggesting 1.21 QALDs (0.0033 QALYs) gained by multiple-aprepitant treatment. The difference in the cost for antiemetic medication between the standard group and multiple-aprepitant group was JPY 6,804 (USD 56.7, GBP 36.8), therefore the ICER was JPY 5,644 (USD 47.0, GBP 30.5)/QALD gained or JPY 2.06 million (USD 17,167 or GBP 11,136)/QALY gained. The estimated ICER was within a range of value configured in the US (USD 50,000/QALY) or UK (GBP 30,000/QALY). Therefore, administration of aprepitant for 5 days in patients receiving FP was found to be cost-effective.

On the other hand, BEP chemotherapy is highly effective for patients with metastatic non-seminomatous germ cell tumors [21-23], however, it causes a number of toxicities such as nausea and vomiting, nephrotoxicity and ototoxicity [24].

In the present study, CP was poor during acute and delayed periods (67% and 33%, respectively) even addition of aprepitant for 5 days to the standard two-drug antiemetic medication. The control rates of nausea and vomiting were both 33% during delayed period. It was notable that the addition of aprepitant for 7 days completely prevented the incidence of vomiting ($P<0.05$) but not nausea, in which the CP during acute and delayed periods were 50% and 58%, respectively. There has been hitherto no study comparing the effect of multiple-day aprepitant treatment with that of 3-day aprepitant treatment. Albany et al [25] reported by a random-

ized placebo control study evaluating the addition of aprepitant to the standard two-drug antiemetic regimen in patients receiving BEP for testicular germ cell carcinoma that aprepitant significantly improved CR during overall (days 1 through 8) period (42% versus 13%, P<0.001). Moreover, the proportion of patients without vomiting episodes was also significantly higher in aprepitant group than in placebo group (80% versus 52%, P<0.001), although the incidence of nausea assessed by patients with VAS scale is not significantly different between the two groups. Hamada et al [26] also reported by an open-label, single-arm, multicenter study in patients receiving 5-day cisplatin (20 mg/m^2)-based regimens, including BEP and VIP (etoposide, ifosfamide, cisplatin), for testicular germ cell carcinoma that the rates of CR and CP are 90% and 80%, respectively, during overall period in the first chemotherapy cycle by the addition of aprepitant (125 mg, day 1, 80 mg, days 2-5) to the standard antiemetic medication, including palonosetron (0.75 mg, day 1) and dexamethasone (9.9 mg, day 1, 6.6 mg, days 2 to 8). At present, we could not explain the reason why CP was much lower in the present study (33%) than in the data reported by Hamada et al [26]. The use of palonosetoron, a second generation 5-HT$_3$ receptor antagonist that is active in preventing only acute but also delayed CINV [27] may be due at least in part to the higher rate of CP in their data.

On the other hand, Olver et al [28] have evaluated the effect of additional treatment with aprepitant for 7 days by an open-label, single-arm, multi-center study in patients receiving 5-day cisplatin (20 mg/m^2)-based regimens, including BEP, EP (etoposide, cisplatin) and VIP, for germ cell carcinoma. They showed that the rates of CR and complete inhibition of no nausea during overall period (days 1-7) in the first cycle are 41% and 27%, respectively, in patients who received aprepitant (125 mg, day 1, 80 mg, days 2-7) in combination with 5HT$_3$ receptor antagonist (days 1-5) and dexamethasone (8 mg, days 1-8). This antiemetic medication used in their study was consistent with that used in the present study. Moreover, the rate of CP or complete inhibition of nausea during overall period was quite similar between the two studies.

In the present study, the cost-effectiveness analysis indicated that the QALDs were 5.13 (0.0141 QALYs) and 5.68 (0.0156 QALYs), respectively, in the standard treatment group and multiple aprepitant treatment group, thereby estimating that the multiple aprepitant treatment caused the gain of 0.54 QALDs (0.0015 QALYs). The ICER was JPY 12,672 (USD 105.6, GBP 68.5)/QALD gain or JPY 4,625,101 (USD 38,543, GBP 25,001)/QALY gain. On the assumption that the ceiling value of ICER is assumed to be USD 50,000/QALY gain or GBP 30,000/QALY gain, the addition of 7-day administration of aprepitant is considered to be cost-effective.

In conclusion, the effect of multiple aprepitant treatment in combination with the standard antiemetic medication on the control of CINV was found to be more effective than the standard antiemetic medication for prevention of CINV in patients receiving multiple-day chemotherapy regimens such as FP for head and neck cancer and BEP for testicular germ cell carcinoma. Moreover, the present multiple aprepitant treatment for 5 days in case of FP and for 7 days in case of BEP was cost-effective, based on the assumption of the upper limit of ICER configured in the US and UK.

Disclosure of conflict of interest

None.

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