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SINGLE-DOSE ORAL GRANISETRON VERSUS MULTIDOSE INTRAVENOUS ONDANSETRON FOR MODERATELY EMETOGENIC CYCLOPHOSPHAMIDE-BASED CHEMOTHERAPY IN PEDIATRIC OUTPATIENTS WITH ACUTE LYMPHOBLASTIC LUKEMIA

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□ *This prospective study was designed to compare the efficacy of ondansetron with granisetron in terms of complete emesis control and time spent in an ambulatory care setting in children with acute lymphoblastic leukemia (ALL) undergoing moderately emetogenic cyclophosphamide-based chemotherapy.The costs for both treatments are also examined. A total of 33 children (mean age: 7.8 ± 4.9 year) were studied during 66 chemotherapy cycles. Analysis was based on 33 courses of a single oral dose of granisetron and 33 courses of ondansetron incorporating 2 intravenous doses of ondansetron 0.15 mg/kg followed by 1 dose of the same dosage orally. There was no significant difference between the 2 treatments in terms of overall efficacy (McNemar's chi-square test). Twenty of 33 patients (60.6%) receiving granisetron and 15 of 33 patients (45.5%) receiving ondansetron experienced no emesis 24 h after chemotherapy ($p = .227$). Boys experienced greater rates of vomiting than did girls despite antiemetic treatment; however, no apparent reason for the gender discrepancy was noted. Both antiemetic regimens have similar antiemetic efficacy for treating the moderately emetogenic effects associated with cyclophosphamide-based chemotherapy. It is possible that the granisetron regimen may be preferable because it is simpler to administer and more cost-effective.*

Keywords. *children, granisetron, moderately emetogenic chemotherapy, ondansetron, vomiting*

The incidence of chemotherapy-induced emesis is difficult to determine, because the cause is likely to be multifactorial and include factors such as

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gender and age [1, 2]. Although both intravenous (iv) and oral antiemetic agents can be used effectively to control chemotherapy-induced emesis, oral antiemetic agents are more convenient and acceptable for outpatient treatment, particularly for children receiving antineoplastic agents [2]. Although many papers in the clinical literature detail the use of iv serotonin (5-HT3) antagonists in adults [3–7], no difference was found in the rate of total control (no emesis, no nausea) between patients receiving oral granisetron and intravenous ondansetron [8]; thus, oral granisetron for children offers a promising alternative to intravenous ondansetron.

Both treating and not treating nausea and vomiting can have consequences. Treatment is associated with economic burden, and excessive vomiting can cause lifelong phobias, which may be associated with the increased use of medical care. Nontreatment can result in the patient experiencing unpleasant events associated with medical treatment, which may cause reluctance to continue potentially beneficial treatment in the future [9].

The purpose of this study was to compare the antiemetic efficacy of a single oral dose of granisetron (Kytril; SmithKline Beecham Pharmaceuticals, Brentford, United Kingdom) with a multidose (2 iv doses and 1 oral dose) of ondansetron (Zofran; GlaxoWellcome, Greenford, United Kingdom) for preventing nausea and vomiting in pediatric patients undergoing moderately emetogenic chemotherapy.

METHODS

Patient Selection

Children with acute lymphoblastic leukemia (ALL) without evidence of central nervous system involvement were studied in a single pediatric oncology center. The interviewer explained the study purpose and obtained verbal consent prior to each interview. Interviews were conducted within 24 h of each chemotherapy session. Patients were recruited into the study from July 2000 to June 2002. To be eligible, patients had to be 3–18 years old and to receive iv cyclophosphamide (300 mg/m^2) plus etoposide (300 mg/m^2) or cyclophosphamide (1000 mg/m^2) alone. No concomitant antiemetic therapy apart from that being tested was given to the patients. Interviews were conducted and completed within 24 h of each chemotherapy session.

To compare the prophylactic antiemetic efficacy, safety and effectiveness in children 3 years of age and younger are not known. Patients were excluded if they were younger than 3 or older than 18, weighed less than 25 kg, suffered from primary or secondary brain tumors, had preexisting chronic nausea or vomiting problems, or suffered from gastrointestinal tumors that appeared likely to lead to bowel obstruction. The coadministration of corticosteroids (including dexamethasone) was prohibited during this study. Patients who

had undergone previous cytotoxic chemotherapy were allowed to participate in the study.

Study Design

This was a single-institution, randomized, open-label, 2-period crossover investigation of the efficacy of 2 antiemetic regimens in children receiving moderately emetogenic chemotherapy in an outpatient setting. Once patients satisfied the entry criteria, they were started on a 4-week run-in period during which they were given antiemetic agents according to the randomization scheme. The 2 agents tested were (1) a single dose of granisetron (0.5 mg for patients weighing 25–50 kg or 1 mg for patients weighing $\geq$ 50 kg) administered orally 1 h before the administration of chemotherapy, and (2) 3 doses of ondansetron (0.15 mg/kg administered iv 1 h prior before the administration of chemotherapy and again 4 h after the first dose, with a further oral dose administered 8 h after the first dose).

Parents were asked to keep a log (in a self-report diary) of their child's emesis episodes during the first 24 h following chemotherapy. Antiemetic efficacy was assessed from the number of vomiting episodes, the need for rescue medication, and the extent of nausea and appetite loss. Nurse practitioners must assess each patient individually, with an assessment of past history of emesis and motion sickness, anxiety, age, gender, and previous chemotherapy.

Definitions and Parameters

Efficacy was assessed within 24 h of chemotherapy. No emetic episodes and no need for rescue medication within this period was considered complete efficacy; 1–2 vomiting attacks was considered major efficacy; 3–5 vomiting attacks was considered minor efficacy; and more than 5 vomiting attacks was considered lack of efficacy. A vomiting episode recurring 1 or more minutes after the previous one was considered a separate episode. Therapeutic failure was used as a dependent variable, and defined as the occurrence of 3 or more patient-described and -reported vomiting episodes during the study. Study investigators recorded the patient's age, gender, height, weight, body surface area, and the current chemotherapy and antiemetic regimen, as well as other chronic or episodic medications that may influence emetic response.

Efficacy End Point

Efficacy end points were nausea and emesis. Secondary efficacy parameters included the number of patients with therapeutic failure (i.e., more than 3 vomiting attacks over the 24-h study period, the need for rescue medication due to the severity of nausea or vomiting, or patient withdrawal from the study due to the lack of antiemetic drug efficacy); the number of patients

demonstrating complete efficacy or a major efficacy; and the time to the first emetic episode, patient withdrawal, and/or use of rescue medication.

Statistical Analyses

McNemar's chi-square test was used to compare the proportion of granisetron-treated patients versus the proportion of ondansetron-treated patients who had complete efficacy with either antiemetic. Analysis was conducted using the Wilcoxon signed rank test, with the emetic protection (minor efficacy or no efficacy was classified as "failure" and complete or major efficacy as "success") serving as the dependent variable and patient characteristics such as age, height, weight, and body surface area serving as independent variables. A comparison between genders was also made (Pearson's chi-square). The significance of observed differences in proportions was tested using Fisher's exact test, when appropriate, for small sample size. Results were expressed as means ± standard deviations.

The null hypothesis of no difference between treatment groups was tested against a two-tailed alternative for each efficacy end point. All statistical tests for treatment effects used a type I error level of .05. The statistical analysis was performed using the SPSS 11.0 statistical package for Windows (SPSS, Chicago, Illinois).

RESULTS

Thirty-five children were included in this study. Two of the initial prospective participants had anticipatory vomiting and were excluded. The remaining 33 patients (21 boys, 12 girls; representing 66 chemotherapy cycles) satisfied the selection criteria and were entered into the study. There were no statistically significant differences between the efficacy of the 2 antiemetics with regard to age or height. Success rates were statistically and inversely associated with the greater weight ($p = .016$; Mann–Whitney U test) and body surface area ($p = .019$; Mann–Whitney U test) in the ondansetron group (Table 1). The therapeutic failure rate was 15.2% (5/33) in the granisetron group and 12.1% (4/33) in the ondansetron group. Regardless of the antiemetic drug used, 53% (35/66) of the cycles were emesis-free. Complete efficacy occurred in 60.6% (20/33) and 45.5% (15/33) and therapeutic success occurred in 84.8% (28/33) and 87.9% (29/33) of granisetron and ondansetron recipients, respectively (Table 2). There was a positive association between the 2 antiemetic regimens with regard to success rates. The kappa statistics denote good reproducibility ($\kappa = 0.615$; $p < .001$) (Table 3).

Although the proportion of patients with complete efficacy with granisetron was higher than that with ondansetron, the difference was not statistically significant for any end point (McNemar test; $p = .227$). Complete efficacy rates for both treatment groups showed that boys were less likely to

TABLE 1 Demographic Characteristics of the Study Population

	Granisetron (mean ± SD)	*p* value[a]	Ondansetron (mean ± SD)	*p* value[a]
Age (months)				
Success	89.68 ± 56.70		88.10 ± 56.23	
		.315		.087
Failure	117.80 ± 68.43		36.25 ± 63.84)	
Height (cm)				
Success	119.95 ± 26.11		119.74 ± 25.82	
		.132		.069
Failure	140.20 ± 29.83		146.75 ± 28.73	
Weight (kg)				
Success	28.08 ± 15.55		27.56 ± 15.34	
		.092		.016
Failure	43.44 ± 24.28		51.05 ± 21.22	
Body surface area (m^2)				
Success	0.95 ± 0.35		0.94 ± 0.35	
		.088		.019
Failure	1.27 ± 0.50		1.42 ± 0.44	

[a]Calculated by Mann–Whitney *U* test.

respond to antiemetic treatment than were girls. In the granisetron group, 100% (12/12) of girls versus 76.2% (16/21) of boys had complete efficacy; in the ondansetron group, 100% (12/12) of girls versus 81.0% (17/21) of boys had complete efficacy. However, these differences did not reach statistical significance (Table 4).

Overall, both treatments led to effective control of emesis, and no patient required rescue medication. Because only 2 episodes of nausea were reported during our study, the effect of antiemetics on either the frequency or severity of nausea following chemotherapy was not analyzed. The most frequently reported adverse experiences were mild headache and constipation. The adverse effects were the same in both groups.

We also examined the cost difference between the 2 treatment modalities. Granisetron costs approximately $10.18 for a 1-mg tablet. This equates to $0.20/kg (20 μg/kg/patient). Ondansetron is more expensive, costing around $20.09 per 8-mg vial or $6.18 for a 4-mg tablet. This equates to

TABLE 2 Antiemetic Response Following Chemotherapy

	Granisetron ($n = 33$)	Ondansetron ($n = 33$)	*p*value[a]
Number of patients, *n* (%)			
Complete efficacy	20 (60.6%)	15 (45.5%)	
			.227
Incomplete control	13 (39.4%)	18 (54.5%)	
Therapeutic success	28 (84.8%)	29 (87.9%)	
			1.00
Therapeutic failure	5 (15.2%)	4 (12.1%)	

[a]Calculated by McNemar's chi-square test.

TABLE 3 Degree of Association with the Antiemetic Efficacy Between Granisetron and Ondansetron

		Ondansetron			
		Therapeutic success	Therapeutic failure	Total	Kappa statistics
Granisetron	Therapeutic success	27	1	28	.615[a]
	Therapeutic failure	2	3	5	
	Total	29	4	33	

[a] $p < .001$ testing kappa statistics equal zero.

about \$0.99/kg (0.15 mg/kg/patient). The drug cost differential between the 2 treatment modalities is \$0.79/kg, thus favoring granisetron therapy on the basis of cost. This cost savings will likely be further enhanced by oral administration of the drug, which eliminates infusion time and consequently reduces nursing time.

DISCUSSION

Although several methods are available to measure emesis, counting the number of emetic episodes appears to be the most frequent measure used [9]. With currently available antiemetic agents, the most desired end point is complete efficacy (i.e., no vomiting). Oral administration of 5-HT3 antagonists has been shown to have similar efficacy to iv administration of such agents for the purpose of antiemesis [10, 11]. Gralla et al. [11] demonstrated the comparable efficacy of a single dose of oral granisetron to a standard ondansetron iv regimen following moderately emetogenic chemotherapy.

Forty micrograms per kilogram appears to have been the optimal dose of granisetron in children with solid tumors receiving highly emetogenic chemotherapy [12–14]. The results of our study, however, have shown that granisetron (10–20 μg/kg administered as a single oral dose prior to chemotherapy) can also reduce the frequency of vomiting following moderately emetogenic chemotherapy with either cyclophosphamide or the combination of cyclophosphamide and etoposide. It was also shown that 0.5–1.0 mg of oral granisetron can lead to a satisfactory antiemetic response, which was

TABLE 4 Therapeutic Response Between Genders

	Granisetron			Ondansetron		
	Success	Failure	$p$value[a]	Success	Failure	$p$value[a]
Male ($n = 21$)	16 (76.2%)	5 (23.8%)	.133	17 (81.0%)	4 (19.0%)	.271
Female ($n = 12$)	12 (100%)	0 (0%)		12 (100%)	0 (0%)	

[a] Calculated by Fisher's exact test.

an impressive outcome for ALL patients treated with moderately emetogenic chemotherapy regimens consisting primarily of cyclophosphamide.

Because the problem of nausea and vomiting appears to be multifactorial, the rigorous control of confounding variables—particularly the patients' age, gender, and medical history—is essential [15]. Also, the acute antiemetic effect of oral granisetron (as with iv granisetron) appears to be dose related [16]. In our study, patients' individual assessments of nausea were similar between the 2 treatment groups. Although chemotherapy-induced emesis can be controlled effectively with iv antiemetic agents [5, 17], an equivalent oral antiemetic regimen administered in an outpatient setting may be more practical and more acceptable to patients.

Control of emesis seemed easier in girls than in boys. The cause of this gender discrepancy is currently unknown, and further investigation is needed. No significant relationship was found to exist between efficacy (emesis protection) and age or height. Interestingly, antiemetic efficacy was inversely related to greater weight and body surface area in ondansetron group.

ALL is the most common malignancy in children. Based on the assumption that simplicity decreases possible mistakes and tends to elicit more reliable results, we included only children with ALL in this study. Prophylactic corticosteroids were not used in our study because reports in the literature of antiemesis using serotonin receptor antagonists and corticosteroids combinations were conflicting [18–20]. Furthermore, patients in our study received cyclophosphamide, and emesis induced by cyclophosphamide is typically characterized by a monophasic response pattern that appears to be more intense within the first 24-h period [21].

The optimal oral dosage of granisetron still remains largely undetermined for pediatric patients [22, 23], and further studies are needed that target this population. Although in patients who receive moderately emetogenic chemotherapy, 5-HT3 receptor antagonists have not been convincingly demonstrated to be superior to metoclopramide plus dexamethasone for the prevention of nausea and vomiting [18], extrapyramidal effects limit the extent of use of traditional antiemetics to some degree [24].

Economic impact becomes an issue when comparing the best regimens and calculating which one is most cost effective. An effective single-dose oral antiemetic is convenient to use, improves antiemetic therapy compliance, and reduces the time spent in an outpatient treatment facility. With careful monitoring and titration of dosage, both granisetron and ondansetron were fairly well tolerated in this population.

CONCLUSIONS

In this study we compared the antiemetic activity of two 5-HT3 antagonists, granisetron and ondansetron, in the treatment of chemotherapy-induced emesis, when such agents were administered within 24 h of

moderately emetogenic chemotherapeutic regimens. Patients, in general, tolerated the antiemetics well, and their responses to these 2 drugs were not significantly different. A single prophylactic oral dose of granisetron (10–20 μg/kg), when given prior to moderately emetogenic chemotherapy, is at least as safe and effective as a triple dose of ondansetron given under similar circumstances.

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