RESEARCH ARTICLE

Cost-Effectiveness Analysis of Granisetron-Based versus Standard Antiemetic Regimens in Low-Emetogenic Chemotherapy: A Hospital-based Perspective from Malaysia

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Abstract

Background: In a prospective cohort study of antiemetic therapy conducted in Malaysia, a total of 94 patients received low emetogenic chemotherapy (LEC) with or without granisetron injections as the primary prophylaxis for chemotherapy-induced nausea and vomiting (CINV). This study is a retrospective cost analysis of two antiemetic regimens from the payer perspective. Materials and Methods: This cost evaluation refers to 2011, the year in which the observation was conducted. Direct costs incurred by hospitals including the drug acquisition, materials and time spent for clinical activities from prescribing to dispensing of home medications were evaluated (MYR 1=$0.32 USD). As reported to be significantly different between two regimens (96.1% *vs* 81.0%; p=0.017), the complete response rate of acute emesis which was defined as a patient successfully treated without any emesis episode within 24 hours after LEC was used as the main indicator for effectiveness. Results: Antiemetic drug acquisition cost per patient was 40.7 times higher for the granisetron-based regimen than for the standard regimen (MYR 64.3 *vs* 1.58). When both the costs for materials and clinical activities were included, the total cost per patient was 8.68 times higher for the granisetron-based regimen (MYR 73.5 *vs* 8.47). Considering the complete response rates, the mean cost per successfully treated patient in granisetron group was 7.31 times higher (MYR 76.5 *vs* 10.5). The incremental cost-effectiveness ratio (ICER) with granisetron-based regimen, relative to the standard regimen, was MYR 430.7. It was found to be most sensitive to the change of antiemetic effects of granisetron-based regimen. Conclusions: While providing a better efficacy in acute emesis control, the low incidence of acute emesis and high ICER makes use of granisetron as primary prophylaxis in LEC controversial.

Keywords: Granisetron - CINV - low emetogenic - cost-effectiveness - Malaysia

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Introduction

Over the past few years, economic evaluation has become increasingly important in the local public health services. Malaysia has been spending approximately 5% of its gross domestic product (GDP) on healthcare and about 98% of cost of public health services was funded directly by government (Hassali et al., 2013). Budgetary pressures and increasing drug acquisition cost have been shifting the payers' attention to the assessment of treatment effects using endpoints other than clinical efficacy (Erntoft, 2011). Consistent with the global trend, economic evaluation is now widely adopted in our country to perform objective comparisons between treatment alternatives in terms of cost and effectiveness.

To conduct an economic evaluation, the randomized and blinded trials are recognized as the most scientifically valid evidence for cost-effectiveness. This would minimize bias and uncertainty, providing only objectively collected data. Meantime, analysis using retrospective data from prospective observational studies is accepted as an alternative approach when trial data is unavailable (Marshall and Hux, 2009). However, it is important to note that using observational data is not always considered optimal in economic evaluation due to potential bias introduced by the lack of randomization.

Economic analysis of cancer treatment has been consistently focusing on supportive care since the last two decades. Antiemetic treatment is always the target of these studies due to its high acquisition cost and the lack of curative effects (Uyl-de Groot et al., 2000). To date, almost all the pharmacoeconomic studies of antiemetic treatment have been targeting the most costly items including aprepitant (Lordick et al., 2007; Moore et al., 2007; Annemans et al., 2008; Lopes et al., 2012) and serotonin type-3 (5HT-3) antagonists (Cox and Hirsch, 1993; Cunningham et al., 1993; Ballatori et al., 1994; Colayco and Hay, 2010). Overall, most of the findings showed that adding these new agents to the traditional antiemetic regimens provides incremental benefits in terms

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of cost-effectiveness.

As the second 5-HT3 antagonist developed after ondansetron, granisetron has been widely used since 1990's (Jordan et al., 2007). It is currently listed in the National Drug Formulary of Malaysia for two indications: chemotherapy-induced and post-operative nausea and vomiting (CINV and PONV) (Pharmacy Services Division Malaysia, 2011). Consistent with the trend reported by two previous studies (Almazron and Alnaim, 2012; Burmeister et al., 2012), it appears to be overprescribed for low emetogenic chemotherapy (LEC) among some of the general hospitals in Malaysia. In fact, it is only recommended to be used as the primary prophylaxis in moderately and highly-emetogenic chemotherapy (MEC and HEC) by both the local and international antiemetic guidelines (Ismail et al., 2011; Ettinger et al., 2012).

It is noted that almost all the previous economic analysis involving granisetron were conducted using MEC and HEC. As described in our previous study, granisetron used as the primary prophylaxis has been demonstrating a better control of acute emesis which occurred within 24 hours after LEC among the local population (Chan et al., 2013). However, its high usage had unavoidably led to a budgetary pressure among the government-funded hospitals. To date, there is a lack of information to justify its use in LEC from the pharmacoeconomic standpoint.

This is an economic evaluation conducted retrospectively using data from our previous study. We compared two antiemetic regimens with and without granisetron in terms of cost and effectiveness from the payer's perspectives.

Materials and Methods

Available data on efficacy and adverse effects

In our previous cohort study of antiemetic therapy, a total of 94 patients had received LEC with or without granisetron injections as the primary prophylaxis for CINV. All of them had received a single chemotherapeutic agent with an emetogenic level of two or below including gemcitabine (n=40), fluorouracil (n=25), vinorelbine (n=22) and docetaxel (n=7). They were warded during the administration of scheduled LEC and discharged after the administration completed. The previous study compared a regimen of granisetron (a single dose of 3mg intravenously) used concurrently with dexamethasone (a single dose of 8mg intravenously) or metoclopramide (a single dose of 10mg intravenously) versus a regimen containing only dexamethasone or metoclopramide.

The results of a five-day follow up showed a higher complete response rate of acute emesis for granisetron-based regimen (n=52) than for standard regimen (n=42) (96.1% *vs* 81.0%; p=0.017). Complete response was defined as a patient successfully treated without any emesis episode or use of rescue medications. No significant differences were found in the control of acute nausea, delayed nausea and delayed emesis between two regimens. With this, the complete response rate of acute emesis was used as the main indicator for effectiveness in this retrospective analysis. There were no cases of extended hospitalization, re-admission and additional visit due to uncontrolled CINV or severe adverse effects reported during the follow-up period. On top of that, none of the acute emesis episodes had occurred during the hospitalization period.

Economic evaluation model

Figure 1 outlines the breakdown of the cost elements incurred in both granisetron-based and standard regimens. The cost and cost-effectiveness analysis were referred to 2011 (MYR 1=$0.32 USD), the year in which the prospective cohort study was conducted. This retrospective analysis was conducted from the hospital's perspectives. Therefore, the intangible and indirect cost which occurred after the patient's discharge was not evaluated. Direct cost was calculated based on clinical activities performed by four groups of hospitals staffs: medical doctors (prescribing and review before discharge), pharmacists (screening and dispensing), pharmacist's assistants (filling and labeling) and nurses (administration). Three categories of cost were evaluated: drug acquisition, materials used and time spent by the medical staffs.

Drug acquisition costs

In Malaysia, injectable granisetron (Kytril®) was available in vials of 3mg (MYR 62.66 each). All patients in granisetron group had received a dosage of 3mg irrespective of their body weight. On top of that, all patients in both groups had received either one vial of metoclopramide or dexamethasone prior to LEC. Metoclopramide and dexamethasone were marketed in 10mg (MYR 0.38 each) and 8mg (MYR 0.69 each) vials, respectively.

There were no additional medications used to manage uncontrolled CINV or adverse effects after the administration of LEC in both groups. All patients were discharged with two oral medications. Each of them was given 24 tablets of dexamethasone (MYR 0.38 per ten 0.5mg tablets) to be taken at a dosage of 2mg twice daily for three days. Ten metoclopramide tablets (MYR 0.19 per ten 10mg tablets) were also given to all patients to be taken at a dosage of 10mg three times daily and used as the rescue medications.

Material costs

All medications were prescribed in the e-Hospital

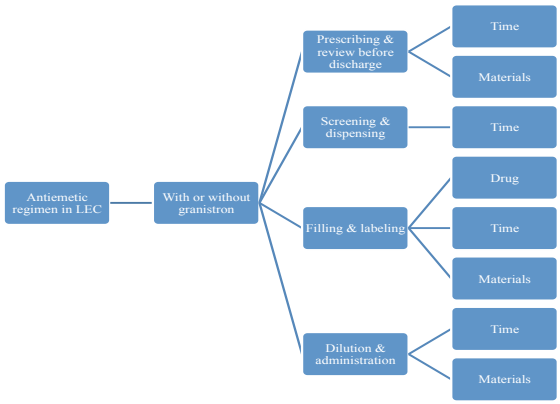

Figure 1. A Breakdown of the Cost Elements Incurred in Both Treatment Arms

Information System (e-His) by doctors and the prescription was then printed out. The cost of a printed prescription was MYR 0.10. Each medication was filled by a pharmacist's assistant into a plastic envelope and labeled with a printed note before it was sent to the ward or dispensed. The cost of an envelope with printed label was MYR 0.20.

To administer antiemetics, an ampoule of 10mL normal saline (MYR 0.03 each), a 10mLsyringe (MYR 0.30) and a 21G needle (MYR 0.06) were needed. Cost of intravenous sets was not included as antiemetics were administered using the same equipment as for LEC.

Time spent for clinical activities

We had performed a time and motion study to assess the time spent by medical doctors, pharmacists, pharmacist's assistants and nurses to perform the related clinical activities. Three samples from each group were observed and estimation was made for time spent in each clinical activity. The mean cost per minute per staff was calculated via dividing the individual monthly income (with allowance excluded) by the number of minutes worked. Each staff worked for eight hours a day and it was estimated that the average working days for each staff were 20.33 days per month. The mean costs were estimated as follows: MYR 0.35 per minute for medical doctors, MYR 0.26 per minute for pharmacists and MYR 0.17 per minute for both pharmacist's assistants and nurses.

Incremental analysis

The average cost-effectiveness ratio (CER), which was defined as mean cost per successfully treated patient in this study, was calculated by dividing the mean cost of antiemetic therapy by the complete response rate (in the fraction of one). Incremental cost-effectiveness ratio (ICER) can be calculated using the difference in mean cost divided by the difference in outcomes (Rothermel, 2013). In this context, we found ICER via dividing the incremental cost by the incremental efficacy (in the fraction of one).

Sensitivity analysis

Considering this was a retrospective study which was unavoidably exposed to uncertainty, a series of one-way sensitivity analysis were conducted to test the robustness of results. Referring to a previous pharmacoeconomic study of ondansetron which used the similar design (Ballatori et al, 1994), we varied the drug acquisition cost, material cost and response rates by ±10%. Due to a high degree of estimation involved, a variation of ±50% for cost (time) spent for clinical activities were applied. Cost changes due to two specific scenarios were also tested: if generic granisetron was used and granisetron dosage was reduced to 1mg as recommended by the updated guidelines (Ismail et al., 2011; Ettinger et al., 2012).

Results

Cost analysis and ratios of cost

Table 1 details the cost incurred in both granisetron and non-granisetron groups. Antiemetic drug acquisition cost per patient was 40.70 times higher for the granisetron-based regimen than for the standard regimen. When both the costs for materials and clinical activities were included, the total cost per patient was 8.68 times higher for granisetron-based regimen. On top of the granisetron acquisition cost, the variations of other costs between two regimens are explained as follows: *i*) A total of 29 and 11 patients were given dexamethasone injections concurrently prior to LEC in granisetron and non-granisetron groups, respectively. The rest of them were given metoclopramide injections. *ii*) Additional materials used in the granisetron group included a drug envelope with printed label, an ampoule of normal saline, a syringe and a needle. All prescribed antiemetics were printed on the same prescription. *iii*) Time (minutes)

Table 1. Summary of Cost (MYR in 2011) Incurred for Granisetron-based and Standard Regimens

Drug/ resource	Granisetron-based regimen (n=52)		Standard regimen (n=42)	
	Total cost	Mean cost	Total cost	Mean cost
i) Drug acquisition				
Granisetron injection	3258.32	62.66	0	0
Dexamethasone injection	20.01	0.38	7.59	0.18
Metoclopramide injection	8.74	0.17	12.54	0.30
Dexamethasone tablet	47.42	0.91	38.30	0.91
Metoclopramide tablet	9.88	0.19	7.98	0.19
Subtotal	3344.37	64.31	66.41	1.58
ii) Materials				
Printed prescription	5.20	0.10	4.20	0.10
Drug envelope with printed label	41.60	0.80	25.20	0.60
Normal saline	2.52	0.06	1.26	0.03
Syringe	25.20	0.60	12.60	0.30
Needle	6.24	0.12	2.52	0.06
Subtotal	80.76	1.68	45.78	1.09
iii) Time Spent for Clinical Activities				
Prescribing	72.80	1.40	44.10	1.05
Screening of prescription	27.04	0.52	21.84	0.52
Filling and labeling	35.36	0.68	21.42	0.51
Dispensing	40.56	0.78	32.76	0.78
Dilution	35.36	0.68	14.28	0.34
Administration	88.40	1.70	35.70	0.85
Review before discharge	91.00	1.75	73.50	1.75
Subtotal	390.52	7.51	243.60	5.80
iv) Hospital resources used for uncontrolled CINV/ adverse effects				
Additional hospitalization/ visit	0	0	0	0
Additional rescue medication	0	0	0	0
Adverse effects management	0	0	0	0
Subtotal	0	0	0	0
Total	3815.65	73.50	355.03	8.47

Table 2. Analysis of Cost-Effectiveness (MYR in 2011) of Granisetron-Based Versus Standard Regimens

	Granisetron regimen	Standard regimen	Ratio
Effectiveness measure			
Complete response	0.961	0.81	1.19
Cost measure			
Cost of treatment (MYR)	73.5	8.47	8.68
Summary measure			
CER[a]	76.48	10.46	7.31
Incremental effectiveness			0.151
Incremental cost (MYR)			65.03
ICER[b]			430.66

[a]CER (MYR per successfully treated patient) = Cost of respective antiemetic regimen divided by complete response rate (in the fraction of one), [b]ICER (MYR per successfully treated patient) = Incremental cost divided by incremental efficacy (in the fraction of one)

Table 3. Results of a One-Way Sensitivity Analysis Varying Treatment Cost and Efficacy

Parameter	ICER[a]	Absolute change from base case	Relative change from base case
Granisetron injection acquisition cost			
10% higher (MYR 68.93)	472.19	41.53	9.60%
10% lower (MYR 56.39)	389.14	-41.52	-9.60%
Dosage of 1mg used (MYR 20.89)	154.04	-276.62	-64.20%
Generic granisetron 3mg (MYR 6.66)	59.8	-370.86	-86.10%
Generic granisetron 1mg (MYR 2.22)	30.4	-400.26	-92.90%
Dexamethasone injection acquisition cost			
10% higher (MYR 0.76)	430.79	0.13	0.03%
10% lower (MYR 0.62)	430.6	-0.06	-0.01%
Metoclopramide injection acquisition cost			
10% higher (MYR 0.42)	430.6	-0.06	-0.01%
10% lower (MYR 0.34)	430.73	0.07	0.02%
Material cost			
10% higher	431.06	0.4	0.09%
10% lower	430.26	-0.4	0.09%
Cost (time) spent for clinical activities			
50% higher	436.36	5.7	1.30%
50% lower	425.03	-5.63	-1.30%
Efficacy of granisetron-based regimen			
10% higher (100% complete response)	342.26	-88.4	-20.50%
10% lower	1300.6	869.94	202.00%
Efficacy of standard regimen			
10% higher	915.92	485.26	112.70%
10% lower	281.52	-149.14	-34.60%

spent for clinical activities in non-granisetron group: prescribing (3), screening of prescription (2), filling and labeling (3), dispensing (3), dilution (2), administration (5) and review before discharge (5). *iv*) Additional time (minutes) spent for clinical activities in granisetron group: prescribing (+1), filling and labeling (+1), dilution (+2) and administration (+5).

Cost-effectiveness analysis

All the information used in calculation and results of the incremental analysis are summarized in Table 2.

Sensitivity analysis

The impact of varied cost and efficacy on ICER is reflected in Table 3. It is found that ICER was most sensitive to the change in the efficacy of granisetron-based regimen, followed by that of standard regimen and the acquisition cost of granisetron injections.

Discussion

To our knowledge, this is the first economic evaluation of antiemetic use for chemotherapy in Malaysia. It is also the only study which had investigated the use of granisetron in LEC from the cost-effectiveness standpoint. Studies of 5HT3-antagonist have been mainly demonstrating its roles in HEC and LEC (Koeller et al., 2002; Kris et al., 2005; Jordan et al., 2007). Our previous cohort study had specifically showed a significant difference between granisetron-based and standard regimens in the acute emesis control after LEC administration. With an absolute difference of 15.1% between two regimens, the complete response rate of acute emesis was used as the indicator for effectiveness in this analysis.

Consistent with an economic analysis of ondansetron in HEC (Ballatori et al., 1994), the acquisition cost of granisetron-based regimen was much higher than that of standard regimen. However, the ratio of costs of 5HT3-antagonist-based to standard regimens in both studies had decreased remarkably after consideration of the cost involved in materials and time spent for related clinical activities. In our study, whilst the ratio of drug acquisition costs for granisetron-based and standard regimens was 40.70, the corresponding ratio of total cost for two sets of treatment was reduced to 8.68 (relative change of 468.9%). This again clearly demonstrated that judging the differential cost between two treatment alternatives based on drug acquisition costs alone could be misleading (Cox and Hirsch, 1993).

On first glance one may assume that not including the costs of hospitalization and rescue medications in this study might have biased the results. Unlike other economic analysis of antiemetic agents in chemotherapy (Ballatori et al., 1994; Lordick et al., 2007; Moore et al., 2007; Lopes et al., 2012), those costs that reflected the healthcare care resource utilization did not give any impact on our analysis. Given that chemotherapy regimens received by our patients were all low emetogenic in nature, the re-admission or additional visit to emergency department due to uncontrolled CINV were expectedly rare. In fact, no such cases were found in patient personal records which were extracted from the e-HIS system. On top of that, the administrative cost of hospitalization during chemotherapy was not included as we assumed that same facilities including beds were used as for chemotherapy itself.

Considering the efficacy, granisetron-based regimen had demonstrated a higher CER than did standard regimen by 7.31 times. This relative ratio of two groups' CER was much higher than that of the study of ondansetron used in HEC (Ballatori et al., 1994). This was mainly attributable to the high differential cost between the original granisetron (Kytril®) and generic metoclopramide or dexamethasone marketed in Malaysia. Unlike most of the previous pharmacoeconomic studies of antiemetics in chemotherapy which had favored the new treatment (Cox and Hirsch, 1993; Cunningham et al., 1993; Lordick et al., 2007; Lopes et al., 2012; Humphreys et al., 2013), our results had indicated a high ICER (MYR 430.66 per successfully treated patient) of granisetron-based regimen relative to standard regimen. To date, Malaysia does not have a published threshold to determine cost-effectiveness of antiemetics. However, considering the limited annual drug budget that a hospital has, this appears to be less economically attractive. Overall, the generally low incidence of acute emesis in LEC and high ICER demonstrated by the incremental analysis had made the use of granisetron as primary prophylaxis remaining controversial.

One-way sensitivity analysis had clearly indicated that the variations in costs of dexamethasone, metoclopramide and material acquisition did not give a high impact on this model (<0.1%). A wide variation of ±50% in the cost (time) spent on the related clinical activities did not even alter the results substantially. Applying the method of a similar study (Ballatori et al., 1994), inaccuracy due to a high degree of estimation in this part was minimized

by the time and motion study. Overall, our model was relatively insensitive to the variations caused by utilization of hospital resources except drugs.

As would be expected, variations in efficacy of both regimens might have completely shifted the direction of the whole model. With the assumption of similar efficacy provided, switching the original brand (Kytril®) to generic granisetron might have reduced the ICER by 86.1% and made granisetron almost as cost-effective as the standard regimen. However, further observation and studies are needed to confirm the therapeutic equivalence of these two products in CINV as our model was highly sensitive to the efficacy variations. To date, the evidence of therapeutic equivalence is only available for post-operative nausea and vomiting (PONV) (Aleyasin A et al., 2012). Another issue worthy of discussion is the dosing of granisetron. It has been given as a single dose of 3mg in our hospital irrespective of patients' body weight. Studies have been demonstrating the similar response rates for doses of 1mg and 3mg (Jordan K et al., 2007; Yonemura et al., 2009). Using 1mg granisetron (Kytril®) might have reduced the ICER by approximately two-third. All in all, reduced cost may be the driven force for government-funded hospitals in Malaysia to implement these two strategies.

There are few limitations in our approach. First, this was an economic evaluation conducted completely from the hospital's perspectives. All the indirect and intangible costs imposed on patients due to uncontrolled CINV which might had given an impact to our model were not included. Second, this was a retrospective analysis using data from a prospective observational study. All the data of CINV were collected from patient diaries and the information were therefore relatively subjective. A high degree of cost estimation was made especially for the time spent for related clinical activities due to the retrospective design of study in nature. Third, all the monetary costs especially the drug acquisition costs were calculated based on the prices offered to government-funded hospitals which might have been lower than prices for private settings. In addition, we did not have data for the combination of metoclopramide and dexamethasone in non-granisetron group. The additional efficacy of this combination might have made it a much more cost-effective alternative compared to the monotherapy.

In conclusion, despite the limitations, our study had suggested a high ICER (MYR 430.66 per successfully treated patient) of granisetron-based regimen relative to the standard regimen. The low incidence of acute emesis among the patients receiving LEC in nature and high ICER had made the use of granisetron as primary prophylaxis remaining controversial. In this context, using standard regimens containing only dexamethasone or metoclopramide, switching to generic granisetron and reducing its dosage may serve as more cost-effective alternatives.

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References

Aleyasin A, Hanafi S, Saffarieh E, et al (2012). Efficacy of generic granisetron *vs* Kytril® for PONV in major gynecological operations: a randomized, double-blind clinical trial. *Iranian J Pharm Res*, **11**, 1059-64.

Almazron S and Alnaim L (2012). Evaluation of adherence to chemotherapy-induced nausea and vomiting guidelines. An observational study. *J Cancer Therapy*, **3**, 613-20.

Annemans L, Strens D, Lox E, et al (2008). Cost-effectiveness analysis of aprepitant in the prevention of chemotherapy-induced nausea and vomiting in Belgium. *Support Care Cancer*, **16**, 905-15.

Ballatori E, Roila F, Berto P, et al (1994). Cost and cost-effectiveness analysis of ondansetron versus metoclopramide regimens: a hospital perspective from Italy. *Pharmacoeconomics*, **5**, 227-37.

Burmeister H, Achi S, Studer C, et al (2012). Adherence to ESMO clinical recommendations for prophylaxis of chemotherapy-induced nausea and vomiting. *Supp Care Cancer*, **20**, 141-7.

Chan HK, Phua G, Kassim MS, et al (2013). Can granisetron injection used as primary prophylaxis improve the control of nausea and vomiting with low-emetogenic chemotherapy? *Asian Pac J Cancer Prev*, **14**, 469-73.

Colayco DC and Hay J (2010). Cost-effectiveness of serotonin-type 3 receptor antagonists for chemotherapy-induced emesis in non-small cell lung cancer patients receiving cisplatin-based chemotherapy. *Value Health*, **13**, 41.

Cox F and Hirsch J (1993). Ondansetron: a cost-effective advance in anti-emetic therapy. *Oncol*, **50**, 186-90.

Cunningham D, Gore M, Davidson N, et al (1993). The real costs of emesis - an economic analysis of ondansetron versus metoclopramide in controlling emesis in patients receiving chemotherapy for cancer. *Eur J Cancer*, **29**, 303-6.

Erntoft S (2011). Pharmaceutical priority setting and the use of health economic evaluations: a systematic literature review. *Value Health*, **14**, 587-99.

Ettinger DS, Armstrong DK, Barbour S, et al (2012). Antiemesis. *JNCCN*, **10**, 456-85.

Hassali MA, Thambyappa J, Nambiar S, et al (2013). TRIPS, Free Trade Agreements and the Pharmaceutical Industry in Malaysia. In "The New Political Economy of Pharmaceuticals: Production, Innnovation and TRIPS in the Global South", Eds Lofgren H and Williams OD. Palgrave Macmillan, Basingstoke pp 152-66.

Humphreys S, Pellissier J, Jones A (2013). Cost-effectiveness of an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer in the UK. *Cancer Manag Res*, **5**, 215-24.

Ismail F, Mohamed AK, Lim KH, et al (2011). Systemic therapy of cancer, 2nd edition. Ministry of Health, Kuala Lumpur, 75-8.

Jordan K, Hinke A, Grothey A et al (2007). A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer*, **15**, 1023-33.

Jordan K, Schmoll HJ, Aapro MS (2007). Comparative activity of antiemetic drugs. *Oncol Hemato*, **61**, 162-75.

Koeller JM, Aapro MS, Gralla RJ, et al (2002). Antiemetic guidelines: creating a more practical treatment approach. *Supp Care Cancer*, **10**, 519-22.

Kris MG, Hesketh PJ, Herrstedt J, et al (2005). Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. *Supp*

Care Cancer, **13**, 85-96.
Lordick F, Ehlken B, Ihbe-Heffinger A, et al (2007). Health outcomes and cost-effectiveness of aprepitant in outpatients receiving antiemetic prophylaxis for highly emetogenic chemotherapy in Germany. *Eur J Cancer*, **43**, 299-307.
Lopes G, Burke T, Pellissier J, et al (2012). Aprepitant for patients receiving highly-emetogenic chemotherapy: an economic analysis for Singapore. *Value Health Regional Iss*, **1**, 66-74.
Marshall DA and Hux M (2009). Design and analysis issues for economic analysis alongside clinical trials. *Med Care*, **47**, 14-20.
Moore S, Tumeh J, Wojtanowski S, et al (2007). Cost-effectiveness of aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with highly emetogenic chemotherapy. *Value Health*, **10**, 23-31.
Pharmacy Services Division Malaysia (2011). Drug Formulary. Ministry of Health, Kuala Lumpur pp 37.
Rothermel C (2013). What is health economics and outcome research? A primer for medical writers. *Am Med Writers Assoc J*, **28**, 98-104.
Uyl-de Groot CA, Wait S, Buijt I (2000). Economics and health-related quality of life in antiemetic therapy: recommendations for trial design. *Eur j Cancer*, **36**, 1522-35.
Yonemura M, Katsumata N, Hashimoto H, et al (2009). Randomized controlled study comparing two doses of intravenous granisetron (1 and 3 mg) for acute chemotherapy-induced nausea and vomiting in cancer patients: a non-inferiority trial. *Jpn J Clin Oncol*, **39**, 443-8.