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ORIGINAL ARTICLE

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Implementing evidence based antiemetic guidelines in the oncology setting: results of a 4-month prospective intervention study

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Abstract There is a considerable gap between obtaining results in randomized trials and implementing them into practice. This is particularly relevant with the high-cost 5HT3 antiemetics, which include ondansetron, dolasetron and granisetron. Randomized trial data suggests that they should be used as a single daily dose during only the first 24 h of chemotherapy because they offer little benefit over less costly agents beyond this period. In this study, six intervention methods (i.e. multifaceted approach) were combined to change physicians' 5HT3 prescribing patterns to comply with evidence-based antiemetic guidelines. A six-step implementation process was adopted, consisting of guideline dissemination, the use of opinion leaders, interactive educational workshops, therapeutic reminders in the form of preprinted orders, clinical interventions by pharmacists for the event of inappropriate antiemetic orders, and physician audit and feedback. Once implemented, the control of emesis was collected in all patients who were enrolled in the intervention program. Multivariable regression analysis was then used to assess whether prescribing within antiemetic guidelines compromised patient care. A total of 195 inpatients were enrolled in the study over the 4-month intervention period. Overall, 88.7% of granisetron prescriptions fulfilled the guidelines with respect to appropriate indication, dosage, and duration of therapy. The multivariable analysis suggested that granisetron prescribing within guidelines did not compromise the control of acute and delayed emesis. In addition, patients who received evidence-based antiemetic therapy experienced a significant reduction in the severity of acute nausea [risk ratio (RR) = 0.69; P=0.03]. The results of this guideline implementation study revealed that a pharmacist-driven multifaceted intervention program for such high-cost agents as 5HT3 antiemetics can promote their use in a clinically appropriate manner and can save unnecessary drug costs without compromising the quality of patient care.

Keywords 5HT3 antiemetics · Guidelines · Drug use evaluation · Evidence based medicine

Background

There is a considerable gap between obtaining results in randomized trials and implementing them in practice. One therapeutic area in which this is of particular relevance is the use of 5HT3 antiemetics. Agents in this therapeutic class include granisetron, ondansetron, tropisetron and dolasetron. Several well-designed double-blind randomized trials have demonstrated the therapeutic value of 5HT3s for the control of nausea and vomit-

ing within the first 24 h (acute phase) after chemotherapy [2, 9, 10]. However, they are no better than dexamethasone alone when used beyond (delayed phase) the first 24 h [8, 12]. In a recent meta-analysis of randomized antiemetic trials conducted by an expert panel from Cancer Care Ontario, the use of a 5HT3 antiemetic beyond the first 24 h was associated with an absolute risk reduction for emesis of only 5% compared with standard therapy [14]. Translating this benefit into a number-needed-treat implies that 20 patients ($0.05^{-1} = 20$) would have to be treated with a 5HT3 to prevent 1 patient from vomiting.

Since these agents are made available at a substantial drug acquisition cost, it is economically important for cancer treatment centers to limit their use to the first 24 h following chemotherapy. To facilitate this objective in our institution, evidence-based guidelines were developed in 1993 for the formulary agent of choice, ondansetron. Our group initially conducted a randomized guideline implementation study in 1994, with the clinical pharmacist acting as the vehicle for promoting evidence-based ondansetron use [3]. In that study, the pharmacist was able to improve the rate of appropriate ondansetron prescribing significantly, from 52% in the control arm to 76% in the group subject to pharmacist's intervention (P=0.007).

The main recommendation in the original 1993 ondansetron guidelines was that it should be given as an 8 mg i.v. dose before chemotherapy and then twice daily p.o. for up to 72 h [3]. Since that time, new evidence became available, highlighting the possibility of giving a 5HT3 as a single daily dose for the first 24 h only, without compromising patient care [15, 17]. A recent drug use evaluation conducted by the Pharmacy Department suggested that ondansetron was being administered as an 8 mg i.v./p.o. dose, 2–3 times per day for up to 5 days after chemotherapy. This was in contrast to the results of randomized trials, which demonstrated that ondansetron 8 mg i.v. dose is equivalent to a 32 mg i.v. dose for the prevention of acute emesis [15, 17]. Therefore, the task of changing physicians' prescribing practices from multiple-day ondansetron to single daily dosing was formidable. Specifically, our objectives were to implement single daily 5HT3 dosing for only the first 24 h after chemotherapy and to promote the use of non-5HT3 antiemetics (e.g. dexamethasone, domperidone) for the control of delayed nausea and vomiting.

Several methods have been used to alter the drug usage patterns of physicians to comply with evidence-based clinical guidelines. These have included the dissemination of written educational materials, the use of opinion leaders, didactic educational sessions, local consensus conferences, audit with prescriber feedback, physician prompting, and educational outreach mechanisms [11, 16]. Bero et al., in their overview of interventions to promote evidence-based medicine, concluded that these approaches had variable effectiveness when used alone [1]. Of all the methods reviewed, physician prompting and educational outreach mechanisms appeared to be the most effective approaches to promoting behavior change. The investigators suggested that a combination of two or more of these methods (i.e. a multifaceted approach) would have the greater likelihood of success [1].

Following a review of the intervention literature on successful promotion of behavior change, a multifaceted approach was adopted for the current study. Another consideration was choosing a 5HT3 that would increase the likelihood of successful guideline implementation. Ondansetron and granisetron are both excellent 5HT3 antiemetics with similar clinical and side effect profiles. Since the former agent had been in use at the institution since 1991, it was felt that changing the pattern of ondansetron prescribing (i.e. from 2–3 times daily to once daily) would be a difficult task because "old habits die hard." Following extensive internal and external discussions, the Oncology Subcommittee of the Pharmacy and Therapeutics Committee decided that changing the formulary antiemetic from ondansetron to granisetron would be the best course of action to facilitate evidence-based 5HT3 prescribing. The rationale behind this decision was that the majority of physicians at this institution did not have prior experience with the drug and the majority of randomized trials of granisetron had used single daily dosing.

In this study, the process and results of a 4-month antiemetic guideline implementation initiative are described. A control group was not considered necessary in this investigation, because our prior randomized 5HT3 intervention study had already created a baseline for comparison of appropriate drug use [3]. Furthermore, there was sufficient evidence available in the literature, which demonstrated the success of the interventions adopted in the current study [1, 11, 16]. Hence, the primary objective of this initiative was to determine whether promoting granisetron use within evidence guidelines could save hospital costs without compromising the quality of patient care.

Patients and methods

Development of antiemetic guidelines

This intervention study followed a four-step process. Before to the start of this initiative, no institutionally approved antiemetic guidelines encompassing all aspects of nausea and vomiting control existed. The only document available was that containing the original ondansetron guidelines developed in 1993. Since then, substantially more randomized trial data have been published. It was therefore decided that a complete set of antiemetic guidelines should be developed, consisting in criteria for the use of granisetron in the prevention of acute nausea and vomiting and for using alternative agents for delayed emesis.

Evidence-based guidelines for the prevention of chemotherapy-induced emesis were developed after a systematic review of

the literature and consultations with local and internationally recognized experts in nausea and vomiting control. Two areas in which limited randomized antiemetic data were available were high-dose chemotherapy with allogeneic or autologous stem cell rescue and induction / consolidation chemotherapy for patients with leukemia. To gain insight into these areas, several large cancer centers in the United States were contacted for discussion, and copies of their guidelines were requested. Following these initiatives, a comprehensive set of institutional antiemetic guidelines dealing with each of the disease sites was developed. Prior to administrative approval, draft copies were sent to leaders of the individual tumor groups for review, comment, and endorsement. The final draft was then approved by the hospital's Medical Advisory Committee (Appendix A).

The educational process

To increase the likelihood of success, the current study adopted a six-step multifaceted approach consisting of guideline dissemination, the use of opinion leaders, interactive educational workshops, therapeutic reminders in the form of preprinted antiemetic orders, educational outreach using the pharmacist as the vehicle for information and physician audit and feedback. Once the guidelines had been approved for institutional use, they were disseminated to all physicians who had prescribing privileges at the Princess Margaret Hospital (PMH). The guidelines and their implementation process were then presented by a local expert in antiemetic research (D.W.) via a hospital-wide "grand rounds" symposium.

To continue the educational process, representatives from the Department of Pharmacy conducted interactive workshops in each of the nursing units. Each session took the form of a "round table" discussion, with participants encouraged to express their thoughts and concerns regarding the switch from ondansetron to granisetron and the overall guideline implementation process. The target audience for these sessions included medical residents, interns, oncology nurses and clinical associates. All participants received a workshop information package consisting of pocket-size dosing cards, granisetron information pamphlets, and handouts focusing on practical issues that could be faced by nurses or physicians. Several sessions were held to ensure that the majority of the target audience was able to attend.

The intervention process

Once the guidelines had been disseminated and the educational programs had been completed, the next step in the initiative was to implement a prospective drug use evaluation (DUE) study with the clinical pharmacist as the instrument for promoting change. The role of the pharmacist was to offer therapeutic reminders to physicians prescribing antiemetics and to provide educational outreach in cases where antiemetic prescribing was contrary to hospital guidelines. The latter intervention is analogous to pharmaceutical representatives offering academic detailing to physicians. To ensure consistency in the intervention process, all pharmacists received training in the methods of educational outreach.

The final component of the process to facilitate change was providing feedback to the prescribing physician. The initial protocol was to conduct a DUE study for 4 months, evaluate the results, provide feedback to physicians and then continue the DUE study for another 4 months if guideline compliance continued to be suboptimal, with a focus on problem areas that were identified during the first 4-month phase.

Measuring clinical outcomes

Once the antiemetic guidelines had been approved, pharmacists monitored granisetron usage in all nursing units. For orders that were outside guidelines, a therapeutic intervention was performed to promote appropriate antiemetic therapy. Following chemotherapy, patients were interviewed to measure the control of nausea and vomiting. The control of acute (first 24 h) and delayed (2–5 days after chemotherapy) nausea was captured using a 5-point Likert scale with a score of 1 representing "no or very little nausea" and 5 representing "very severe nausea." To measure emesis control, the number of vomiting or retching episodes during the acute and delayed phases was also recorded. Additional information collected by clinical pharmacists consisted of patients' demographic characteristics, diagnosis, risk factors for chemotherapy induced emesis and antiemetic-induced side effects.

To facilitate data collection, each pharmacist was equipped with a handheld Palm Pilot, which contained an electronic data collection form. At the end of each week, the outcomes data stored in the Palm Pilot were easily downloaded into the main computer database. The use of this device not only improved the efficiency of data collection and transfer, but also reduced the risk of errors because it eliminated data transcription and entry. The prospective intervention study was then continued for approximately 4 months, at the end of which an interim analysis was conducted.

Statistical analysis

Patient demographic and clinical characteristics were presented as descriptive statistics as means, medians, or proportions. The Chi-square statistic was used to compare the rates of complete control of acute and delayed emesis between patients who received granisetron within guidelines relative to those who did not. To determine which factors were associated with improved acute and delayed emesis, a multivariable logistic regression analysis was conducted. The dependent variable in the models was complete emesis control, defined as no vomiting. Since the outcomes of acute and delayed nausea were on a 5-point Likert scale, Poisson regression was used to identify factors that were associated with poorly controlled nausea.

Before each regression analysis was initiated, the relevant covariates for model inclusion were identified by a bivariate screening process with a preset alpha = 0.15. This is a recommended approach for removing unimportant covariates so that a more manageable set of variables can be submitted to multivariate techniques [6]. Categories were collapsed in cases where the number of observations within cells was less than 5. The cut-off for significance for all of the statistical procedures was P=0.05.

Results

A total of 195 inpatients were enrolled in the study over the 4-month intervention period. Demographic and clinical characteristics and risk factors for emesis are presented in Table 1. Nearly 50% of patients had either leukemia or lymphoma and had been admitted to hospital to receive chemotherapy for their disease. Approximately 61% of patients had previously received chemotherapy, and 15% had experienced at least one emetic episode (Table 1). The majority of patients were receiving multiple-day chemotherapy as opposed to a single day of treatment (78% vs 22%). Since the current study was confined to hospitalized patients, multiple-day chemotherapy typically consisted of induction / consolidation protocols for acute leukemia, salvage therapy for refractory lymphoma, and stem cell transplantation.

Clinical pharmacists evaluated 183 of the 195 (93.4%) granisetron orders and compared them to the antiemetic

Table 1 Patient demographic and clinical characteristics

Characteristics	*N*=195
Mean age (SD)	50.0 (16.0)
Gender (%)	
Male	52.8
Female	47.2
Alcohol status (%)	
Nonregular drinker	92.8
1–3 drinks/week	2.0
4–8 drinks/week	2.6
>10 drinks/week	2.6
Cancer site (%)	
Allo- / autotransplantation[a]	20.0
Leukemia/lymphoma	49.2
Solid organ tumor	30.8
Previously received chemotherapy (%)	61.0
Previous history of emesis (%)	
Previous chemotherapy but no emesis	45.1
Previous chemotherapy with emesis	15.9
Chemotherapy naive	39.0
Type of chemotherapy (%)	
Single day	22.0
Multiple day	78.0

[a] Bone marrow or peripheral stem cell transplantation

guidelines. Twelve orders were not reviewed because they were prescribed on weekends when clinical pharmacy service was reduced. Of the 183 prescriptions evaluated, pharmacists identified 49 as being outside of guidelines and contacted the physician for therapeutic modification as described in the protocol. The physician changed the antiemetic prescription to comply with guidelines in 39 of these 49 orders, for an overall pharmacist success rate of 80%. The average time required by the pharmacist to perform an intervention was 10 min, with a range of 5–15 min.

A breakdown of the ten granisetron prescriptions that were outside of guidelines despite the pharmacist intervention showed that one was used prior to an infusion of single-agent paclitaxel, two were for first-line treatment of delayed emesis, two were for antibiotic-induced nausea and vomiting, two were for a correct indication but granisetron was dosed at 1 mg twice daily following chemotherapy, and three were for a duration beyond 24 h following chemotherapy. In the cases of the 12 orders that were missed because the prescription was written on weekends, the duration of therapy was beyond 24 h in 8 cases and the appropriateness of the remaining 4 prescriptions was inconclusive.

Following these interventions, 97.4% of all granisetron prescriptions were for an appropriate indication as recommended in the guidelines (Appendix A). Similarly, 99% of granisetron orders used the approved dosage (i.e. 1 mg i.v. per day) and 94.4% used the recommended duration (i.e. 24 h after chemotherapy only). When all three prescribing criteria (e.g. indication, dosage, duration) were considered together, 173 of 195 (88.7%) fulfilled the guidelines (Table 2).

An economic analysis was not part of the study protocol. However, based on our previous experience with multiple daily doses of ondansetron, a cost saving of between $Can10.00 and $Can20.00 was realized with each granisetron order prescribed according to guidelines. Given the volume of 5HT3 antiemetics prescribed annually (>10,000 doses), substantial cost savings will be realized by the institution through this intervention program. Through this ongoing process, the economic benefits to the institution would more than offset the requirement in terms of pharmacist time, program start-up and maintenance costs.

Following the administration of chemotherapy, the control of acute and delayed nausea and vomiting was also assessed. The data suggested that the 173 patients who received antiemetic therapy within hospital guidelines achieved complete control of acute emesis in 83% of cases. Comparison with patients who received therapy outside of guidelines revealed no statistically significant differences in acute emesis control (83% vs 71%, *P*=0.19). Similarly, for delayed emesis 79% of patients receiving antiemetic therapy within the guidelines achieved complete control, compared with 82% of those who received antiemetics outside of guidelines (*P*=0.77). This latter group typically received 5HT3s beyond the first 24 h.

When all of the outcome data were compiled, approximately 80% of patients in the study cohort achieved complete (i.e. no vomiting episodes) control of acute and delayed emesis. In addition, 75–80% of patients scored 1 or 2 on the 5-point nausea severity scale. Antiemetic outcomes in the various patient subgroups were also determined (Table 3). The results implied that patients undergoing high-dose chemotherapy followed by allo- / autotransplantation tended to have poorer antiemetic control

Table 2 Granisetron prescribing relative to antiemetic guidelines

Usage criteria	Within guidelines (*N*=195)
Indication (moderate to highly emetogenic chemotherapy)	97.4%
Dosage (1 mg i.v. per day)	99.0%
Duration (24 h after chemotherapy only)	94.4%
All three usage criteria fulfilled[a]	88.7%
Cost savings per appropriate prescription[b]	$10.00–$20.00

[a] Pharmacists intervened on 49 occasions
[b] Relative to previous ondansetron 8 mg i.v. 2–3 times daily prescribing data

Table 3 Control of acute and delayed nausea and vomiting

Evaluation period	Outcome (*N*=195)
All patients	
Complete control of acute emesis	81.8%
Complete control of delayed emesis	79.6%
Major control of acute nausea[a]	79.7%
Major control of delayed nausea[a]	76.4%
Patient subgroups	
Complete control of acute emesis:	
Allo- / autotransplantation[b]	73.7%
Solid organ tumor	89.3%
Leukemia/lymphoma	80.6%
Complete control of delayed emesis:	
Allo- / autotransplantation[b]	52.6%
Solid organ tumor	94.7%
Leukemia/lymphoma	85.2%
Complete control of acute nausea[a]	
Allo- / autotransplantation[b]	65.8%
Solid organ tumor	88.0%
Leukemia / lymphoma	80.6%
Complete control of delayed nausea[a]:	
Allo- / autotransplantation[b]	57.9%
Solid organ tumor	86.8%
Leukemia / lymphoma	80.2%

[a] Defined as 1 or 2 on a 5-point nausea severity scale
[b] Bone marrow or peripheral stem cell transplantation

than patients with solid tumor or those on the leukemia / lymphoma service.

A series of multivariable analyses were then conducted to confirm that prescribing within hospital antiemetic guidelines had not compromised patient care and to identify other factors that were associated with improved nausea and vomiting control (Table 4). In the case of acute and delayed emesis, the data suggested that granisetron use (i.e. a single daily 1 mg i.v. dose vs multiple doses) within guidelines did not have a negative effect on patient care (OR=0.42; *P*=0.16 and OR=0.54; *P*=0.42).

Factors that were identified as significantly associated with a reduced risk of acute and delayed emesis included previous history of chemotherapy, the antiemetic prescription being written by a staff physician as opposed to others, and increasing patient age (Table 4). There was also a trend for patients receiving treatment for solid tumors or leukemia / lymphoma to have a substantially lower risk of delayed emesis than the auto- / allotransplantation group (Table 4).

The final set of analyses consisted of the application of Poisson regression to the nausea severity rating scale score for both the acute and the delayed periods (Table 5). The most interesting finding was that antiemetic prescribing within hospital guidelines was associated with a reduction in the severity of acute nausea (Table 5). This outcome may have been due to promoting the use of dexamethasone 20 mg i.v. before chemotherapy instead of the previous standard of 10 mg. If substantiated with additional research, these findings have important implications, in that not only are costs saved with the appropriate use of antiemetics in cancer patients, but also and more importantly, there is a potential to increase the quality of patient care.

In the case of delayed nausea, the data revealed that increasing the duration of 5HT3 antiemetics beyond the first 24 h post-chemotherapy did not have a significant impact on the control of delayed nausea (Table 5). These observations are consistent with the results of several randomized trials evaluating 5HT3 antiemetics in the control of delayed nausea and vomiting [8, 12, 14]. Another finding that was not surprising was that patients who had experienced previous chemotherapy-induced emesis had a higher risk of severe nausea than those who had not had prior emesis (Table 5).

The final set of outcomes collected in this study were the side effects associated with granisetron therapy (Table 6). The data did not reveal any major deviations, with side effect rates as reported in the literature. Overall, granisetron was well tolerated by most patients.

Table 4 Results of logistic regression analysis on risk factors for acute and delayed emesis. Dependent variables = acute and delayed emesis (yes/no) when assessed at 24 and 120 h. (*Prior chemo* patients had received prior chemotherapy, *NS* no significant effect)

Variable	Odds ratio	95% CI	*P*-value	Risk of emesis
Acute emesis				
Within guidelines[a]	0.42	0.13 to 1.39	0.16	NS
Prior chemo	0.41	0.17 to 0.99	0.046	Overall ↓ by 59%
Staff physician[b]	0.42	0.18 to 1.0	0.05	Overall ↓ by 58%
Solid tumor[c]	0.30	0.08 to 1.15	0.079	NS
Leukemia / lymphoma[c]	0.62	0.23 to 1.68	0.35	NS
Delayed emesis				
Within guidelines[a]	0.54	0.12 to 2.45	0.42	NS
Patient age (years)	0.97	0.94 to 0.99	0.039	↓ risk in older patients
Solid tumor[c]	0.07	0.01 to 0.40	0.003	Overall ↓ by 93%
Leukemia / lymphoma[c]	0.19	0.07 to 0.54	0.002	Overall ↓ by 81%

[a] The antiemetic order met hospital guidelines with respect to indication, duration and dosage
[b] Antiemetic therapy prescribing by staff physicians relative to interns/resident/clinical associates
[c] Relative to allogeneic/autologous transplantation patients

Table 5 Results of Poisson regression analysis on risk factors for acute and delayed nausea. Dependent variable = risk of nausea measured on a 5-point nausea severity scale (*NS* no significant effect)

Variable	Risk ratio	95% CI	*P*-value	Risk of nausea
Acute nausea				
Within guidelines[a]	0.69	0.50 to 0.97	0.03	Overall ↓ by 31%
Staff physician[b]	0.72	0.56 to 0.91	0.007	Overall ↓ by 28%
Solid tumor[c]	0.73	0.52 to 1.03	0.07	NS
Leukemia / lymphoma[c]	0.78	0.60 to 1.03	0.085	NS
Delayed nausea				
5HT3 duration≤24 h[d]	0.79	0.46 to 1.35	0.30	NS
Previous emesis[e]	1.44	1.05 to 1.96	0.024	Overall ↑ by 56%
Solid tumor[c]	0.72	0.50 to 1.04	0.079	NS
Leukemia / lymphoma[c]	0.81	0.61 to 1.07	0.13	NS

[a] The antiemetic order met hospital guidelines with respect to indication, duration and dosage
[b] Antiemetic therapy prescribing by staff physicians relative to interns / resident / clinical associates
[c] Relative to allogeneic/autologous transplantation patients
[d] Granisetron was administered as a single 1 mg i.v. dose for the first 24 h. Non-5HT3 therapy was used beyond the first 24 h, as recommended in the guidelines (Appendix A)
[e] Relative to patients who had not experience previous chemotherapy-induced emesis

Table 6 Documented side effects of granisetron therapy

Side effect	% Incidence
Headache	14.9
Constipation	4.1
Diarrhea	7.7
Asthenia	1.0
Somnolence	3.6
Abdominal irritation	6.1

Discussion

In North America alone, the 5HT3s represent almost a billion-dollar market. There is evidence in the drug use evaluation literature demonstrating that these agents are overdosed and often used in situations where a less expensive agent would provide at least comparable efficacy [3, 13, 18]. This is particularly relevant in the control of delayed emesis, where serotonin receptor stimulation does not have a dominant role in the mechanisms of action [7]. To manage our limited medical resources more efficiently, therapeutic areas need to be identified in which the use of less costly interventions would not compromise the quality of patient care. Improving the appropriate use of the 5HT3 antiemetics is one area where this objective could be realized, because there is a wealth of randomized trial data supporting the use of cost-effective alternatives to the 5HT3 antiemetics.

The task of the health policy researcher is to identify practical methods that would achieve these objectives. In their systematic review of the literature, Bero et al. identified several interventions that have been used to promote change in physician prescribing practices [1]. The investigators concluded that the most consistently effective interventions were educational outreach visits, which are analogous to academic detailing by the pharmaceutical industry, prompting, and interactive educational meetings. In addition, it was suggested that multifaceted initiatives (consisting of two or more interventions) appear to be more effective than single interventions [1, 10]. Bero et al. [1] concluded that greater emphasis should be given to conducting studies that evaluate two or more interventions in a specific clinical setting.

The current investigation combined six methods to improve physician prescribing of antiemetics in cancer patients. The results of this guideline implementation study revealed that a pharmacist-driven multifaceted intervention program for high-cost agents such as 5HT3 antiemetics can promote their use in a clinically appropriate manner and save unnecessary drug costs without compromising the quality of patient care. The implementation model and these findings have important implications for promoting evidence-based drug use in the oncology setting. Furthermore, such a model can easily be adapted to other important drugs, such as antibiotics, whose overuse has been implicated in the development of resistant microorganisms, and to colony-stimulating factors [4, 5].

There are several reasons behind the success of this intervention study. These included the collaboration of local antiemetic experts (D.W.) and clinical pharmacists, support from the hospital administration, the utilization of novel data collection technology, and an open partnership with the manufacturer, who was committed to promoting evidence-based use of granisetron. In addition, a solid clinical pharmacy program with motivated clinical pharmacists was also essential.

There are several limitations in the analysis of the final results, which should be addressed. This was not a randomized trial, but a single-arm prospective cohort study. As a result, it is not possible to state definitively that the process adopted in the current study was responsible for all the documented effects. However, our previous attempt to implement ondansetron guidelines had an overall success rate of only 76% [3]. One of the findings of the Poisson regression model was that patients who received antiemetic treatment within hospital guidelines had better control of acute nausea than those who received treatment outside of guidelines. This outcome

may have come about because patients treated outside of guidelines had severe uncontrolled nausea requiring the physician to use more intensive antiemetic therapy.

In conclusion, the results of this study reveal that evidence-based guidelines can be effectively implemented in a cancer treatment center through a carefully designed and well-managed intervention program. The benefits that can be realized by the institution are reduced drug costs and, more importantly, the potential for improved patient care. Future guideline implementation initiatives are urgently needed in other therapeutic areas, such as infectious diseases and the use of colony-stimulating factors. Only by such an approach to drug therapy can our limited oncology resources be used more efficiently, which would allow more patients to be treated within a fixed health-care budget.

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Appendix A

Evidence based guidelines for the prevention of chemotherapy induced emesis

	Mildly emetogenic agents or protocols	Moderately to highly emetogenic agents or protocols
	Use non-5HT3 antagonist premed	Use 5HT3 antagonist premed Automatic substitution of granisetron for all in-hospital 5-HT_3 antagonists prescribed
Before chemotherapy[a]	– No prophylaxis if emesis not anticipated *OR* – Dexamethasone 10–20 mg p.o./i.v.[c]	Out-patient[b]: Granisetron 1 mg i.v. or p.o. In-patient: Granisetron 1 mg i.v. *PLUS* – Dexamethasone 20 mg p.o./i.v.[c] *PLUS* (for high risk patients only) – Metoclopramide 0.5 mg/kg every 6 h i.v./ p.o. (plus diphenhydramine 50 mg p.o. every 4 h p.r.n. for restlessness and dystonic reactions) *OR* – Domperidone 20 mg p.o. q.i.d.
After chemotherapy (first 24 h)	– If dexamethasone alone continue to provide inadequate acute emesis prophylaxis, add 5HT3 (add 5HT3 antagonist in subsequent cycles)	Outpatient prescription: – Granisetron 1 mg p.o. (or other 5HT3 antagonists equivalent) 12 h after chemotherapy if oral granisetron was used before chemotherapy *Add p.r.n.* – Metoclopramide 0.5 mg/kg p.o. every 6 h (plus diphenhydramine 50 mg p.o. every 4 h p.r.n. for restlessness or acute dystonic reactions) *OR* – Domperidone 20 mg p.o. q.i.d. Inpatients: – Same p.r.n. medications as outpatients (i.v. or p.o.). In rescue situation, use i.v. metoclopramide (0.5 mg/kg every 6 h) (plus diphenhydramine)
Delayed emesis (24 h after chemotherapy to 3–5 days)	– Dexamethasone 4–8 mg p.o. b.i.d. for 3–5 days if delayed emesis is anticipated[c] *ADD p.r.n.* – Metoclopramide 0.5 mg/kg p.o./i.v. every 6 h (plus diphenhydramine 50 mg p.o. every 4 h p.r.n. for restlessness or acute dystonic reactions) *OR* – Domperidone 20 mg p.o. q.i.d. Note: 5HT3 antagonists reserved for patients who do not respond to the above	– Dexamethasone 4–8 mg p.o. b.i.d. for 3–5 days if delayed emesis is anticipated[c] *ADD p.r.n.* – Metoclopramide 0.5 mg/kg i.v./p.o. every 6 h (plus diphenhydramine 50 mg p.o. every 4 h p.r.n. for restlessness or acute dystonic reactions) *OR* – Domperidone 20 mg p.o. q.i.d. Note: 5HT3 antagonists reserved for patients who do not respond to the above

[a] For anticipatory nausea/vomiting, add lorazepam 1–2 mg s.l./p.o. before chemotherapy. Prechemotherapy antiemetics can be given anytime within 30 min before chemotherapy

[b] Prechemotherapy recommendation applicable only to patients who have *not* been premedicated with 5HT3 at home

[c] The use of steroids is usually avoided in AML patients

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