RESEARCH ARTICLE

Can Granisetron Injection Used as Primary Prophylaxis Improve the Control of Nausea and Vomiting with Low-Emetogenic Chemotherapy?

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Abstract

Background: The purpose of this study is to examine the risk of uncontrolled chemotherapy-induced nausea and vomiting (CINV) among patients receiving low emetogenic chemotherapy (LEC) with and without granisetron injection as the primary prophylaxis in addition to dexamethasone and metochlopramide. Materials and Methods: This was a single-centre, prospective cohort study. A total of 96 patients receiving LEC (52 with and 42 without granisetron) were randomly selected from the full patient list generated using the e-Hospital Information System (e-His). The rates of complete control (no CINV from days 1 to 5) and complete response (no nausea or vomiting in both acute and delayed phases) were identified through patient diaries which were adapted from the MASCC Antiemesis Tool (MAT). Selected covariates including gender, age, active alcohol consumption, morning sickness and previous chemotherapy history were controlled using the multiple logistic regression analyses. Results: Both groups showed significant difference with LEC regimens ($p<0.001$). No differences were found in age, gender, ethnic group and other baseline characteristics. The granisetron group indicated a higher complete response rate in acute emesis (adjusted OR: 0.1; 95% CI 0.02-0.85; p=0.034) than did the non-granisetron group. Both groups showed similar complete control and complete response rates for acute nausea, delayed nausea and delayed emesis. Conclusions: Granisetron injection used as the primary prophylaxis in LEC demonstrated limited roles in CINV control. Optimization of the guideline-recommended antiemetic regimens may serve as a less costly alternative to protect patients from uncontrolled acute emesis.

Keywords: Granisetron - CINV - low emetogenic chemotherapy - primary prophylaxis

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Introduction

Two decades ago, chemotherapy-induced nausea and vomiting (CINV) had forced up to 20% of cancer patients to postpone or refuse potentially curative treatment (Herrstedt et al., 2002; Jordan et al., 2007). These symptoms have been highly ranked in the list of expected, feared and distressing side effects (Hesketh et al., 2003; Schnell., 2003; Hofman et al., 2004; Brigitte et al., 2006; Mulders et al., 2008; Hassan and Yusoff, 2010; Rigacci et al., 2011; Schwartzberg et al., 2011; Bourdeanu et al., 2012). Studies have been consistently indicating the association of CINV with young age, female gender, non-alcoholic group, morning sickness history and previous experience of chemotherapy (Jordan et al., 2007; Dranitsaris et al., 2012). To date, the impacts of CINV are still often underestimated by physicians and nurses (Grunberg et al., 2004; Foubert and Vaessen, 2005; Hesketh et al., 2012).

Given such fear in patients towards these symptoms, many guidelines for the management of CINV were developed and periodically updated. Among the well-accepted guidelines in Malaysia are those published by the National Comprehensive Cancer Network (NCCN), the Multinational Association for Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO) and the Ministry of Health (MOH) of Malaysia (Gralla et al., 2005; Hensley et al., 2009; Ismail et al., 2011; Ettinger et al., 2012). In these guidelines, chemotherapeutic agents are classified based on their emetogenic potentials into four categories: minimal (<10% of patients), low (10-30% of patients), moderate (30-90% of patients) and high (>90% of patients). Antiemetics are recommended according to the emetogenic potentials of chemotherapy regimens.

The development of selective type-3 serotonin (5-HT3) antagonists has been one of the most significant advances in CINV control. With its combined use with other antiemetics such as the neurokinin-1 (NK-1) antagonists, corticosteroids and dopamine antagonists, nausea and vomiting can be completely prevented in up to 40-60% and 60-80% of patients, respectively (Hesketh

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et al., 2003; Poli-Bigelli et al., 2003; Foubert and Vaessen, 2005; Jordan et al., 2007; Smith et al., 2012). Almost all the previous studies demonstrated that the prevention of acute CINV (within 24 hours after chemotherapy) was dramatically improved by adding a prophylactic 5-HT3 antagonist (Koeller et al., 2002; Kris et al., 2005; Jordan et al., 2007). However, its use in delayed CINV prevention (24 hours to 5 days after chemotherapy) remains controversial and was not supported by the guidelines as the first-line prophylaxis (Jordan et al., 2007; Ettinger et al., 2012).

Granisetron was the second 5-HT3 antagonist developed after ondansetron and used worldwide since 1994 (Jordan et al., 2007). Both of them (granisetron 3 mg injection and ondansetron 8 mg injection) are the only injectable 5HT-3 antagonists listed in the National Drug Formulary of Malaysia (Pharmacy Services Division Malaysia, 2011). Most of the local general hospitals have been making granisetron the standard pre-medication for chemotherapy for it is considered as the "latest" 5HT-3 antagonist. In fact, most of the previous studies comparing granisetron and ondansetron did not clearly demonstrate superiority of one agent over another (Barrajon, 2000; del Giglio et al., 2000; Jordan et al., 2007). From our observation, granisetron injection appears to be overprescribed for the low emetogenic chemotherapy (LEC) in these settings at the maximum dosage of 3mg (0.04mg/kg). The similar trends were reported in Saudi Arabia and Switzerland recently (Almazron and Alnaim, 2012; Burmeister, 2012). It is believed to be crucial in order to provide patients the highest level of protection from CINV in LEC by some of the local prescribers including oncologists.

In fact, current guidelines recommended the use of only a single agent of corticosteroid or dopamine antagonist in LEC (Ettinger et al., 2012). It is noted that almost all the previous studies on granisetron were conducted using moderately and highly-emetogenic chemotherapy (MEC and HEC). There is a lack of information available to quantify the benefits of granisetron as the primary prophylaxis for CINV in LEC. Some patients still experience CINV despite receiving the guideline-recommended prophylaxis (Hesketh et al., 2012). Given that granisetron injection is a burden on our hospital's drug budget due to its high usage in LEC, this study aimed to compare the control of CINV among the patients receiving LEC (≤30% of expected CINV incidence) with and without granisetron as the primary prophylaxis.

Materials and Methods

Setting and study design

The Sultanah Bahiyah Hospital is the biggest general hospital in Kedah State, Malaysia. The number of cancer patients receiving chemotherapy in this hospital is over 1500 annually. This was a single-centre, prospective cohort study. It was undertaken in 5 selected wards of the Department of Surgery (2), Obstetrics and Gynaecology (2) and Pulmonary Diseases (1) during September and December 2011. These are the wards found to use granisetron widely for LEC. This study was registered with the National Medical Research Registry (NMRR) and approved by the Medical Research Ethics Committee (MREC). Written informed consent was provided by all patients before initiation of any study procedures.

Patient and treatment

This study involved patients with confirmed malignant diseases without any record of uncontrolled CINV during the previous LEC cycles. Patients were required to be at least 18 years of age. Those receiving any antiemetics within 24 hours before the administration of LEC other than the pre-medications were excluded (with the exception of oral dexamethasone for prophylaxis of taxane-induced hypersensitivity reactions).

Pre-medications were given prior to the scheduled LEC administration according to the prescribers' orders which were strongly determined by their preferences and the common practices of departments. The first group of patients received an intravenous bolus dexamethasone of 8 mg or metochlopramide of 10 mg. The second group was given an addition of intravenous bolus granisetron of 3 mg to the standard regimen. Both groups were discharged after the chemotherapy with dexamethasone and metochlopramide tablets to be taken 2-4 mg two times and 10 mg three times daily for 3 days, respectively.

Sample size and sampling

This study was powered with a sample size to detect a 30% difference in complete control rate between the two antiemetic regimens (based on a local oncologist's opinion). Sample size calculation showed that a total of 42 patients were needed in each of the granisetron and non-granisetron group to obtain a power of 0.80 at a Type I error level of 0.05. The total number of patients was elevated to account for a 10% dropout rate. They were randomly selected from the full list of patients receiving LEC during study period generated using the e-Hospital Information System (e-His).

Data collection and CINV assessment

The control of CINV was evaluated for 120 hours after the completion of LEC administration (day 1 to day 5) via recordings in the patient diaries which were adapted from the MASCC Antiemesis Tool (MAT) (Molassiotis et al., 2007). On day 6, a telephone contact was made to confirm the completeness and results of recordings. Completion of study was defined as the next visit of patients when they returned the diaries to ward pharmacists. This validated, eight-item scale in MAT is able to comprehensively assess the experience of acute and delayed nausea as well as the extent and incidence of vomiting. Results of assessment were reflected as (i) the complete control rate, defined as totally no nausea and vomiting experience from day 1 to day 5 without taking any rescue medications; (ii) the complete response rate, defined as no nausea or vomiting on day 1 (acute phase) and from day 2 to day 5 (delayed phase) without taking any rescue medications.

Statistical analysis

Categorical data were expressed as the frequencies and percentages while continuous data were expressed as

the mean±standard deviations (SD). Pearson chi-square, Fisher's exact and independent t tests were utilized to compare the differences in baseline characteristics. Unadjusted complete control and complete response rates were compared using the Pearson chi-square tests. Five separate multiple logistic regression analyses were performed for the overall complete control rate as well as the complete response rates in acute nausea, acute emesis, delayed nausea and delayed vomiting, respectively. The covariates used were those proven to be associated with CINV control including gender, age, active alcohol consumption, morning sickness history and previous chemotherapy history. The resulting adjusted odds ratio (OR) and 95% confidence interval (CI) reflected the likelihood of experiencing a CINV event in the granisetron group relative to the non-granisetron group. The threshold of significance was fixed at the 5% level.

Results

Baseline patient characteristics

A total of 111 patients receiving LEC met the eligibility criteria. Only 94 patients returned the diaries and included in the analyses (52 in granisetron group and 42 in non-granisetron group). Baseline demographic and clinical characteristics are shown in Table 1. All the characteristics were similar between the groups except the LEC agents received by the patients.

Rates of complete control

Overall, there were 61 cases (64.9%) of completely controlled CINV in 5 days after chemotherapy. The unadjusted incidences of CINV were 28.9% and 42.9% for granisetron group and non-granisetron group, respectively (p=0.157). After controlling the confounding variables of interest, both groups showed no difference in the complete control of CINV (adjusted OR 0.5; 95%CI 0.19-1.22; p=0.112).

Table 1. Baseline Characteristics: Granisetron Versus Non-Granisetron Groups

	Granisetron Group (n=52)	Non-Granisetron Group (n=42)	p value
Age (years)	51.7±10.92	54.7±10.92	0.181 (NS)
Weight (kg)	57.4±9.46	55.6±15.34	0.529 (NS)
Height (cm)	157.0±14.30	161.2± 10.39	0.117 (NS)
Gender, female	29 (55.8%)	17 (40.5%)	0.140 (NS)
Ethnic group			
Malay	36 (69.2%)	31 (73.8%)	0.626 (NS)
Non-Malay	16 (30.8%)	11 (26.2%)	
Active alcohol consumption (≥1 drink/week)			
	1 (1.9%)	1 (2.4%)	0.697 (NS)
Morning sickness history			
	3 (5.8%)	1 (2.4%)	0.393 (NS)
Naive chemotherapy history			
	10 (19.2%)	8 (19.1%)	0.597 (NS)
LEC regimen			
Gemcitabine	29 (55.8%)	11 (26.2%)	<0.001
Vinorelbine	20 (38.5%)	2 (4.8%)	
Fluorouracil	2 (3.8%)	23 (54.8%)	
Docetaxel	1 (1.9%)	6 (14.3%)	

Table 2. Unadjusted Incidences of CINV: Granisetron Versus Non-Granisetron Groups

	Unadjusted Incidence		P value
	Granisetron Group (n=52)	Non-Granisetron Group (n=42)	
Acute nausea	8 (15.4%)	12 (28.6%)	0.120 (NS)
Acute emesis	2 (3.9%)	8 (19.0%)	0.017
Delayed nausea	6 (14.3%)	8 (19%)	0.309 (NS)
Delayed emesis	2 (3.9%)	4 (9.5%)	0.243 (NS)

Table 3. Likelihood of CINV after Controlling the Covariates: Granisetron Versus Non-Granisetron Groups

	Adjusted OR	95%CI	P value
Acute nausea	0.4	0.14-1.22	0.112 (NS)
Acute emesis	0.1	0.02-0.85	0.034
Delayed nausea	0.5	0.16-1.89	0.309 (NS)
Delayed emesis	0.6	0.09-3.89	0.580 (NS)

Rates of complete response

Of 94 patients, 21.3% and 14.9% of them experienced acute and delayed nausea, respectively. Acute and delayed emesis episodes were found in 10.6% and 6.4% of the cases. Consistent with the analysis for complete control of CINV, no significant differences were found between two groups in the complete response rates of acute nausea, delayed nausea and delayed emesis. However, granisetron group demonstrated a lower unadjusted incidence of acute emesis than did non-granisetron group (Table 2). Its strength in lowering acute emesis risk was maintained after the selected covariates were controlled (Table 3).

Discussion

This study is the first to specifically evaluate the efficacy of granisetron as primary prophylaxis in cancer patients receiving LEC. The complete control rate of CINV in granisetron group is higher than that of non-granisetron group but the difference is not statistically significant (71.1% versus 57.1%; p=0.157). The same result was obtained after several covariates of interest were controlled (adjusted OR 0.5; 95%CI 0.19-1.22; p=0.112). It is noticeably comparable to a previous finding that showed similar outcomes in overall control of CINV among the patients receiving LEC, regardless of the antiemetic regimens selected (Vermeulen et al., 2000). Therefore, granisetron was not a necessary pre-medication to improve the complete control of CINV in this group of patients as recommended by guidelines (Gralla et al., 2005; Hensley et al., 2009; Ismail et al., 2011; Ettinger et al., 2012).

The efficacy of antiemetic regimens with granisetron was most pronounced in the prevention of acute emesis. No emesis occurred during acute phase in 96.1% of patients receiving granisetron. The unadjusted incidence of acute emesis is significantly higher in the non-granisetron group (19.0%; p=0.017). Logistic regression proves that granisetron used as the primary prophylaxis is able to lower the risk of acute emesis among the patients receiving LEC (adjusted OR: 0.1; 95%CI 0.02-0.85; p=0.034). This

is consistent with the recently-published findings that indicated the roles of palonosetron used as secondary prophylaxis in lowering acute emesis risk caused by LEC (Hesketh et al., 2012). However, using prophylactic granisetron in LEC to improve acute emesis control remains controversial. It was defined as "overtreatment" and reported to bring about collateral side effects including stypsis, headache and gastrointestinal disturbances in patients already being subjected to the administration of toxic drugs. It had also led to the unnecessarily high cost (Almazron and Alnaim, 2012). According to the recently updated NCCN guidelines, 5-HT3 antagonist is not recommended to be used in chemotherapy regimens with low or minimal emetogenic potentials. Optimization of the standard pre-medication regimens by increasing the dose of dexamethasone (from 8-12 mg) or adding other agents that act with different mechanisms pharmacologically (for examples, prochlorperazine or lorazepam) may serve as less costly alternatives as recommended (Ettinger et al., 2012).

The unadjusted delayed emesis rate in all 94 cases (6.4%) is slightly lower than the findings in UK that reported the rates of 7.1-11% in patients receiving LEC across the cycles, regardless of antiemetic regimens used (Molassiotis et al., 2008). Due to its relatively short duration of action, the efficacy of granisetron in lowering delayed emesis risk secondary to LEC is not significant as what was demonstrated by palonosetron in the previous study (Hesketh et al., 2012). In fact, 3.9% and 9.5% of patients were found to experience delayed emesis after receiving LEC in granisetron and non-granisetron groups, respectively. This is the subgroup predicted to have more difficulties with delayed emesis in their subsequent cycles of LEC (Schwartzberg et al., 2011; Hesketh et al., 2012). There is a need for physicians to identify this population and optimize their oral antiemetic regimens in order to achieve a better control of delayed emesis.

Consistent with the previous studies of 5-HT3 antagonists with MEC and HEC, the control of nausea with or without granisetron shown in our study is worse than the control of vomiting (Jordan et al., 2007; Giuliani et al., 2008; Rigacci et al., 2011; Hesketh et al., 2012). The unadjusted incidences of acute nausea (15.4% versus 28.6%; p=0.120) and delayed nausea (14.3% versus 19.0%; p=0.309) in granisetron group is lower than that of non-granisetron group but the differences are not significant. Logistic regressions prove that granisetron has given the same impacts on acute nausea (adjusted OR 0.4; 95%CI 0.14-1.22; p=0.112) and delayed nausea (adjusted OR 0.5; 95%CI 0.16-1.89; p=0.809) control as the standard antiemetic regimen has. As both regimens are unable to control nausea effectively, the need to establish new strategies may therefore warrant more attention. In fact, nausea has been believed to be a neglected symptom and there is undoubtedly room for improvement regarding its treatment (Foubert and Vaessen, 2005).

It is noted that this is a limited study and we may be cautious with its representative nature. We only studied the use of granisetron in four drugs and the main chemotherapy regimens received by granisetron and non-granisetron groups are different. More patients from the granisetron group received vinorelbine which is identified with lower emetogenic potential (<10% of frequency) than that of the other three drugs. Furthermore, data collection was based entirely on self-reporting, which may have led to the under-reporting of CINV events. Recognizing nausea accurately is another challenge as it can only be reported subjectively by patients.

In conclusion, the addition of granisetron as primary prophylaxis to a standard regimen consisting of dexamethasone and metochlopramide improve only the control of acute emesis in LEC. Granisetron does not improve the complete control rate of CINV from day 1 to day 5 after the administration of LEC. In addition, the outcomes in the control of acute nausea, delayed nausea and delayed emesis were similar in granisetron and non-granisetron groups.

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