Predictors of Control of Chemotherapy-Induced Nausea and Vomiting; experience from a tertiary oncology center in Pakistan

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Abstract

Background: CINV is a known distressful symptom in pediatric cancer patients. In a resource-limited setting, insight regarding CINV frequency and current practice can help optimize symptom control. Methods: Prospective study in the pediatric oncology daycare and inpatient services within a tertiary care hospital over 6 months. Patient demographics, chemotherapy and antiemetic regimen details were recorded. Frequency of acute nausea, vomiting and nausea severity for each session was recorded using a self-report questionnaire. Primary outcome was complete control (CC) (defined as no acute nausea or vomiting). Secondary outcomes included nausea severity and antiemetic prescription patterns. Results: A total of 61 (median age 7 years, 45.9% girls) patients received chemotherapy over 265 visits (85 single-day, 56 blocks). Inpatient sessions were more frequently of high emetogenicity (47.8% of 138 sessions) and most daycare sessions moderately emetogenic (79.5% of 127). Overall CC was 65.7%, significantly better for inpatients (73.2%, P<.009) and for sessions with weight-appropriate ondansetron dosing (p = 0.033). Odds of experiencing nausea (median severity 4) were higher in day care (OR 2.11, 95% CI 1.13-3.92) and lower (OR 0.25, 95% CI 0.09-0.72) when ondansetron dosing was weight-appropriate. CC did not vary significantly with age or gender. Conclusion: The overall CC rate was 65%, and was significantly higher for inpatients, highly emetogenic regimens, and when appropriate ondansetron dosing was used. This study identified gaps in our antiemetic practice, with moderately emetogenic sessions failing to receive guideline-recommended antiemetics, correlating with significantly lower complete control for daycare sessions.

Title

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Abbreviations

CINV Chemotherapy-induced nausea and vomiting

CC Complete Control

OR Odds Ratio

CI Confidence Interval

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Conclusion : The overall CC rate was 65%, and was significantly higher for inpatients, highly emetogenic regimens, and when appropriate ondansetron dosing was used. This study identified gaps in our antiemetic

practice, with moderately emetogenic sessions failing to receive guideline-recommended antiemetics, correlating with significantly lower complete control for daycare sessions.

Introduction

Acute chemotherapy-induced nausea and vomiting (Acute CINV) is nausea and vomiting that occurs within 24 hours of chemotherapy. The likelihood of acute CINV occurrence depends on the emetogenic potential of a chemotherapy regimen. Regimens are classified as having high (>90% risk of experiencing nausea and vomiting), moderate (30-90%), low (10-30%) and minimal (<10%) emetogenic potential[1]. Few pediatric studies have assessed patient-related risk factors for Acute CINV, reporting occurrence increasing with age, female sex and non-white patients[23]. Acute CINV prevention guidelines recommend antiemetic prophylaxis based on the emetogenicity of the chemotherapy regimen. The aim of antiemetic prophylaxis is to achieve "complete control", to prevent any nausea and vomiting over the duration of the chemotherapy regimen.

CINV has been reported to be one of the most distressful symptoms in pediatric cancer patients[4]. Nausea and/or vomiting are among the top five reasons for an emergency room visit and one of the most common reasons resulting in hospital admission[5].

In Pakistan 8,000 children are diagnosed with cancer every year[6] out of which it is estimated that less than 50% receive appropriate healthcare. To date, there has only been one local study assessing chemotherapy induced nausea and vomiting in pediatric patients, with a reported 72% (n = 50) incidence of nausea and vomiting in the first 6 months of treatment[7].

With no recent local data and the impact of CINV on pediatric patients' quality of life and healthcare resources associated with treating CINV, the aim was to conduct an institution-wide prospective study at our tertiary care center to determine 1) the frequency of acute CINV, 2) antiemetic prophylaxis practices and 3) the rate of complete control achieved with these practices.

Methods

The study was conducted in the Pediatric Oncology Daycare and Inpatient locations within a tertiary care hospital (Aga Khan University Hospital, Karachi, Pakistan) from October 2018 to March 2019. Patients aged 6 months to 18 years admitted to daycare or inpatient floor care receiving chemotherapy and antiemetic prophylaxis whose parents consented were included. Patients with intracranial tumors were excluded. Institutional ethical review committee approval was obtained beforehand.

Demographics, chemotherapy and antiemetic regimen details were recorded. Chemotherapy regimens were classified as minimal, low, moderate and highly emetogenic based on emetogenecity classification guidelines. For multiple-agent chemotherapy regimens, overall emetogenicity was determined by the most highly emetogenic agent, unless a pre-defined emetogenicity for the specific combination existed. For multiple-day chemotherapy, emetogenicity was determined by the most highly emetogenic chemotherapy given each day.

A self-report questionnaire was given to parents to document frequency of vomiting, whether nausea was experienced and its severity using the BARF scale for reference[8]. For single day chemotherapy regimens acute CINV was defined as nausea or vomiting occurring in the 24 hours after receiving chemotherapy. For multiple-day chemotherapy, i.e. blocks, acute CINV was defined as nausea or vomiting starting with the first dose of chemotherapy up to 24 hours after the last chemotherapy dose. To improve compliance, parents were contacted via telephone to document symptoms. The filled questionnaire was retrieved in the subsequent daycare, clinic or floor visit. Data were analyzed using the Students' t, Fisher's exact, Chi-squared and Mann Whitney U tests as appropriate.

Results

A total of 61 patients participated in the study with roughly equal gender distribution and a median age of 7 years (Table 1). 8 patients were chemotherapy naïve. All 61 patients received chemotherapy over 265 visits, 85 of which were single day sessions and 56 were chemotherapy blocks. Overall, moderate and high emetogenicity regimens made up the bulk of chemotherapy visits (Table 2). Most inpatient sessions were highly emetogenic chemotherapy (Table 2) with more daycare sessions being moderately emetogenic. Antiemetics administered were ondansetron (n 255, 96.2%), dimenhydrinate (87, 32.3%), domperidone (48, 18.1%), aprepitant (70, 26.4%) and dexamethasone (37, 14%).

Most chemotherapy visits were not associated with any acute nausea or vomiting, achieving an overall complete control for 65.7% of sessions (Table 3). Overall, 71 (26.8%) chemotherapy sessions were associated with nausea with a median of 2 episodes of nausea per chemotherapy (Table 4). Median nausea severity was 4 out of 10 on the BARF scale. Complete control by emetogenicity of chemotherapy regimens is shown in Table 3 and was highest for highly emetogenic chemotherapy regimens. Complete control did not differ significantly by age, gender or single vs block therapy, but was significantly better for inpatient sessions with highly emetogenic chemotherapy and for sessions with weight-appropriate ondansetron dosing. Across all visits, inpatient complete control was significantly better ($p = .009$). For nausea, these effects were robust to multivariable adjustment (Table 5) with daycare patients having more than twice the odds of experiencing nausea, and weight-appropriate ondansetron dosing having much lower odds of associated nausea. Additionally, logistic regression for predictors of vomiting showed decreasing odds with increasing age and location, with ondansetron dosing no longer significant.

Table 6 shows the distribution of antiemetic drugs across regimens of different emetogenicity, with a higher total number of different drugs being used correlating for increasing regimen emetogenicity. Figures 1 and 2 illustrate the distribution of nausea and vomiting episodes by day of chemotherapy and demonstrate that almost all events occurred in days 1-4 of block chemotherapy.

Discussion

This prospective study provides insight into control of chemotherapy induced nausea and vomiting. Overall complete control was toward the higher end of rates reported in current literature for high and moderately emetogenic chemotherapy (45-79%).

We found that the highest control of CINV was achieved for highly emetogenic chemotherapy. Antiemetic prescription patterns for highly emetogenic chemotherapy were closer to the CINV prophylaxis guidelines employing steroids and aprepitant in addition to ondansetron. Also, most highly emetogenic chemotherapy was given as an inpatient, which could have ensured higher compliance, appropriate dosing and more regular dosing intervals for antiemetic prophylaxis, all contributing to better symptom control. This observation was supported by the results of improved control in the inpatient versus day care setting (73.2% vs 57.5%), with daycare patients over twice as likely to experience nausea and over three times as likely to vomit compared to those receiving inpatient chemotherapy even after controlling for the effects of regimen emetogenicity (Table 4).

Most daycare sessions were of moderate emetogenicity, with a lower complete control rate. Not only were fewer antiemetics used for moderately emetogenic chemotherapy but the type of antiemetic employed also differed from guideline recommendation, with dimenhydrinate and domperidone being employed more frequently then aprepitant and dexamethasone, the latter two given for only 10 and 4 sessions, respectively (Table 3). In contrast, for 13 out of 15 minimally emetogenic chemotherapy sessions at least one anti emetic was prescribed when the guideline recommends none. Similar overuse was seen with chemotherapy sessions of low emetogenicity with 14 of the 16 sessions receiving at least 2 or more antiemetics.

Complete control did not vary significantly for single versus block chemotherapy sessions. One of the limitations of the study is that for block sessions the overlap in acute and delayed chemotherapy induced nausea and vomiting is not accounted for in the current analysis. Another limitation is that our study relies on self- and parent-reported data. The study did not evaluate admissions or ER visits for nausea or vomiting for daycare sessions.

Based on our findings, we hope to optimize antiemetic prophylaxis to achieve consistently better complete control starting with adherence to prophylaxis guidelines across chemotherapy sessions of all emetogenicities. Incorporating guideline-based prophylaxis recommendations in our computerized physician order entry system may help with adherence and efficient use of available antiemetics avoiding over- and under-usage. The routine recording of CINV is also expected to help improve this key aspect of patient care.

Conclusions

An overall complete control rate of 65% was achieved, this was higher for inpatient and highly emetogenic regimens and significantly better with appropriate ondansetron dosing. This study has led us to identify gaps in our antiemetic prescription and dosing for our daycare group and demonstrates the need for aggressive, guideline-compliant antiemetic use to improve complete control rates for CINV in children.

Author Contributions:

Dr Sheri Pariha had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SP, SA Acquisition, analysis, or interpretation of data: SP, NA Drafting of the manuscript: SP Critical revision of the manuscript: SP, SA Statistical analysis: SP

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Tables

Table Patient and Chemotherapy Demographics

Total patients *n*	61
Female *n (%)*	28 (45.9%)
Age in years *median (IQR)*	7.3 (3.7-12.7)
Weight in kg *median (IQR)*	20.5 (14.0-40.1)
Chemotherapy naïve *n (%)*	8 (13.1%)
Chemotherapy sessions *n*	265
Single-day n	85
Block regimens n	56 (median 3 days)
Inpatient *n (%)*	138 (52%)
Daycare *n (%)*	127 (48%)

Table Chemotherapy location and emetogenicity

	Regimen Emetogenicity*	**Regimen Emetogenicity***	**Regimen Emetogenicity***
Location	**Minimal**	**Low**	**Moderate**
Inpatient	3 (2.2%)	13 (9.4%)	56 (40.6%)
Daycare	12 (9.4%)	3 (2.4%)	101 (79.5%)
Total	15 (5.7%)	16 (6%)	157 (59.2%)
percentages are of row totals	**percentages are of row totals*	**percentages are of row totals*	**percentages are of row tota*

Table Complete control and patient attributes

Complete Control Overall	174 (65.7%)	
Single-day	56 (65.9%)	p = .22
Block regimens	31 (55.4%)	
Complete Control by Emetogenic Potential	Complete Control by Emetogenic Potential	Complete Control by Emetogeni
Minimal	12 (80%)	**p <0.001**
Low	9 (56.3%)	
Moderate	90 (57.3%)	
High	63 (81.8%)	
Ondansetron dosing weight-appropriate	n = 255	
Yes	162 (68.1%)	**p = .033**
No	7 (41.2%)	
Gender		
Male	77 (61.6%)	p = .198
Female	97 (69.2%)	
Age		
Under 12	115 (62.5%)	p = .123

Complete Control Overall	174 (65.7%)	
Over 12	59 (72.8%)	
Chemotherapy Location		
Inpatient	101 (73.2%)	**p = .009**
Daycare	73 (57.5%)	

Table Chemotherapy-induced nausea and vomiting events

Nausea	71 (26.8%)
Episodes	2 (1-3.5)
Median Severity (IQR)	4 (2-6)
Vomiting	54 (20.4%)
Median Episodes (IQR)	2 (1-3)

Table Multivariate logistic regression for predictors of nausea and vomiting

Predictors of Nausea	**OR (95% CI)**	**Sig**
Age (per year)	0.96 (0.91-1.02)	0.19
Chemotherapy Location (Daycare)	2.11 (1.13-3.92)	**0.02**
Chemotherapy Naive	0.59 (0.15-2.36)	0.46
Gender (Male)	1.05 (0.58-1.91)	0.87
Emetogenicity of Regimen	0.91 (0.59-1.41)	0.67
Ondansetron Dosing Appropriate	0.25 (0.09-0.72)	**0.01**
Predictors of Vomiting		
Age (per year)	0.82 (0.74-0.91)	**<0.01**
Chemotherapy Location (Daycare)	3.42 (1.3-9.05)	**0.01**
Chemotherapy Naive	1.99 (0.24-16.19)	0.52
Gender (Male)	1.33 (0.51-3.45)	0.56
Emetogenicity of Regimen	1.19 (0.58-2.43)	0.63
Ondansetron Dosing Appropriate	1.2 (0.28-5.12)	0.81
Nausea	52.5 (20-138)	**<0.01**

Table Antiemetic medication use by regimen emetogenic potential

	Regimen Emetogenicity*	**Regimen Emetogenicity***	**Regimen Em**
Antiemetic	**Minimal**	**Low**	**Moderate**
Ondansetron	11 (4.3%)	16 (6.3%)	153 (60%)
Dimenhydrinate	1 (1%)	13 (12.5%)	47 (45.2%)
Domperidone	5 (6.9%)	10 (13.9%)	27 (37.5%)
Aprepitant	0	9 (12.9%)	10 (14.3%)
Dexamethasone	0	2 (5.4%)	4 (10.8%)
Number of Antiemetics Used	**Number of Antiemetics Used**	**Number of Antiemetics Used**	**Number of A**
0	2 (50%)	0	2 (50%)
1	10 (8.8%)	2 (1.8%)	92 (80.7%)
2	2 (3.2%)	3 (4.8%)	45 (71.4%)

	Regimen Emetogenicity*	**Regimen Emetogenicity***	**Regimen Em**
3	1 (2.2%)	4 (8.9%)	12 (26.7%)
4	0	5 (17.9%)	5 (17.9%)
5	0	2 (18.2%)	1 (9.1%)
Total	15	16	157
percentages are of row totals	**percentages are of row totals*	**percentages are of row totals*	**percentages a*

Figures

Figure Distribution of nausea episodes per day of chemotherapy

Figure Distribution of vomiting episodes per day of chemotherapy