INNOVATIONS in pharmacy lip

Volume 2 | Number 3 Article 52

2011

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Acknowledgments: The authors like to acknowledge the pharmacy staff at the University of Minnesota Medical Center for their help in collecting data necessary for this project. We also like to acknowledge Brian Isetts, Ph.D, BCPS, FAPhA for his role as an administrative advisor for this project.
Disclosure: Authors of this paper have no disclosures concerning any financial or personal conflicts.
Key Words: Chemotherapy induced nausea and vomiting, CINV, pharmacist, pharmacist management, pharmacist protocol, oncology, chemotherapy.

Abstract
Chemotherapy-induced nausea and vomiting (CINV) is a major adverse event associated with cancer treatments. There are clinical practice guidelines that assist practitioners in managing CINV. Many cancer centers develop protocols for physicians and pharmacists to guide prophylaxis and breakthrough treatments of CINV based on published guidelines. The purpose of this study was to evaluate the outcome differences between pharmacist and physician -driven management of CINV in adult hospitalized cancer patients in a large academic medical center. This is a single center retrospective chart review study. The primary outcome of the study was the number of breakthrough antiemetic doses needed throughout the hospitalization. A total of 106 adult patients receiving inpatient chemotherapy were reviewed for CINV management. Fifty-five patients (52%) were managed according to the pharmacist-driven protocol, and fifty-one patients (48%) were managed by the physician. There was no difference between the two groups in the primary outcome. Patients in the pharmacist-managed group needed 6.4 breakthrough antiemetic doses; whereas, patients in the physician managed group needed 5.9 doses throughout the hospital stay (P-value = 0.7). No difference was seen when results were adjusted for length of hospitalization. There was a difference in adherence to the institution CINV guidelines favoring the pharmacist-driven approach (85% versus 33%, P < 0.0001). In conclusion, pharmacist-run protocol for CINV management was as effective as the standard of care. Protocols that are based on practice guidelines may offer the advantage of care standardization and potential cost savings.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is a major adverse event associated with cancer treatments. CINV significantly affects a patient's quality of life, and the severity of episodes may also affect their compliance and the intended treatment intensity.[1] It is considered one of the most distressing and feared adverse effects experienced by patients receiving chemotherapeutic or radiation treatments.[2,3] There are clinical practice guidelines that assist the effective management of CINV symptoms by oncology practitioners.[4,5,6] Guidelines aim to prevent CINV from developing following the administration of chemotherapy or radiation treatments. CINV is classified into five distinct categories: acute, delayed, anticipatory, refractory and breakthrough nausea and vomiting.[4,5,6] The type and intensity of chemotherapy or radiation treatments affect the severity of CINV episodes and therefore, the recommended treatment regimens. Some patient specific risk factors contribute to the incidence and intensity of CINV. Risk factors in the acute phase include female sex, younger age, history of refractory CINV, history of motion sickness, anxiety and absence of alcohol use.[4,7] Risk factors in the delayed phase include female sex and poor control in the acute phase.[4,7] Clinical practice guidelines classify chemotherapeutic agents based on the incidence of emesis. They are classified into high (incidence >90%), moderate (30-90%), low (10-30%) and minimal (<10%).[4,5,6]

Despite the recent advances in antiemetic agents, including the introduction of 5-HT_3 antagonists starting in the 1990s and Neurokinin-1 (NK1) antagonists in 2006, patients continue to struggle with CINV.[7] Recent studies suggest that an element of the continued struggle with CINV can be the failure of health care providers to adequately anticipate its incidence, understand its complex physiology and adhere to recommended guidelines.[7,8]

Clinical practice guidelines provide agent and dosage recommendations, but agent of choice and dosing algorithm may differ among cancer centers and oncology practitioners.[9] Cancer centers develop institution-specific protocols for CINV prophylaxis and breakthrough treatments that are based on published practice guidelines. These guidelines assist practitioners and house staff in decision making. Many

institutions also develop pharmacist-driven protocols approved by the *Pharmacy &Therapeutics Committee* for the prophylaxis and breakthrough treatments of CINV. Such protocols allow clinical pharmacists to provide appropriate antiemetic regimens based on chemotherapy administered and other patient specific factors. They also allow clinical pharmacists to provide regimens for breakthrough symptoms without the prior authorization of the prescribing oncologist. This not only provides a tool to standardize treatment strategies across the institution, but also saves needed time when patients are experiencing breakthrough episodes. The use of such protocols remains voluntary, and oncologists can prescribe antiemetic regimen based on their clinical judgment.

The purpose of this study was to evaluate the clinical outcome differences between pharmacist and physician-driven management of CINV in adult cancer patients in a large academic medical center.

Methods

Study design and patient population

This is a single center retrospective chart review study. The Investigational Review Board of the academic medical center approved the study protocol. Medical records of patients admitted to the Medical Hematology/Oncology unit for scheduled inpatient chemotherapy between February 2010 and August 2010 were reviewed. Inclusion criteria included age over 18 years, confirmed cancer diagnosis and active inpatient chemotherapy during the hospitalization. Patients with confirmed cancer diagnosis were defined as those with a documented new or recurrent cancer diagnosis at time of hospital admission including solid organ tumors, leukemia and lymphoma. Exclusion criteria included surgical patients, non-cancer diagnoses and those admitted for chemotherapy desensitization.

Data Collection

Data was extracted from patients' electronic medical records by the study principal investigator. Data collected included general characteristics of patients such as demographic data, diagnosis and clinical course throughout the hospital stay. Chemotherapy admission orders were reviewed to determine whether the patient's antiemetic regimen was managed by the prescribing oncologist or the pharmacist-managed protocol. Electronic medication administration records were reviewed by the investigator to determine the number of breakthrough doses needed during the hospital stay,. Breakthrough doses were defined as all doses needed for breakthrough nausea and vomiting and did not include any scheduled prophylaxis antiemetic doses.

Outcome Assessments

The primary outcome of the study was the number of breakthrough antiemetic doses needed throughout the hospital stay as a surrogate marker of the quality of CINV management. Secondary outcomes included the rate of adherence to the institution protocol which is largely based on the nationally and internationally recognized clinical practice guidelines.[4,5,12] Patients' chemotherapy and antiemetic regimens were compared against the institution CINV protocol by the study investigator to determine the appropriateness of prophylaxis and breakthrough regimens prescribed at the time of admission. Adherence to the institution protocol was defined as prescribing prophylaxis and breakthrough regimens that are in accordance with the institution CINV protocol. Inappropriate regimens were defined as those lacking one or more antiemetic agents. Excessive prophylaxis regimens were defined as those providing more antiemetic doses than recommended by the institution CINV guidelines. The antiemetic agent, its frequency and the total number of doses used were evaluated to determine the appropriateness of the regimen. However, the dose of antiemetic agents was not used in the review criteria. Secondary outcomes also included the total number of breakthrough doses and number of doses per hospital day stratified according to chemotherapy regimen and its corresponding risk of CINV.

Statistical Analysis

The mean or median was calculated for continuous variables such as age, number of doses and number of doses per hospital day. We used the Student *t*-test or the Wilcoxon rank sum test to assess differences in the means or medians, respectively. Categorical variables-such as gender, appropriateness of regimen and rate of adherence-were compared using the X^2 test or Fisher exact test. All tests were two-tailed, and a p-value of < 0.05 was considered to be statistically significant. A sample size of 86 (43 per group) was calculated prospectively to yield a statistical power of 80% to detect a difference of five breakthrough antiemetic doses needed throughout the hospital stay.

Results

Patients

A total of 110 patient charts were reviewed. Four charts did not meet the inclusion criteria. The remaining 106 charts met the inclusion criteria and were reviewed. Fifty-five patients (52%) were managed according to the pharmacist-managed protocol, and fifty-one patients (48%) were managed by the prescribing oncologist and the house medical staff. Overall, there were more male than female patients (65% versus 35%, P = 0.003). The most common diagnosis was lymphoma (40% of all patients), followed by sarcoma (21%) then leukemia

(17%). Most patients in the pharmacist-managed group (54 of 55, 98%) were diagnosed with either leukemia or lymphoma. The most common diagnosis in the physician-managed group was sarcoma (43%) followed by ovarian cancer (18%). The median age of all patients was 51 (range 18-87). Summary of demographics and diagnoses on admission is shown in Table 1. Most chemotherapy regimens used were those with moderate to high emetic risk with high risk for delayed CINV. Chemotherapy regimens with moderate emetic risk were the most common in the pharmacist-managed group (40% of all regimens), followed by regimens with high emetic risk with high risk for delayed effects (31%). Regimens with moderate emetic risk with high risk for delayed CINV were the most common in the physician-managed group (37% of all regimens), followed by regimens with moderate emetic risk (27%). (Table 2)

Primary End Point

There was no statistically significant difference between the two study groups in the primary outcome. Patients managed according to the pharmacist protocol needed an average of 6.4 breakthrough antiemetic doses throughout the hospital stay; whereas, patients managed by the prescribing oncologist or the house medical staff needed an average of 5.9 doses throughout the hospital stay (P = 0.7). Length of hospital stay was similar between the two study groups, 7.6 days in the pharmacist-managed group and 5.6 days in the physician-managed group (P = 0.07) (Table 1). Adjustment for length of hospital stay was performed. Patients in the pharmacist managed group needed an average of 0.85 breakthrough doses per day of hospitalization; whereas, patients managed by the oncologist or house medical staff needed an average of 0.91 breakthrough doses per day of hospitalization (P = 0.78).

Secondary End Points

There was a statistically significant difference in the rate of adherence to the institution guidelines. In the pharmacist-managed group, the rate of adherence was 85% (47 out of 55 cases), while in the physician managed group the rate of adherence was 33% (17 out of 51 cases) (P < 0.0001). (Table 3) The most common reason for non-adherence in the physician-managed group was the lack of appropriate coverage for delayed CINV. In the physician managed group, 22 of 34 non-adherence cases (65%) were due to inappropriate delayed CINV antiemetic regimen, 10 of 34 non-adherence cases (29%) were due to excessive prophylaxis regimen, 1 case (3%) was due to inappropriate prophylaxis regimen and 1 case (3%) was due to lack of breakthrough regimen. In the pharmacist-managed group, 7 of 8 non-adherence cases (87%) lacked appropriate delayed CINV antiemetic regimen and 1 case (13%) was due to excessive prophylaxis regimen (Figure 1). Data was stratified into five distinct categories according to CINV risk associated with chemotherapy regimen used. There was no statistically significant difference in outcomes in all categories except one. In chemotherapy regimens with high emetic risk with high risk for delayed CINV, there was a difference favoring the physician-managed group (0.65 versus 1.1 breakthrough doses per day of hospitalization; P = 0.05). There was no difference in all the other groups (Table 4).

Discussion

In this retrospective chart review study, there was no statistically significant difference between the two study groups in the total number of breakthrough doses needed for CINV: 6.4 doses per encounter in the pharmacist managed group compared to 5.9 in the physician managed group (P = 0.7). There was also no significant difference when results were adjusted for length of hospital stay (0.85 doses per day versus 0.91, P = 0.78). There was a significant difference in the rate of adherence to the institution protocol favoring the pharmacist-managed approach (85% versus 33%, P < 0.0001). When data was stratified according to CINV risk associated with chemotherapy regimens used, there was a difference favoring the physician-managed group for regimens with high CINV risk with high risk for delayed symptoms.

In the physician-managed group, 20% of patients (10 of 51 cases) received excessive CINV prophylaxis regimens compared to only 2% in the pharmacist-managed group (1 of 55 cases). Four of eleven patients who received chemotherapy regimens with high emetic risk with high risk for delayed CINV, and who were managed by the physician, had excessive antiemetic prophylaxis regimens. Excessive prophylaxis regimens generally included scheduled ondansetron, dosed three to four times per day throughout the hospital course regardless of the chemotherapy schedule. However, it is unclear if this pattern of excessive prophylaxis regimens can explain the difference seen in this subgroup. This observation suggests that over prescribing prophylactic antiemetic regimens may not correlate with less breakthrough CINV episodes. This also presents an economical aspect and an area of potential cost savings.

To our knowledge, this is the first study that directly compares the two management approaches. Several studies had demonstrated the added value when clinical pharmacists were directly involved in cancer patients' care as the drug experts.[10,11] The results of this study are consistent with that notion. The need for the pharmacist involvement grew significantly with the shift from a disease-centered to a patient-centered care.[10] With that shift, patient's quality of life became a measure that is, perhaps, as important as the

disease progression.[11] Areas in cancer supportive care where pharmacists contribute to patient care and quality of life includes pain management, anemia, co-morbid conditions and chemotherapy or radiation induced nausea and vomiting.

The interpretation of the results of this study is limited by the retrospective nature of the study design. Patients in the two study groups were not well matched with regard to gender and admission diagnosis. Other variables that may have affected the outcomes of the study, but could not be studied due to limited data, include severity of disease, CINV risk factors, co-morbid conditions and history of radiation treatments.

Clinical Practice Guidelines are defined as systemically developed statements, for specific clinical circumstances, that assist practitioner and patient decisions about appropriate health care.[13] Given the evidence-based nature of clinical practice guidelines, it is essential to adhere to their recommendations especially when clinical outcomes are tied to clearly defined measures such as mortality or cure rates. The implementation of such guidelines can be difficult in the area of supportive care due to its subjective nature and the lack of clearly defined outcomes like mortality or cure rates. In such case, one can argue that guidelines for CINV management should serve as an educational tool to improve practitioners' understanding of chemotherapy- induced nausea and vomiting and its effective management. Kaiser and colleagues argue that better adherence to antiemetic guidelines can only be achieved through a complex and long-term process, consisting of efficient education, training, and monitoring of all individuals involved.[14] The purpose of this study was not to advocate for the strict adherence to nationally recognized guidelines for CINV management. Indeed, there are some patient specific factors that can drive the clinical decision away from suggested treatments such as history of adverse reactions or existence of co-morbid conditions. When such factors are not contributing to the decision making process, the argument for following the suggested treatments is much stronger.

In conclusion, pharmacist-managed protocol for the clinical management of CINV was as effective as the standard of care. Pharmacist-managed protocols that are based on nationally recognized practice guidelines might offer the advantage of standardization of care and potential cost savings.

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Table-1. Demographic Characteristics of Patients

Characteristic		Pharmacist managed Group (N=55)	Physician Managed Group (N=51)	All Patients (N=106)	P-Value
Gender, n (%)					
	Male	41 (75)	28 (55)	69 (65)	0.003
	Female	14 (25)	23 (45)	37 (35)	0.003
Age, Years[1]		47±16	52±14	49±15	0.12
Diagnosis, n (%)					
	Leukemia	16 (29)	2 (4)	18 (17)	
	Lymphoma	38 (69)	5 (10)	43 (40)	
	Sarcoma	0 (0)	22 (43)	22 (21)	
	Ovarian Cancer	0 (0)	9 (18)	9 (8)	
	Testicular Cancer	0 (0)	1 (2)	1 (1)	
	Renal Cell Carcinoma	0 (0)	2 (4)	2 (2)	
	Small Cell Lung Carcinoma	1 (2)	1 (2)	2 (2)	
	Head and Neck Cancer	0 (0)	3 (6)	3 (3)	
	Other	0 (0)	6 (12)	6 (6)	
LOS, Days[1,2]		7.6±5.7	5.6±3.6	6.7±5	0.03

1) Plus–minus values are means ±SD

2) LOS: Length of Stay

Table-2. Emetogenecity of Chemotherapy Regimens Used

Emetic Risk[#]	Pharmacist managed Group N=55 n (%)	Physician Managed Group N=51 n (%)	All Patients N=106 n (%)	P-value
HEC	0 (0)	0 (0)	0 (0)	--
HEC+D	17 (31)	11 (22)	28 (26)	0.15
MEC	22 (40)	14 (27)	36 (34)	0.05
MEC+D	13 (24)	19 (37)	32 (30)	0.05
LEC	1 (1.5)	4 (8)	5 (5)	0.03
Minimal	2 (3.5)	3 (6)	5 (5)	0.4

HEC: High Emetogenic Chemotherapy
HEC+D: High Emetogenic Chemotherapy with High Risk of Delayed Nausea and Vomiting
MEC: Moderate Emetogenic Chemotherapy
MEC+D: Moderate Emetogenic Chemotherapy with High Risk of Delayed Nausea and Vomiting
LEC: Low Emetogenic Chemotherapy
Minimal: Minimal Emetogenic Chemotherapy

[#] Risk according to nationally recognized practice guidelines.[4,5,6]

Table-3. Rate of Adherence to The Institution Protocol and guidelines

Adherence to Guidelines	Pharmacist Managed Group N= 55[*]	Physician Managed Group N= 51[*]	All Patients N= 106
Yes, n (%)	47 (85)	17 (33)	64 (60)
No, n (%)	8 (15)	34 (67)	42 (40)

1) P-value < 0.0001 favoring the pharmacist group for rate of adherence to the institution CINV protocol.

Table-4. Summary of Number of Breakthrough Doses Based on Chemotherapy Regimen Used

Emetic Risk [#]	Pharmacist-Managed Group	Physician-Managed Group	All Patients	P-Value
HEC+D	10 (1.1) n = 17	3.5 (0.65) n = 11	7.4 (0.9) n = 28	0.05
MEC	6.5 (0.8) n = 22	10.2 (1.6) n = 14	7.9 (1.1) n = 36	0.48
MEC+D	3.4 (0.8) n = 13	5.3 (0.7) n = 19	4.5 (0.7) n = 32	0.37
LEC	0 (0) n = 1	4.25 (0.7) n = 4	3.4 (0.6) n = 5	-
Minimal	0.5 (0.1) n = 2	1.7 (0.5) n = 3	1.2 (0.4) n = 5	-

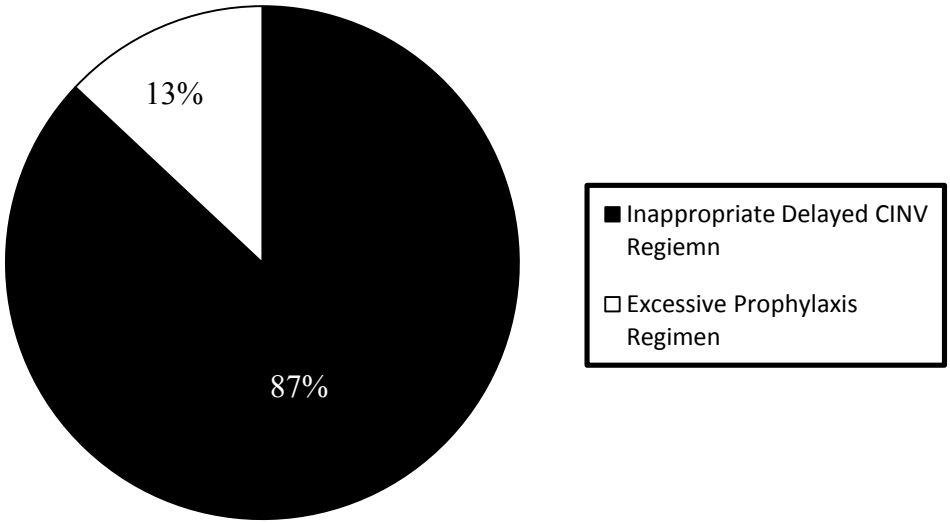
1) Values are presented as average number of breakthrough doses per hospitalization (number of doses per day of hospitalization). All Patients column presents average values for all patients receiving chemotherapy with the respective risk category.

2) HEC: High Emetogenic Chemotherapy
HEC+D: High Emetogenic Chemotherapy with High Risk of Delayed Nausea and Vomiting
MEC: Moderate Emetogenic Chemotherapy
MEC+D: Moderate Emetogenic Chemotherapy with High Risk of Delayed Nausea and Vomiting
LEC: Low Emetogenic Chemotherapy
Minimal: Minimal Emetogenic Chemotherapy

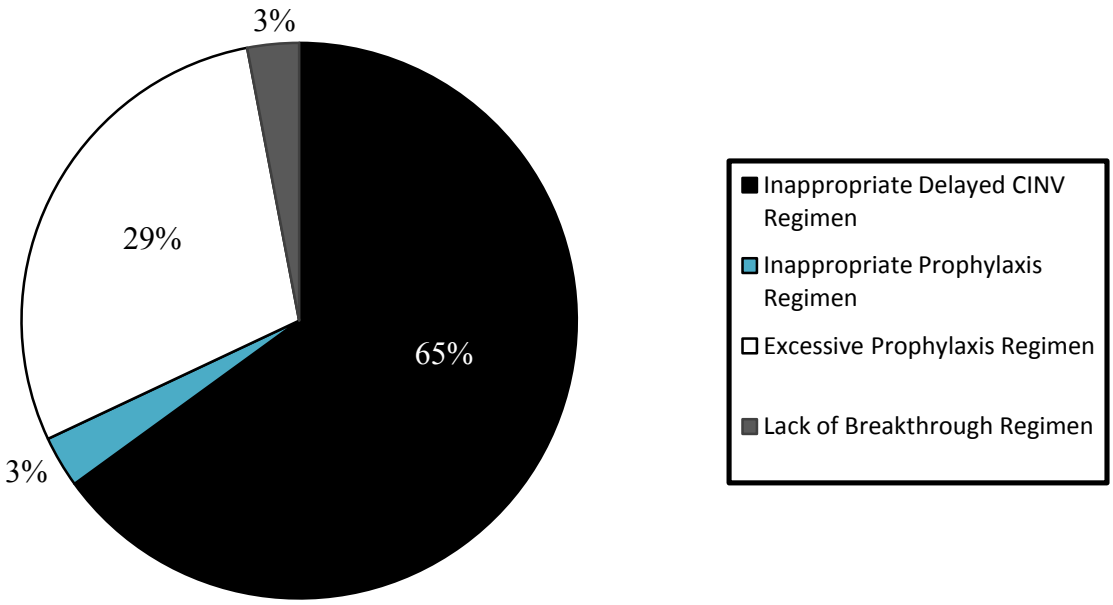
3) [#] Risk according to nationally recognized practice guidelines.[4,5,6]

Figure 1. Reasons for Non-Adherence to The Institution Protocol and Guidelines

Pharmacist Managed Group, N = 8 Non-Adherence Cases



Physician Managed Group, N = 34 Non-Adherence Cases



Appendix A: Institutional Guidelines for the Management of CINV

Highly Emetogenic Chemotherapy (HEC):
- Ondansetron 12 mg PO or IV 30-60 minutes before each dose of HEC
- Dexamethasone 12 mg PO or IV 30 to 60 minutes before each dose of HEC
- Dexamethasone 8 mg PO daily x3 days (starting the day after the last day of HEC)
- Aprepitant 125 mg PO x1 dose 30 to 60 minutes before chemo dose on day 1
- Aprepitant 80 mg PO daily for 2 days (starting day 2)

Moderately Emetogenic Chemotherapy with High Risk of Delayed CINV (Carboplatin, Cyclophosphamide, Doxorubicin, Epirubicin, Ifosfamide, Irinotecan, Methotrexate) (MEC+D):
- Ondansetron 8 mg PO or IV 30-60 minutes before each dose of MEC+D
- Dexamethasone 8 mg PO or IV 30 to 60 minutes before each dose of MEC+D
- Dexamethasone 8 mg PO daily x3 days (starting the day after the last day of MEC+D)
- Aprepitant 125 mg PO x1 dose 30 to 60 minutes before chemo dose on day 1
- Aprepitant 80 mg PO daily for 2 days (starting day 2)

Moderately Emetogenic Chemotherapy (MEC):
- Ondansetron 8 mg PO 30 to 60 minutes before each dose of MEC
- Dexamethasone 8 mg PO 30-60 minutes before each dose of MEC

Low Emetogenic Chemotherapy (LEC):
- Prochlorperazine 10 mg PO 30-60 minutes before each dose of LEC

PRN Antiemetic for Patients ≥65 years old:
- Prochlorperazine 5-10 mg PO or IV every 6 hours as needed
- Lorazepam 0.5-1 mg PO or IV every 6 hours as needed

PRN Antiemetic for Patients <65 years old:
- Prochlorperazine 10 mg PO or IV every 6 hours as needed
- Lorazepam 0.5-1 mg PO or IV every 6 hours as needed