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Assessment of the Adherence Rate of Acute Chemotherapy Induced Nausea and Vomiting Prophylaxis Regimens by Medical Team to NCCN Clinical Recommendations: Cross-Section Observation

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ABSTRACT

Background: Chemotherapy induced nausea and vomiting (CINV) is still distressing adverse effect for patients. Thus, we conducted this study to assess the compliance of CINV prophylaxis patterns with NCCN guideline.

Methods: 136 Patients with any kind of malignancy who undergoes chemotherapy in Shahid Ghazi hospital, Tabriz, Iran, were included in this study. Adherence rate to the NCCN guideline of antiemetic therapy for different emetogenic potential chemotherapy regimens was evaluated.

Results: All patients received their prophylaxis 30 min before chemotherapy, which is completely adherent to guideline. Hematological malignancies were associated with higher adherence rate (P=0.032). For high and moderate emetic risk patients, dexamethasone and ondansetron were remarkably under-dosed, whereas Granisetron was over-dosed. Adherence rate to guideline in high and moderate and minimal emetic risk chemotherapy was 72.3%, 22.9% and 69.2% respectively. None of low emetic risk patients received guideline compliant prophylaxis. In all emetic risk levels, 50 (36.8%) patients received guideline adherent prophylaxis.

Conclusion: As results indicated, adherence rate wasn't optimal. Available dosage form of a medication has great impact on appropriate prescription. Thus, it is suggested for pharmaceutical companies to be informed about recent guidelines' updates and subsequently produce proper dosage forms for different indications.

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Introduction

Chemotherapy induced nausea and vomiting (CINV) are concomitantly described by patients undergoing treatment as their worst fear (1). Two major phases of CINV can be differentiating. Acute phase of CINV, which occurs within 24 hour of chemotherapy application. Delayed phase of CINV occurring from day 2 to 6 after receiving chemotherapy (2 , 3).

Chemotherapies are categorized into four classes according to the emetogenicity including; high risk (>90%), moderate risk (30–90%), low risk (10–30%), and minimal risk (<10%) (4). Despite antiemetic therapy administration, the incidence of acute nausea and vomiting are 35% and 13%, respectively. Delayed nausea and vomiting are more common with the incidence of 16% and 15% for moderate risk agents and 27% and 38 %for high risk agents (5).

The Development of 5-HT3 antagonists was a major breakthrough in antiemetic therapy (5). Since then serotonin antagonists prescribed in combination with different medications and has significantly improved antiemetic efficacy (5). Despite considerable accomplishments, antiemetic prophylaxis outcomes aren't satisfactory (5). Inadequate

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CINV control can be related with medical complications such as dehydration, malnutrition and electrolyte imbalance which may necessitate medical intervention (6, 7). Furthermore, CINV incidence is associated with a remarkable decline in patient's quality of life (8).

Guidelines are assisting tools that provide health care professionals with high quality recommendations in order to optimize treatment of clinical circumstances. Consequently, guidelines should be updated systemically to adapt to novel evidence provided by clinical trials (2). Despite the fact that CINV prophylaxis guidelines are developed by different organizations and institutes such as NCCN (National Comprehensive Cancer Network), ASCO (American Society of Clinical Oncology), ESMO (European Society for Medical Oncology) their clinical implementation has significantly lagged behind their development (9). Although, a meaningful correlation between adherence to guidelines and better antiemetic results has been reported, guidelines clinical practicality still remains low (2). Several barriers including unawareness of guidelines, inappropriate education and physicians' disapproval of guidelines have disrupted complete adherence (6).

We conducted this retrospective observational study to assess the compliance of CINV prophylaxis patterns with NCCN guideline in Shahid ghazi hematology and oncology center, Tabriz, Iran.

Methods

This study was performed in a tertiary care center affiliated to Tabriz University of Medical Sciences in a six-month period from April to September 2016. In this retrospective cross-sectional observational study all patients with any kind of malignancy who undergoes chemotherapy were eligible for inclusion. Patients' demographic information, cancer type and hospitalization length were recorded from their documents. In addition, dose, the administration time and the combination regimen of antiemetic combinations to control of CINV were recorded. The study was approved by the Research Ethics Committee of Tabriz University of Medical Sciences. All patients' information from their documents was confidential and not released by their identity.

Finally, Adherence rate to the NCCN guideline of anti-emetic therapy for different emetogenic potential chemotherapy regimens (version 2. 2016) was evaluated. According to the NCCN recommendation, several prophylactic regimens have been suggested for the prevention of acute nausea and vomiting regarding different classes of emetogenic potential chemotherapy (Table 1). Unavailable medication containing regimens (in our country) such as netupitant, fosaprepitant, rolapitant, palonosetron and dolasetron were omitted. According to the guideline, no routine prophylaxis is recommended for patients with minimal emetogenic potential. Adherence failure was determined (1) if approved antiemetic choice (single or combination) was not administered, (2) if the approved dose was not ordered, (3) if a non-approved antiemetic (single or combination) was administered and (4) if the administration time is not correct.

The primary outcome of this study is to assess the adherence rate of medical team to the current guidelines. The secondary outcome is finding the solution for the reasons of any non-adherence.

Continuous variables were described as mean and standard deviation (SD). Categorical variables were expressed as frequency and percentage. Chi-square test (or Fisher's exact test if indicated) was performed to show the relationship between two categorical variables. P-values less than or equal to 0.05 were considered statistically significant. Statistical analysis was performed using the IBM SPSS statistics for Windows, version 20.0.

Results

In this study, 136 eligible patients who received chemotherapy were enrolled. From 136, 48 (35.3%) and 88 (64.7%) were female and male, respectively. Patients age ranged were from 15 to 90 years, with mean age of 48.3±16.7 years. Patients weight ranged were from 35.9 to 100 kg, with mean weight of 67.5±16.9 kg. Among enrolled patients 87 (64%) of them diagnosed with solid tumors and 49 (36%) had hematologic malignancies. Table 2 summarizes the incidence of all cancer types.

Table1. NCCN guideline (Antiemetic-version 2. 2016) recommendation for acute phase CINV prophylaxis.

Emetogenic potential	Anti-emetic prophylaxis regimen	Dosage
High	Corticosteroid + 5HT3-RA + NK1-RA	• Dexamethasone 12 mg PO/IV once • Granisetron 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once Ondansetron 16–24 mg PO once or 8–16 mg IV once • Aprepitant 125 mg PO once
Moderate	Corticosteroid + 5HT3-RA ± NK1-RA	
Low	Corticosteroid or 5HT3-RA or metoclopramide or prochlorperazine	• Dexamethasone 8–12 mg PO/IV • Granisetron 1–2 mg PO • Ondansetron 8–16 mg PO • Metoclopramide 10–20 mg PO/IV • Prochlorperazine 10 mg PO/IV

5HT3-RA: 5-hydroxytryptamine-3 receptor antagonist; NK1-RA: neurokinin-1 receptor antagonist.

Table 2. Cancer types frequencies

Category of malignancy	Type of Cancer	Number (%)	Total
Solid Tumors	Upper GI Cancer	30 (34.2)	87 (64)
	Colorectal	16 (18.2)	
	Head and Neck	14 (16)	
	Sarcoma	12 (13.7)	
	Breast	5 (6)	
	Ovarian	2 (2.4)	
	Others	8 (9.2)	
Hematologic Malignancies	NHL	15 (30.6)	49 (36)
	AML	8 (16.3)	
	ALL	7 (14.3)	
	CLL	6 (12.3)	
	MM	4 (8.2)	
	HL	4 (8.2)	
	HCL	2 (4.1)	
	APL	2 (4.1)	
	MF	1 (2)	

Values demonstrate number (%) of patients.

GI: Gastrointestinal; NHL: Non Hodgkin Lymphoma; AML: Acute Myeloid Leukemia; ALL: Acute Lymphocytic Leukemia; CLL: Chronic Lymphocytic Leukemia; MM: Multiple Myeloma; HL: Hodgkin Lymphoma; HCL: Hairy Cell Leukemia; APL: Acute Promyelocytic Leukemia; MF: Mycosis Fungoides

Our data showed that, all prophylaxis medications were administered 30 minutes before chemotherapy infusion and completely adherent to the guidelines recommendations. The doses of anti-emetic prophylaxis of intravenous medications for all kind of chemotherapy regimen were including: dexamethasone one ampule (8 mg); granisetron one ampule (3 mg); ondansetron one ampule (4 mg). Aprepitant was taken orally, 120 mg for day one and 80 mg for the two consecutive days. The prophylactic doses of aprepitant for all indications and dexamethasone in low emetic risk patients was adherent to the guideline. In this study patients received different chemotherapy regimen with different emetogenic potential. Table 3 demonstrated the frequency of emetogenic potential chemotherapy regimens and adherence to the guideline. From 136 patients 70 (51.5%) received high emetogenic chemotherapy. The most frequent administered high emetogenic potential agent was cisplatin 39 (55.8%) Followed by ifosfamide≥2 g/m2 17 (24.3%), cyclophosphamide> 1500 mg/m2 10 (14.3%), dacarbazine 2 (2.8%), and dacarbazine plus ifosfamide 2 (2.8%).

In the type of medication choice for prophylaxis regimen of nausea and vomiting, 32 (36.7%) of patients with solid tumors and 32 (65%) of patients with hematologic malignancies had administered accurate prophylaxis regimen according to the guideline. Analysis showed the significant relation between the adherence rate and type of malignancy (hematologic or solid tumor) p=0.032.

From all anti-emetic prophylaxis regimens, dexamethasone and granisetron combination was the most frequent administered regimen 59 (43.4%). In high and moderate emetic risk chemotherapy, 16 (22.9%) and 34 (72.3%), were adherent, respectively to the guideline recommendations. Whereas, none of the patients in low emetic risk chemotherapy category, were adherent to the NCCN recommendations. All administered anti-emetic prophylaxis agents in different emetogenic potential chemotherapy regimen are shown in Table 4. Prophylaxis of acute CINV was adherent in 50 (36.8%) and non-adherent in 86 (63.2%) patients to NCCN recommendations.

Table 3. Frequency of emetogenic potential of chemotherapy regimens and adherence to the guideline

Emetogenic potential	Adherence to the NCCN recommendations		
	Yes N (%)	No N (%)	Total N (%)
High	16 (22.9)	54 (77.1)	70 (51.5)
Moderate	34 (72.35)	13 (27.65)	47 (34.5)
Low	-	6 (100)	6 (4.5)
Minimal	-	13 (100)	13 (9.5)
Total	50 (36.8)	86 (63.2)	136 (100)

Values demonstrate number (%) of patients.

Table 4. Prophylactic anti emetic agents' administration frequency in different emetic risk chemotherapy in all patients

Prophylactic agents	Type of Nausea				
	High N (%)	Moderate N (%)	Low N (%)	Minimal N (%)	Total N (%)
Dexamethasone	-	1 (2.1)	-	-	1 (0.7)
Ondansetron	-	-	-	1 (7.7)	1 (0.7)
Aprepitant	1 (1.4)	-	-	-	1 (0.7)
Dexamethasone + granisetron	26 (37.1)	29 (61.7)	1 (16.7)	3 (23.1)	59 (43.4)
Granisetron + aprepitant	-	1 (2.1)	-	-	1 (0.7)
Dexamethasone + granisetron + ondansetron	6 (8.6)	-	-	-	6 (4.4)
Dexamethasone + granisetron + aprepitant	16 (22.9)	5 (10.6)	2 (33.3)	-	23 (16.9)
Dexamethasone + aprepitant + ondansetron	-	-	1 (16.7)	-	1 (0.7)
Dexamethasone + granisetron + aprepitant + ondansetron	1 (1.4)	-	-	-	1 (0.7)
Without any prophylactic regimen	20 (28.6)	11 (23.4)	2 (33.3)	9 (69.2)	42 (30.9)
Total	70 (51.5)	47(34.5)	6(4.5)	13(9.5)	136 (100)

Values demonstrate number (%) of patients.

Discussion

Our results showed that the rate of adherence was significantly higher in patients with hematological malignancies rather than solid tumors (p=0.032). The time of antiemetic administration was adherence to guideline's suggestion. About the type of antiemetic regimen, the adherence rate was 22.9% in high emetic risk patients. Highest adherence was reported among patients with moderate emetogenic potential chemotherapy 34 (72.3%). The nonadherence rate was 100% Among patients with low emetogenic potential chemotherapy. Unless aprepitant the doses of dexamethasone and 5HT3 antagonists were nonadherent to the guideline.

Our data demonstrated that patients with hematological malignancies had received prophylactic regimens that were more consistent with NCCN guideline recommended dose and pattern (p=0.032). This was in accordance to a similar study, which reported that hematological cancer types were associated with higher adherence rate to guidelines (10). Numerous studies reflected the fact that hematological patients are involved with physical symptoms (including nausea, fatigue, constipation, mucositis, tiredness) with equal or exceeding severity to those of patients with solid tumor (11 , 12). As a result, it is logical that health care professionals paid more attention to hematological patients. In addition, a study concluded, that the number

of basic researches in hematological malignancies are higher by approximately a three times fold compared with solid tumors. Subsequently there is greater tendency for physicians to obtain information related to hematological malignancies (13).

In our study, all patients received their antiemetic therapy 30 minutes prior to chemotherapy, resulting in 100% adherence to guideline's suggestion regarding time of prophylaxis application. This proves to be valuable since, a study indicated that as the gap between chemotherapy application time and antiemetic therapy increased, CINV control rate became lower (14).

Considering patients that were undergoing highly emetogenic potential chemotherapy, we identified that 20 (28.6%) cases did not receive antiemetic therapy. Additionally, given the NCCN guideline recommendations, prophylactic regimens that had been administrated for 26 (37.1%) patients were determined as prescription errors. Therefore, only 16 high emetic risk patients were treated with guideline adherent regimens, resulting to a 22.9% adherence rate.

Focusing on the results of patients that were undergoing highly emetogenic potential chemotherapy, adherence rate was significantly lower in comparison with a study that reported 71% of prophylactic regimens were adherent with guideline (15).

Chemotherapy agents are classified into four levels base on their emetogenic activity [11]. CINV incidence could be predicted if chemotherapy agents emetogenicity is noticed (5, 6).

As demonstrated in Table 1, NCCN guideline recommends a combination of three antiemetic (corticosteroid + 5HT3 antagonist + NK1 antagonist) as optimum CINV treatment for highly emetogenic potential chemotherapy. However, a combination of dexamethasone and granisetron were prescribed for 26 (37.1%) patients with highly emetogenic potential chemotherapy. This is responsible for major deviation from guideline's recommendation. A similar study reported this issue as a major non-adherence factor as well (6). Therefore, addition of aprepitant into prophylactic regimens of a considerable proportion of highly emetogenic potential chemotherapy may increase adherence rate significantly. Similarly, according to Intercontinental Medical Statistics (IMS) health oncology database, only 25% of all patients undergoing highly emetogenic potential chemotherapy in five European countries (England, France, Italy, Germany, and Spain) received aprepitant (16).

Highest adherence to guideline recommended prophylaxis in our study was seen among patients undergone moderate emetogenic potential chemotherapy, since 34 (72.3%) patients were treated with proper prophylactic regimen. Our results showed better compliance with NCCN guideline compared to a similar study which reported 45.5% of patients within moderate emetogenic potential group received adequate prophylaxis (14). This is mainly due to frequent administration of dexamethasone and granisetron regimen for moderate emetogenic potential chemotherapy in our center, which is in agreement with NCCN guideline. Furthermore, aprepitant application for moderate emetic risk chemotherapy is regarded as an option up to physician's decision. Among 47 patients in moderate emetic risk category, only 6 (12.8%) received aprepitant. Although, Rapoport et al. has shown that a neurokinin1 antagonist use could be an advantage for CINV prophylaxis in patients with moderate emetogenic potential chemotherapy (15).

Among patients with low emetogenic potential chemotherapy, 100% of deviation from guideline's recommended regimen was found. Despite NCCN guideline approves selecting monotherapy with one of the recommended antiemetics, patients received either a combination of antiemetic or no antiemetic at all. Likewise, a study that assessed CINV prophylaxis adherence to ESMO guideline indicated that only 11% of prophylactic regimens prescribed for patients with low emetogenic potential chemotherapy were compliant with guideline, mainly due to concomitant use of dexamethasone and a 5HT3 antagonist for majority of patients (15).

No antiemetic treatment is recommended by NCCN guideline for minimal emetogenic potential chemotherapy, except in the case of breakthrough emesis occurrence. Among patients with minimal emetogenic potential chemotherapy, 9 (69.2%) patients did not receive any antiemetics. Previous study reported that 83% of cases with minimal emetic risk adherent the guideline (15).

We also found critical issues related to prescribed doses of three antiemetic agents (dexamethasone, ondansetron, granisetron). Minimum recommended dose of dexamethasone for high and moderate emetogenic potential chemotherapy is 12 mg by intravenous injection route. In our country dexamethasone is available in 8 mg intravenous dosage form. Therefore, all patients with highly and moderate emetogenic potential chemotherapy who received 8 mg of dexamethasone were under-dosed. Consequently, dexamethasone under-dose could increase risk of failure in CINV protection (17).

In the case of patients with low emetogenic potential chemotherapy, administrated dose of dexamethasone was compliant with guideline. However, a recent study reported that among the patients who received non-adherent prophylactic regimens in all emetogenic potential levels, dexamethasone was the most frequently over-dosed medication (10).

In our country, ondansetron is available in 4 mg oral and intravenous dosage forms. NCCN guideline recommends

administrating 8-16 mg of intravenous ondansetron for highly and moderate emetogenic potential chemotherapy. In contrast to this recommendation, patients with highly and moderate emetogenic potential chemotherapy received only 4 mg of ondansetron. As a result, they were notably under-dosed, receiving only 25-50% of appropriate dose.

In low emetogenic potential chemotherapy there was no need for intravenous application of ondansetron, since only oral form is supported by guideline. Parenteral use of ondansetron is invasive and increases antiemetic treatment cost. Administration of intravenous ondansetron instead of oral ondansetron for low emetic risk patients is an issue arises mainly from unawareness of guidelines and simple delivery of intravenous form of ondansetron along with intravenous dexamethasone by a volume expander.

In our country, granisetron is available in 3 mg intravenous dosage form. Maximum approved dose by NCCN guideline for granisetron in highly and moderate emetogenic potential chemotherapy is 1 mg. Although in our study a dose of 3 mg was administrated for all patients. Therefore, granisetron was overdosed unlike ondansetron. Overdose of granisetron is associated with QT prolongation which may prove to be a serious clinical condition, since many chemotherapy agents could potentially prolong QT interval as well (18, 19). Therefore, an overdose of granisetron is probably associated with more treatment cost and higher risk of adverse reactions. For low emetogenic potential chemotherapy only oral form of granisetron is suggested similar to ondansetron.

Aprepitant was prescribed with appropriate dose in all prophylactic regimens regardless of emetogenic potential chemotherapy. This is due to availability of fixed dosage form of aprepitant in our market containing one 120 mg tablet for first day, and 80 mg tablets for two consecutive days. Since aprepitant is more expensive than other antiemetic medications, considering rational use of aprepitant could reduce treatment expenses significantly. In this study, a total number of 92 (69.6%) patients in high, moderate and low emetogenic potential chemotherapy categories, received aprepitant in their prophylactic regimens. Whereas, only in 27 (29.3%) cases aprepitant prescription is approved by NCCN guideline.

A study which investigated antiemetics overuse in a considerable population of cancer patients in United States (where NK1 antagonists were also the most expensive medication), concluded that antiemetics overuse could increase treatment expenses dramatically (7). It is strongly believed that more adherences to guidelines is associated with less treatment expenses (10).

We believe that inconsistency of CINV prophylactic regimen with guideline suggested prophylaxis may be associated with lower control rates and higher treatment expenses. However, there are practical proposals to enhance adherence to CINV management guidelines.

Constant education of physicians (along with other health care professionals) could prove to be more effective than periodical education as mentioned by authors of a similar study conducted in Switzerland (15).

Several studies highlighted the impact of using standard, guideline based software tools on increasing adherence to guidelines. These softwares are capable of calculating emetogenicity of chemotherapy regimens and determining appropriate prophylactic regimen (15, 20). Clinical pharmacists could play a critical role in the process of CINV management, by assisting physicians to estimate chemotherapy regimens emetogenicity potential and choosing proper prophylactic regimen (6).

Our study was conducted retrospectively in a single hospital. Therefore, this study's results may not be generalized to other care centers throughout the country. In addition, we did not assess the efficacy of the CINV prophylactic regimens and existence of acute, delayed and breakthrough CINV in our patients.

It is obvious that available dosage form of a medication in market has great impact on appropriate medication prescription. Thus, it is advised for pharmaceutical companies to be informed about most recent guidelines' updates and subsequently produce proper dosage forms for different indications. Otherwise, education of health care professionals should be emphasized. Administration of intravenous antiemetic agents for minimal emetogenic potential chemotherapy has no preference over oral antiemetic therapy. Our results showed that overall adherence to clinical recommendations of NCCN guideline for management of CINV isn't satisfactory. Appropriate CINV prophylaxis won't be achieved unless adequate attention is devoted to emetogenicity of patient's chemotherapy regimen and guideline's recommendations. Active contribution of clinical pharmacists in this process could be of great assistance.

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