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ORIGINAL ARTICLE

Cost-effectiveness analysis of olanzapine-containing antiemetic therapy for managing highly emetogenic chemotherapy in Southeast Asia: a multinational study

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Abstract

Purpose Recent studies suggested that olanzapine, together with dexamethasone and serotonin-3 receptor antagonist (5HT3RA), is effective in preventing chemotherapy-induced nausea and vomiting (CINV) following highly emetogenic chemotherapy (HEC). This regimen is particularly useful in Southeast Asia (SEA) countries where resources are limited. We aimed to evaluate the cost-effectiveness of incorporating olanzapine into standard antiemetic regimens for the prevention of CINV in patients receiving HEC among SEA countries.

Methods Using a decision tree model, clinical and economic outcomes associated with olanzapine-containing regimen and standard antiemetic regimen (doublet antiemetic regimen: dexamethasone+first generation 5HT3RA) in most SEA countries except in Singapore (triplet antiemetic regimen: dexamethasone+first generation 5HT3RA + aprepitant) for CINV prevention following HEC were evaluated. This analysis was performed in Thailand, Malaysia, Indonesia, and Singapore, using societal perspective method with 5-day time horizon. Input parameters were derived from literature, network meta-analysis, government documents, and hospital databases. Outcomes were incremental cost-effectiveness ratio (ICER) in USD/quality-adjusted life year (QALY) gained. A series of sensitivity analyses including probabilistic sensitivity analysis were also performed.

Results Compared to doublet antiemetic regimen, addition of olanzapine resulted in incremental QALY of 0.0022–0.0026 with cost saving of USD 2.98, USD 27.71, and USD 52.20 in Thailand, Malaysia, and Indonesia, respectively. Compared to triplet antiemetic regimen, switching aprepitant to olanzapine yields additional 0.0005 QALY with cost saving of USD 60.91 in Singapore. The probability of being cost-effective at a cost-effectiveness threshold of 1 GDP/capita varies from 14.7 to 85.2% across countries.

Conclusion The use of olanzapine as part of standard antiemetic regimen is cost-effective for the prevention of CINV in patients receiving HEC in multiple SEA countries.

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Keywords Olanzapine · Cost-effectiveness analysis · Chemotherapy-induced nausea and vomiting · CINV

Introduction

Chemotherapy-induced nausea and vomiting (CINV) remains one of the most common and debilitating side effects experienced by cancer patients [1, 2]. This side effect can significantly affect patients' adherence with cancer treatments and impair quality of life [1]. Uncontrolled CINV can also increase health care expenditure and resource utilization [3]. Newer antiemetic agents such as neurokinin-1 receptor antagonists (NK1RA) appears to significantly improve CINV control rates when adding to the selective $5HT_3$ receptor antagonists (5HT3RA) + dexamethasone antiemetic regimen, with reported complete response (CR) rate of 80–90 and 65–75% for acute and delayed CINV, respectively [4, 5]. Despite improving emesis control rate following the use of NK1RA, patients from low- and middle-income countries still cannot get access to this newer NK1RA due to cost barriers. Identifying an alternative effective yet less costly antiemetic remains an unmet need among cancer patients.

Studies have reported advantages of olanzapine, an atypical antipsychotic drug, in improving control of acute and delayed CINV. Two meta-analyses have also confirmed that olanzapine-containing regimen is effective in preventing acute, delayed CINV as compared to non-olanzapine-containing regimens (aprepitant -or fosaprepitant-containing regimen) [6, 7]. Olanzapine-containing regimen has been consistently shown to be superior comparing to non-olanzapine-containing regimens in various end points of all three phases (acute, delayed, overall) and no nausea end points in delayed and overall phases.

CINV significantly affects patients' quality of life, and the efficacy of current treatment is suboptimal without the use of NK1RA. Olanzapine demonstrates promising efficacy in the control of CINV with risk ratios (RR) of 1.10 (95% CI 1.03–1.17), 1.31 (95% CI 1.14–1.52), and 1.41 (95% CI 1.18–1.68) in acute, delayed, and overall phase, respectively [6, 8], but its comparative clinical and economic benefits among several available antiemetic options in the usual clinical practice are not yet fully elucidated. A cost-effectiveness analysis is needed to demonstrate its econo mic value in regions where resources are constrained. This study aims to estimate the cost-effectiveness of incorporating olanzapine into standard antiemetic regimen for the prevention of CINV in patients receiving single-day highly emetogenic chemotherapy (HEC) in four Southeast Asia (SEA) countries including Thailand, Malaysia, Indonesia, and Singapore.

Methods

Overall description

A decision tree model (Fig. 1) was constructed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA) to evaluate the costs and health outcomes associated with olanzapine (OLN)-containing regimens dexamethasone + first generation serotonin-3 receptor antagonists + olanzapine (DEX + 5HT3RA1 + OLN; regimen C) or dexamethasone+ second generation serotonin-3 receptor antagonists + olanzapine (DEX + 5HT3RA2 + OLN; regimen D) compared with standard doublet dexamethasone + first generation serotonin-3 receptor antagonists (DEX + 5HT3RA1; regimen A) or doublet dexamethasone + second generation serotonin-3 receptor antagonists (DEX + 5HT3RA2; regimen B), dexamethasone + first generation serotonin-3 receptor antagonists + aprepitant triplet (DEX + 5HT3RA1 + APR; regimen E), dexamethasone + second generation serotonin-3 receptor antagonists+aprepitant triplet (DEX + 5HT3RA2 + APR; regimen F), or dexamethasone+second generation serotonin-3 receptor antagonists + aprepitant + olanzapine quadruplet (DEX + 5HT3RA2 + APR + OLN; regimen G) regimens for the prevention of CINV in patients treated with single-day HEC in outpatient setting, e.g., platinum-based and AC (adriamycin and cyclophosphamide)-based regimen. A patient could experience CR, defined as no emesis without use of rescue medication, or incomplete response (IR), defined as some emesis with use of rescue medication, in acute (0–24 h) or delayed (24–120 h) phases over the 5-day evaluation period. We performed a cost-utility analysis using societal perspective. Direct medical costs and non-direct medical costs were included, while indirect cost associated with loss of productivity was excluded in this analysis, to avoid double counting of disutility of quality-adjusted life year (QALY) [9]. A 5-day time horizon was selected for the evaluation of economic and CINV outcomes, in accordance with the clinical trial study period. No discounting was applied due to time horizon of less than a year.

Interventions of interest and comparator

We simultaneously compared seven different antiemetic regimens including (A) DEX + 5HT3RA1, (B) dexamethasone + palonosetron (DEX + 5HT3RA2), (C) DEX + 5HT3RA1 + OLN, (D) DEX + 5HT3RA2 + OLN, (E) DEX + 5HT3RA1 + APR, (F) DEX + 5HT3RA2 + APR, and (G) DEX + 5HT3RA2 + OLN + APR, as shown in Fig. 1. All regimens were compared to the usual practice in each country. In

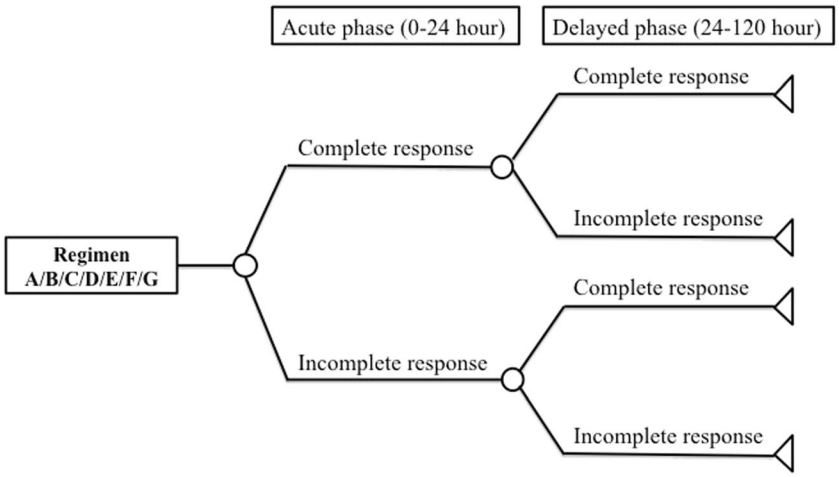


Fig. 1 Decision tree model. The decision tree model shows the possible outcome that a patient can experience after receiving antiemetic regimen—(A) DEX + 5HT3RA1, (B) DEX + 5HT3RA2, (C) DEX + 5HT3RA1 + OLN, (D) DEX + 5HT3RA2 + OLN, (E) DEX + 5HT3RA1 + APR, (F) DEX + 5HT3RA2 + APR, and (G) DEX + 5HT3RA2 + OLN + APR. In the acute phase (0–24 h), a patient could achieve complete response (CR) or emesis/incomplete response (IR). A patient who achieved CR or experienced IR could have CR or IR in delayed phase (24–120 h)

Thailand, Malaysia, and Indonesia, the standard doublet regimen (regimen A) is considered usual care, while the aprepitant triplet regimen (regimen E) is for Singapore for preventing CINV with HEC regimens.

Baseline response rate and relative efficacy

The probabilities of CR of reference treatment were obtained from local literature review and confirmed by experts for each country [10–13]. In patients who receive doublet antiemetic regimen before moderately emetogenic chemotherapy (MEC) or HEC, the CR rate in acute phase was 65, 55, 68, and 33% in Thailand, Malaysia, Singapore, and Indonesia, respectively (Table 1). The probabilities of CR in delayed phase were 36, 51, 71, and 37% in Thailand, Malaysia, Singapore, and Indonesia respectively if a patient achieved CR in the acute phase and 36, 11, 30, and 30% if a patient had IR in the acute phase. The risk ratios of incomplete response in acute (0–24 h) and delayed (24–120 h) phases of each treatment option were estimated based on a comparative efficacy analysis using a systematic review and network meta-analysis of 24 randomized controlled trials involving 7151 patients (Table 2) (see Supplementary Appendix for details). The CR rates of each antiemetic regimen were calculated by the multiplication of the baseline response rate and risk ratios obtained from our network meta-analysis.

Health state utilities

We used the utility weight of 0.7 and 0.2 for CR and IR, respectively, based on international literature [2]. These utility values were also used in an economic evaluation study of aprepitant for the prophylaxis of CINV in Singapore [18].

Costs

Direct medical costs data were collected from published government documents and hospital database of respective countries [14, 15] and adjusted to 2016 values using the country-specific Consumer Price Index [19–22] (Table 1). The medical costs include cost of general services in outpatient/day care center and cost of laboratory tests (including complete blood count, hematocrit, liver function test, renal profile, total bilirubin/direct bilirubin) prior to chemotherapy administration. According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines, additional agent utilizing different mechanisms of action from current prevention regimen should be given for the control of breakthrough emesis [23]. To reflect current practice, patients in Thailand who experienced breakthrough emesis were modelled to receive eight doses of lorazepam 1 mg as rescue treatment while patients who experienced emesis in both acute and delayed phases (refractory breakthrough emesis) were modelled to receive additional eight doses of metoclopramide 20 mg [24]. On the other hand, patients in Malaysia, Singapore, and Indonesia receive eight doses of metoclopramide as rescue treatment for breakthrough emesis and additional eight doses of lorazepam for refractory breakthrough emesis. The costs of rescue treatment included costs of medications and day care. It was assumed that the antiemetic medications were well tolerated and did not result in adverse events requiring additional medical attention. Direct non-medical costs, such as cost of additional food and transportation for patient who visited hospital for chemotherapy and rescue treatment, were included (Table 1). These costs were collected from literature, published government documents [15], and expert estimates and adjusted to 2016 values [19–22].

Table 1 Efficacy of usual care and cost estimates at base case of four countries

Parameters	Thailand	Malaysia	Singapore	Indonesia	Ref
Complete response (CR) rate (A: DEX + 5HT3RA1)					
CR in acute phase	0.65	0.55	0.68	0.33	*
CR in delayed phase (following CR in acute phase)	0.36	0.51	0.71	0.37	
CR in delayed phase (following CINV in acute phase)	0.36	0.11	0.30	0.30	
Costs (2016 USD)					
Direct medical costs					
Drug component					
Olanzapine 10 mg tablet	2.51	0.15	2.88	1.43	†
Aprepitant 125/80 mg tri-pack	73.84	50.39	68.25	63.19	
Palonosetron 0.25 mg IV	62.74	40.49	39.40	59.69	
Ondansetron 4 mg IV	0.50		3.29	0.35	
Ondansetron 8 mg tablet	0.21		0.35	0.15	
Granisetron 3 mg IV		1.24			
Dexamethasone 4 mg IV	0.12	0.08	0.80	0.15	
Dexamethasone 4 mg tablet	0.04	0.07	0.06	0.03	
Lorazepam 1 mg tablet	0.01	0.06	0.10	0.01	
Metoclopramide 10 mg IV	0.07	0.16			
Metoclopramide 10 mg tablet			0.01	0.01	
Medical device component					
Sodium chloride 0.9% 100 ml solution	0.57	0.31	1.32	0.49	
IV set	0.24	4.50	4.22	2.48	
Needle, disposable no. 18	0.01	0.01	7.04	0.05	
Syringe, disposable 10 ml	0.06	0.07	4.22	0.14	
Medical care component					
General services at outpatient/day care	11.45	27.00	28.15	131.40	‡
Total laboratory tests	17.93	58.49	78.77	22.15	
Direct non-medical costs					
Transportation cost per round trip	4.33	4.85	28.15	7.51	§
Additional food per visit	1.60	2.36	14.07	2.25	

*Complete response (CR) rate in Thailand is estimated from meta-analysis of two studies [10, 11], CR rate in Malaysia is extracted from published literature [12], and the CR rate of remaining countries are provided by local experts

† Sources of costs of drug and medical device: Thailand—DMSIC [14], Malaysia—Kuala Lumpur Hospital, Singapore—Singapore General Hospital and National Cancer Centre Singapore, Indonesia—"Dharmais" Cancer Hospital

‡ Sources of cost of medical care: Thailand—HITAP standard cost list [15], Malaysia—Ministry of Health fee schedule for foreigners, Singapore—National Cancer Centre Singapore, Indonesia—"Dharmais" Cancer Hospital

§Sources of direct non-medical costs: Thailand—HITAP standard cost list [15], Malaysia—cost of transportation is calculated from published literature and government data [16, 17] while cost of additional food is estimated from standard meal allowance in government, Singapore and Indonesia—estimation by local experts

Base case analyses

The primary outcomes were incremental costs, life year gained, QALYs gained, and incremental cost-effectiveness ratio (ICER). In base case analysis, the expected costs and outcomes for each antiemetic regimen were calculated. The cost outcomes were reported in 2016 US dollars (USD) (equal to 35.82 Thai Baht, 4.49 Malaysian Ringgit, 1.45 Singapore Dollar, and 13,436 Indonesian Rupiah) [25–28]. The results were presented as incremental cost per QALY gained. The willingness-to-pay (WTP) threshold of 1.2 times gross national income (GNI) per capita (THB 160,000/QALY–USD 4467/QALY) was applied in Thailand model, as recommended in the Thailand health technology assessment guideline [29, 30]. The value of 1 gross domestic pro duct (GDP) per capita in 2016 value was applied to Malaysia (MYR 39,000/QALY–USD 8695/QALY) [31], Indonesia (IDR 48 million/QALY–USD 3572/QALY) [32], and

Table 2 Risk ratio of complete response and health state utility model estimates

Parameter	Base case	Range	Reference(s)
Risk ratio*			
Acute CINV			
A: DEX + 5HT3RA1	Reference		
B: DEX + 5HT3RA2	1.538	1.310–1.806	NMA†
C: DEX + 5HT3RA1 + OLN	1.084	0.887–1.324	
D: DEX + 5HT3RA2 + OLN	2.370	1.342–4.186	
E: DEX + 5HT3RA1 + APR	1.671	0.662–4.217	
F: DEX + 5HT3RA2 + APR	1.621	1.123–2.342	
G: DEX + 5HT3RA2 + OLN + APR	3.313	1.925–5.701	
Delayed CINV			
A: DEX + 5HT3RA1	Reference		
B: DEX + 5HT3RA2	1.577	1.440–1.727	NMA‡
C: DEX + 5HT3RA1 + OLN	1.227	1.109–1.358	
D: DEX + 5HT3RA2 + OLN	17.788	4.466–70.850	
E: DEX + 5HT3RA1 + APR	2.382	1.578–3.595	
F: DEX + 5HT3RA2 + APR	1.982	1.626–2.416	
G: DEX + 5HT3RA2 + OLN + APR	2.482	1.858–3.315	
Utilities			
Complete response	0.7	0.56–0.84	[2]
Incomplete response	0.2	0.16–0.24	[2]

*Dexamethasone (DEX) + first generation selective serotonin-3 receptor antagonist (5HT3RA1) was used as the reference treatment

† Network meta-analysis of 24 randomized clinical trial included by systematic review (See Supplementary Appendix 1 for details)

‡ Network meta-analysis of 23 randomized clinical trial included by systematic review (See Supplementary Appendix 1 for details)

Singapore (SGD 73,000/QALY–USD 50,474/QALY) [33] as a cutoff of cost-effectiveness threshold.

Sensitivity analyses

To evaluate the robustness of the findings, we conducted a series of sensitivity analyses, which included one-way sensitivity analysis and multivariate probabilistic sensitivity analyses. One-way sensitivity analysis was conducted to investigate the effect of alteration of each key variable on the results, including chemotherapy regimen (e.g., platinum-based, high dose cyclophosphamide and AC-based regimen) antiemetic regimen effectiveness, costs, and health state utilities. The results of one-way sensitivity analysis were presented using Tornado diagram. Multivariate probabilistic sensitivity analyses were undertaken to simultaneously examine the effects of all parameter uncertainty using Monte Carlo simulation performed in Microsoft Excel 2010 (Microsoft Corp., Redmond, WA). All input parameters were assigned a probability distribution, and 10,000 random samples were drawn within a range of values that each parameter could attain. The results of probabilistic sensitivity analyses were presented using cost-effectiveness acceptability curves (CEAC). Threshold analysis was performed to determine the cost of drug that would make the ICER equivalent to the country-specific WTP threshold.

Results

Base case analyses

Using societal perspective, the cost and clinical outcomes of seven treatment strategies for the prevention of CINV were estimated. The total costs of DEX + 5HT3RA1 (regimen A) are USD 62.19, USD 161.83 and USD 267.90 in Thailand, Malaysia, and Indonesia, respectively, and the total cost of DEX + 5HT3RA1 + APR treatment in Singapore is USD 238.13. The addition of olanzapine into the regimen would save USD 2.98, USD 27.71 and USD 52.20 in Thailand, Malaysia, and Indonesia, respectively. Switching of aprepitant to olanzapine would save a total of USD 60.91 in Singapore. Addition of or switching to olanzapine is associated with a gain of 0.0005–0.0026 QALY across the countries. The use of olanzapine triplet regimen is cost saving in all four countries.

We found that DEX + 5HT3RA1 + OLN (regimen C) dominated DEX + 5HT3RA2 (regimen B), DEX + 5HT3RA1 + NK1 (regimen E), and DEX + 5HT3RA2+ NK1 (regimen F) in all four countries. Regimens B, E, and F were associated with higher costs and less QALY compared to C. Because of this extended dominance, they were excluded from further analysis. Likewise, DEX + 5HT3RA2 + OLN + APR (regimen G) was dominated by DEX + 5HT3RA2 + OLN (regimen D) in all four countries (Table 3). The calculation of corresponding ICER from regimen D to C was performed. The ICER of D relative to C ranged from USD 9886.90 (Indonesia) to USD 35,529 (Thailand) across the countries (Table 3). The use of regimen D was cost-effective only in Singapore, when compared to regimen C.

Sensitivity analyses

The results of one-way sensitivity analysis of regimen C are displayed in tornado diagrams, illustrating the ten most influential variables on the ICER (Fig. 2). The cost-effectiveness of addition of olanzapine into standard DEX + 5HT3RA1 regimen was generally robust in Thailand, Malaysia, and Indonesia models. Singapore was sensitive to the risk ratio for complete response of regimen C relative to regimen A. Given the higher estimate of the risk ratio of complete response of C vs A, C is not a cost-effective option in Singapore.

We found that the risk ratio of complete response in delayed phase of regimens C and D had the greatest influence on the ICER when D was compared to C. Given the higher estimates of risk ratio of complete response in delayed phase of C and D, the results were similar to the base case model, where regimen D was cost-effective in Singapore model, but not cost-effective in Thailand, Malaysia, and Indonesia. Hence, our findings were considered as robust (see Supplementary Appendix for details).

Threshold analysis was performed to determine the cost of palonosetron in order for DEX + 5HT3RA2 + OLN (regimen D) to be cost-effective compared to DEX + 5HT3RA1 + OLN (regimen C). If the cost of palonosetron was reduced by 18% in Indonesia and 32% in Malaysia, D would be a cost-effective option relative to C. In Thailand, the cost of palonosetron was needed to be reduced by more than 70% in order for D to be cost-effective against C. In Singapore, as D was a cost-effective option at base case value, we performed a threshold analysis to determine the cost of palonosetron at which D would be cost-saving. We found that if palonosetron was cheaper by 21%, D would be a cost-saving treatment option (see Supplementary Appendix for details).

The probability of regimen C being cost-effective at a cost-effectiveness threshold of 1 GDP/capita varies from 14.7% (Singapore) to 85.2% (Thailand) across countries. The probability of regimen D being cost-effective at cost-effectiveness threshold of 1 GDP/capita ranges from 14.8% (Thailand) to 85.0% (Singapore). An example of cost-effectiveness acceptability curve (CEAC) of Thailand is shown in Fig. 3. At cost-effectiveness threshold of 160,000 THB, the probability of regimen C being cost-effective is 85.2% while regimen D has 14.8% chance of being cost-effective. Other regimen are never cost-effective (see Supplementary Appendix for details, Fig. 6a).

Discussion

Our findings provide economic evidence supporting the addition of olanzapine in standard regimens for management of CINV among cancer patients in SEA countries. This is the first assessment of olanzapine for the prevention of HEC-induced CINV from the cost-effectiveness standpoint in multinational perspective utilizing data from SEA countries including Thailand, Malaysia, Indonesia, and Singapore.

Olanzapine demonstrated comparable efficacy or even more effective than aprepitant in CINV prophylaxis, based on two randomized clinical trials [34, 35]. Higher efficacy of olanzapine-based regimen can be translated into lower number of CINV events, leading to improved patients' adherence to chemotherapy with an overall positive impact on health-related quality of life for cancer patients receiving HEC [34].

This study has also demonstrated the value for money for using olanzapine-containing regimens for prophylaxis in SEA. Olanzapine-containing regimen (DEX + 5HT3RA1 + OLN) was cost-saving in Thailand, Malaysia, and Singapore and cost-effective in Indonesia. Addition of/switching to olanzapine resulted in an incremental QALY of 0.0005–0.0026 with a cost-saving of USD 2.98–USD 60.91.

The cost of olanzapine was offset by the improved efficacy compared with usual care, defined as either DEX + 5HT3RA1 or DEX + 5HT3RA1 + APR, in SEA countries. Even though the acquisition cost of olanzapine-based regimen was higher than that of usual care doublet regimen, the overall cost of olanzapine-based regimen was remarkably lower after consi dering costs associated with hospitalization, use of rescue medication, and other related clinical activities due to CINV. The cost-saving finding is quite attractive to policy makers as it is not commonly seen in most cases of new technology. The reason for this might be the availability of generic product with affordable price which makes access to olanzapine-containing regimens feasible for policy implementation.

There are some limitations in our approach that must be addressed. Firstly, all probabilities and utilities used to populate the model are estimates derived from the available published literature and national database in the respective countries. Each of these estimates carries inherent uncertainty. We reduced possible selection bias associated with utilizing data from a network meta-analysis. The practice differences

Table 3 Primary outcomes of the cost-effectiveness analysis

Antiemetic regimen	Total cost (USD)	QALY (QALY)	Incremental cost (ΔUSD)	Incremental QALY (ΔQALY)	Incremental cost/QALY (ΔUSD/ΔQALY)
Thailand					
A: DEX + 5HT3RA1 (ref)	62.19	0.0056	–	–	–
B: DEX + 5HT3RA2	116.25	0.0063	–	–	Dominated*
C: DEX + 5HT3RA1 + OLN	59.21	0.0078	(2.98)	0.0022	713.29
D: DEX + 5HT3RA2 + OLN	108.95	0.0092	47.74*	0.0014*	36,583.63*,‡
E: DEX + 5HT3RA1 + APR	124.50	0.0071	–	–	Dominated*
F: DEX + 5HT3RA2 + APR	352.64	0.0075	–	–	Dominated*
G: DEX + 5HT3RA2 + OLN + APR	368.87	0.0080	–	–	Dominated†
Malaysia					
A: DEX + 5HT3RA1 (ref)	161.83	0.0053	–	–	–
B: DEX + 5HT3RA2	193.80	0.0061	–	–	Dominated*
C: DEX + 5HT3RA1 + OLN	134.12	0.0078	(27.71)	0.0025	Cost-saving
D: DEX + 5HT3RA2 + OLN	158.43	0.0092	24.31*	0.0013*	15,508.03*,‡
E: DEX + 5HT3RA1 + APR	190.82	0.0071	–	–	Dominated*
F: DEX + 5HT3RA2 + APR	439.77	0.0075	–	–	Dominated*
G: DEX + 5HT3RA2 + OLN + APR	422.46	0.0082	–	–	Dominated†
Singapore					
E: DEX + 5HT3RA1 + APR (ref)	238.13	0.0080	–	–	–
C: DEX + 5HT3RA1 + OLN	222.21	0.0085	(60.91)	0.0005	Cost-saving
D: DEX + 5HT3RA2 + OLN	230.24	0.0093	8.03*	0.0008*	9861.17*,‡
F: DEX + 5HT3RA2 + APR	549.66	0.0083	–	–	Dominated*
G: DEX + 5HT3RA2 + OLN + APR	564.78	0.0087	–	–	Dominated†
Indonesia					
A: DEX + 5HT3RA1 (ref)	267.90	0.0050	–	–	–
B: DEX + 5HT3RA2	301.96	0.0057	–	–	Dominated*
C: DEX + 5HT3RA1 + OLN	215.70	0.0075	(52.20)	0.0026	Cos-saving
D: DEX + 5HT3RA2 + OLN	230.30	0.0090	14.60*	0.0015*	9886.90*,‡
E: DEX + 5HT3RA1 + APR	292.70	0.0067	–	–	Dominated*
F: DEX + 5HT3RA2 + APR	646.97	0.0072	–	–	Dominated*
G: DEX + 5HT3RA2 + OLN + APR	237.72	0.0079	–	–	Dominated†

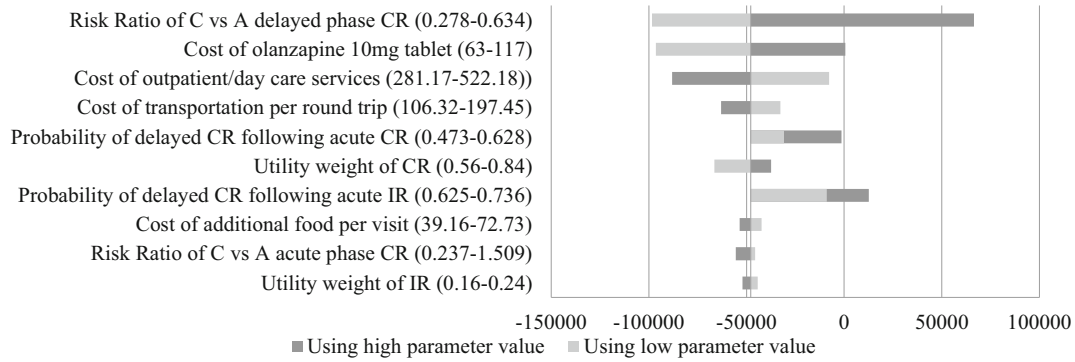
*Compared to regimen C: DEX + 5HT3RA1 + OLN

† This regimen was more costly with less QALYs compared to regimen D: DEX + 5HT3RA2 + OLN

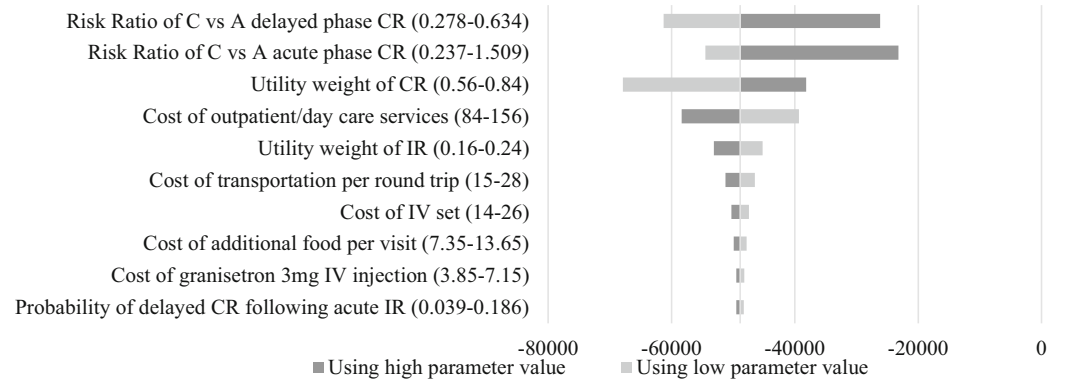
‡ This indicates that the treatment option is not cost effective based on the cost-effectiveness threshold of respsctive countries (Thailand—USD **4467**/QALY, Malaysia USD **8695**/QALY, Singapore—USD **50,474**/QALY, Indonesia—USD **3572**/QALY)

between the clinical trials and actual clinical application may have influenced our base case effectiveness assessment by either over- or underestimating our model parameters. Nevertheless, both univariate and probabilistic sensitivity analyses were performed to elaborate uncertainty in parameter estimates by exploring variability in each probability, cost, and outcome domains. Secondly, our analysis assumed that patients who received intravenous rescue medication would have been admitted to day care for treatment, while patients who received oral medication would have been taking the medications at home. It is possible that the costs of rescue treatment were underestimated if patients who experienced CINV required intervention that is more aggressive. Nevertheless, a recent study by Chan et al. [13] showed that only 1.7% of patients who experience CINV required hospitalization. Thirdly, the inclusion of actual treatment costs might improve the cost-effectiveness of olanzapine containing regimen. Although our study modelled ondansetron at a dose range between 8 and 16 mg IV, several studies show that the dose of ondansetron can be lowered to 8 mg rather than 32 mg without compromising its efficacy [36–38]. Fourthly, even though a total of 11 countries was included in SEA region, only 4 countries were chosen representing a broad socioeconomic status ranging from low-income, upper middle-income, and high-income countries. We chose Indonesia as a representative of low-income country, while Thailand and Malaysia

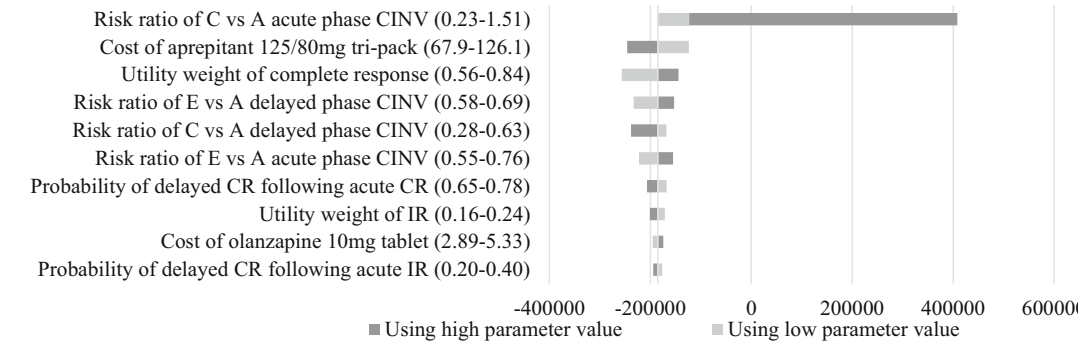
Thailand: C vs A (THB/QALY)



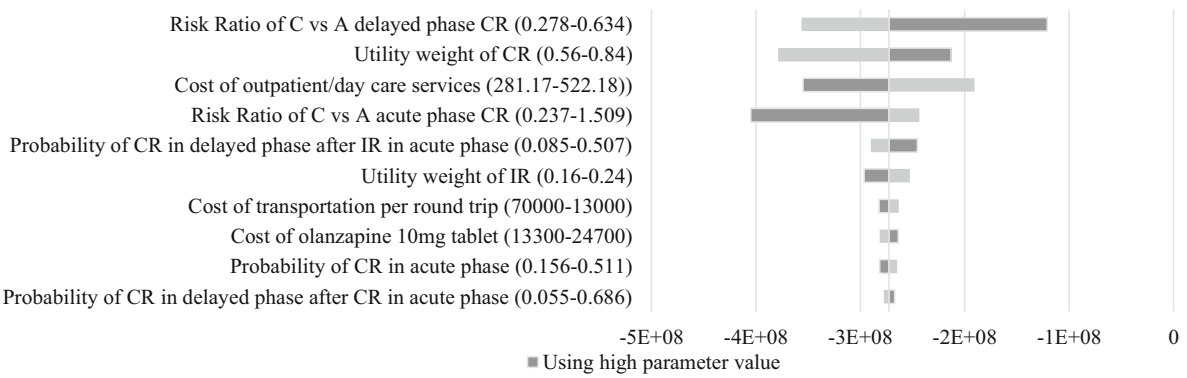
Malaysia: C vs A (MYR/QALY)



Singapore: C vs E (SGD/QALY)



Indonesia: C vs A (IDR/QALY)



◀ **Fig. 2** Tornado diagrams illustrating the ten most influential variables on the incremental cost-effectiveness ratio (regimen C: DEX + 5HT3RA1 + OLN vs standard doublet—Thailand, Malaysia, Indonesia, or aprepitant triplet—Singapore antiemetic regimen)

for upper middle-income country, with Singapore for high-income country. We truly believe that our results would be potentially applicable to variety of countries with differing socioeconomic status in this region. Fifthly, according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) practice guideline, it is strongly recommended to use high-quality real-world evidence, especially local studies, as inputs in health economics study. In our study, we have tried our best to use evidence from each country to reflect situation so that it is more applicable to that particular country. Different incidence rates of CINV were reported in observational studies across the Philippines, Singapore, and Malaysia. There might have been some (risk and contributory factors) that might be varied among patients in respective countries. Ethnic differences and genetic polymorphisms may contribute to CINV and affect the utility of antiemetic treatment [39, 40].

Several strengths of our research work deserve attention. Our study was conducted and reported according to the standard guideline [41]. We performed an economic evaluation from the societal perspectives utilizing government documents, and hospital databases from respective countries to reflect a real-world health and economic outcome as much as possible. All the indirect and intangible costs imposed on patients due to uncontrolled CINV which might have given an impact to our model were included. Our analysis is very context-specific. We considered country-specific standard regimens. Throughout multiple analyses, clinical response data was carefully drawn from a systematic review and network meta-analysis. Our findings should help illustrating a potential role of olanzapine in managing CINV form global perspective.

Currently, the NCCN clinical practice guideline has recommended olanzapine, palonosetron, and dexamethasone triple-drug regimen as an alternative CINV prophylactic regimen in patients receiving HEC and MEC [23]. Recently, an update of the American Society of Clinical Oncology (ASCO) guideline recommends the addition of olanzapine to standard antiemetic regimens the combination of a 5-HT3 receptor antagonist, an NK1 receptor antagonist and dexamethasone in CINV prophylaxis for adults receiving chemotherapy with a high risk for nausea and vomiting (e.g., cisplatin, the combination of cyclophosphamide and an anthracyclines). The use of olanzapine as a rescue medication in breakthrough CINV is otherwise endorsed in the ASCO guideline [42].

Furthermore, the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) guidelines recommend the triple association (the combination of a 5-HT3 receptor antagonist, an NK1 receptor antagonist, and dexamethasone) with the addition of olanzapine in the case of rescue therapy needs [43].

Conclusion

In conclusion, our study had demonstrated value for money of the use of olanzapine-based regimen relative to the standard regimen. The use of olanzapine is cost-effective and viable to prevent CINV in patients receiving HEC in multiple SEA countries. Policy makers and clinicians may consider this economic data as part of key evidence to support the role of olanzapine-containing regimen in managing CINV in SEA countries.

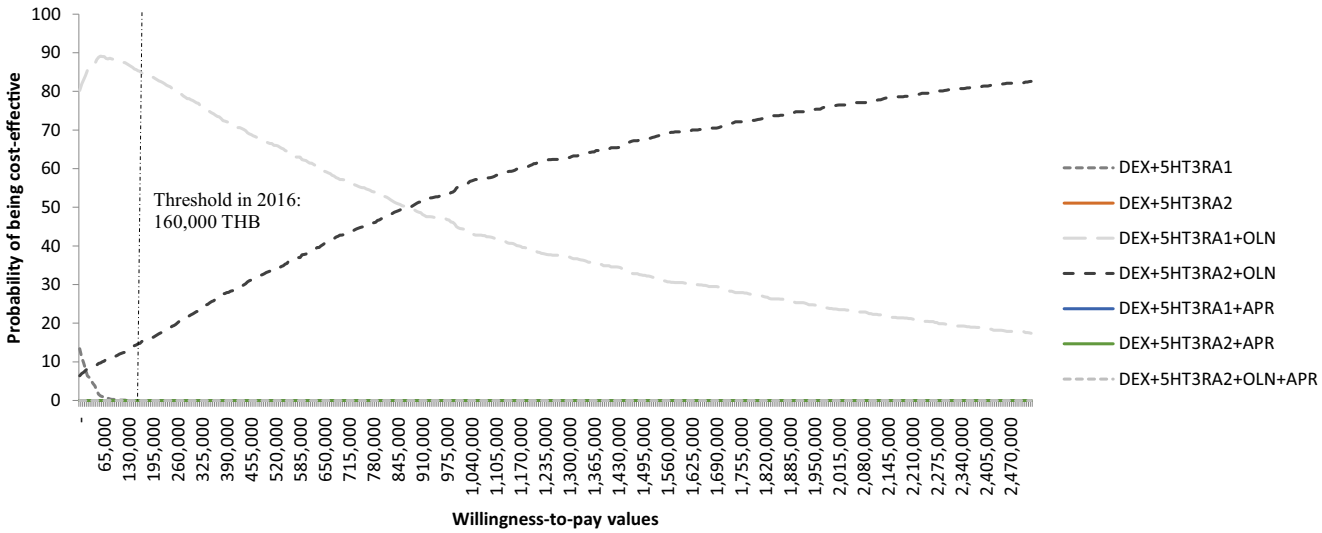


Fig. 3 Cost-effectiveness acceptability curves (CEAC) (example: Thailand)

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Compliance with ethical standards

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

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