


# Adherence to guidelines on prophylaxis of chemotherapy-induced nausea and vomiting in the National Cancer Institute, Sudan

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**Dates:**

Received: 12 Jan. 2016  
Accepted: 06 Feb. 2016  
Published: 28 Feb. 2017

**How to cite this article:**

Elhassan MMA, Ali AASA, Elmustafa MOM. Adherence to guidelines on prophylaxis of chemotherapy-induced nausea and vomiting in the National Cancer Institute, Sudan. *S. Afr. j. oncol.* 2017;1(0), a9. <https://doi.org/10.4102/sajo.v1i0.9>

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**Objective:** To evaluate the adherence to American Society of Clinical Oncology (ASCO) guidelines for antiemetic prophylaxis of chemotherapy-induced nausea and vomiting and assess the outcomes of the prescribed antiemetic drugs.

**Methods:** This prospective, observational study enrolled chemotherapy-naïve cancer patients who were admitted to the National Cancer Institute between May and July 2015 for intravenous chemotherapy. Patient's demographic data, chemotherapy protocols and types of antiemetic drugs were collected by reviewing patients' files, chemotherapy prescription forms and interviewing the patients.

**Results:** The data revealed that 90% of pre-chemotherapy antiemetic prescriptions did not adhere to antiemetic guidelines. The trends of non-adherence included an overuse of ondansetron (14%), under-prescribing of dexamethasone (16%) and corticosteroid duplication (14%). Regarding antiemetic use for the prevention of delayed emesis, the data showed that 90% of antiemetic prescriptions were non-adherent with ASCO guidelines, with overuse of ondansetron (20%) and metoclopramide (37%) and lack of dexamethasone prescriptions (80%) on days 2 and 3 being the most frequently reported trends. The percentage of patients with complete response (no emesis or rescue therapy) over 5 days post chemotherapy was 36%.

**Conclusion:** The study indicated an extremely low adherence rate to ASCO guidelines for antiemetic prophylaxis of chemotherapy-induced nausea and vomiting. Non-adherence included a trend of both underuse and overuse of indicated antiemetic medications.

## Introduction

Chemotherapy is the cornerstone in the management of different malignant disorders. Anticancer drugs have a narrow therapeutic index and are known to cause significant acute and delayed adverse drug reactions.<sup>1</sup> Chemotherapy-induced nausea and vomiting (CINV) is a serious side effect that can impact quality of life (QOL) and impair patients' adherence to treatment.<sup>2</sup> The intrinsic emetogenicity of the chemotherapeutic agents is the most important factor determining the likelihood of development of acute or delayed emesis during chemotherapy.<sup>3,4</sup> In fact, all chemotherapeutic agents have emetogenic potential of different intensities and accordingly are classified into four emetic risk groups depending on the percentage of cases they cause emesis in: high (> 90%), moderate (30% – 90%), low (10% – 30%) and minimal (< 10%).<sup>5</sup>

Three distinct forms of CINV can be distinguished depending on the time at which emesis occurs after initiation of treatment. These are acute emesis arising within 24 h of chemotherapy administration, delayed emesis arising after the first 24 h and lasting for up to 6 days, and anticipatory emesis that occurs prior to the administration of chemotherapy.<sup>6</sup>

In the absence of antiemetic prophylaxis, about 70% – 80% of cancer patients receiving chemotherapy experience CINV.<sup>7</sup> However, proper use of antiemetic medication has the potential to improve control of CINV, maximise patients' QOL and reduce associated symptoms' management costs.<sup>8,9</sup> Several clinical guidelines have addressed the importance of the prophylactic administration of antiemetic drugs for preventing CINV, including the American Society of Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology (MASCC/ESMO) and National Comprehensive Cancer Network (NCCN).<sup>10,11,12</sup> There is constancy among these guidelines on key principles with only minor differences.<sup>5,13</sup> Although these guidelines are widely available and regularly updated, adherence is often low.

Although the adherence rate to antiemetic guidelines for the prevention of CINV has been studied extensively in the medical literature, there is lack of adequate information about adherence to the guidelines for antiemetic prophylaxis in cancer patients in Sudan. In this study, the adherence to ASCO guidelines for the use of antiemetic medications was studied in cancer patients who received chemotherapy at the outpatient chemotherapy unit, The National Cancer Institute (NCI), Wad Medani, Sudan.

## Patients and methods

### Study design

This was a prospective observational study conducted at the oncology department at the NCI, University of Gezira in central Sudan, over a 3 month period from May to July 2015.

### Patients

Previously untreated patients (chemotherapy naïve) who underwent intravenous chemotherapy during the study period were eligible for inclusion in this study. Exclusion criteria were brain metastases, concurrent radiation therapy and pregnancy. In addition, patients who were on any other emetogenic drugs were excluded.

### Data collection

Data extracted from patients' files included patient demographics and baseline clinical characteristics, chemotherapy protocol and prescribed antiemetic regimen. In addition, patients were followed up through telephone to answer questions about emesis events, severity of nausea and vomiting and compliance with dose instructions for antiemetic therapy for 7 days post chemotherapy administration. Day one was the day of chemotherapy and first day of antiemetic therapy. Chemotherapies were classified according to their emetogenic risk as high, moderate and low or minimal according to the ASCO classification. Pharmacists and physicians working with these patients were unaware of the study to minimise the risk of bias. A pilot with 10 cases was carried out to determine if the data collection form was able to capture all the information required for data analysis. All data were collected after obtaining patient consent and were analysed anonymously without identifying patient information.

### Statistical analyses

Data were analysed using the Statistical Package for Social Sciences for Windows (SPSS II; ver. 20 SPSS Inc., Chicago, IL, USA). Descriptive statistical analysis was carried out; the results were presented as frequencies and percentages.

## Results

A total of 100 cancer patients met the inclusion criteria. The mean age was 26.06 years. The majority of the study population were female patients ( $n = 63$ ) representing 63%,

whilst male patients were 37 (37%) cases. There were 12 paediatric patients (< 16 years old), representing 12% of the total study population. The performance status of all participants was either I or II according to the Eastern Cooperative Oncology Group. Breast cancer was the most common diagnosis followed by non-Hodgkin's lymphoma (NHL). Patient characteristics and tumour sites are shown in Table 1.

The majority of chemotherapy prescriptions were classified as high emetic risk chemotherapy (HEC) regimens. The most frequent regimens were an anthracycline plus cyclophosphamide (52%), followed by cisplatin-based regimens (21%). The distribution of chemotherapy according to their emetogenic potential is shown in Table 2.

The data showed that 90% of pre-chemotherapy antiemetic prescriptions did not adhere to ASCO guidelines. The trends of non-adherence included an overuse of ondansetron (5-HT<sub>3</sub> receptor antagonist) in 2 and 12 patients treated with minimal emetic risk chemotherapy (MinEC) and low emetic risk chemotherapy (LEC), respectively. There was also a trend of under-prescribing of dexamethasone for 16 patients receiving HEC and moderate emetic risk chemotherapy (MEC) regimens. Corticosteroid duplication was reported in 14% of patients. None of the patients who were on HEC received NK 1 receptor antagonists because of unavailability of this treatment choice in our facility.

**TABLE 1:** Patient characteristics ( $N = 100$ ).

Characteristics	%
Sex	
Male	37
Female	63
Age	
1–15	12
16–30	12
31–45	40
46–60	23
61–85	13
Residence	
Rural	71
Urban	29
Diagnosis	
Breast cancer	27
Non-Hodgkin's lymphoma (NHL)	14
Acute lymphoblastic leukaemia	9
Nasopharyngeal carcinoma	8
Acute myeloid leukaemia	7
Colon cancer	5
Cervical cancer	5
Ovarian cancer	4
Others	10

**TABLE 2:** Distribution of chemotherapy according to emetogenic potential of chemotherapeutic agents ( $N = 100$ ).

Emetogenic potential	No. (%)
High	73 (73)
Moderate	7 (7)
Low	16 (16)
Minimal	4 (4)

**TABLE 3:** Analysis of frequently used single and combination prophylactic antiemetic regimens.

Regimens	HEC	MEC	LEC	MinEC	Total
Single antiemetic					
Ondansetron	5	1	3	2	11
Combination of two antiemetic drugs					
Ondansetron + dexamethasone	39	5	8	0	52
Ondansetron + metoclopramide	1	1	0	0	2
Dexamethasone + metoclopramide	22	0	4	2	28
Combination of three antiemetic drugs					
Ondansetron + dexamethasone + metoclopramide	6	0	1	0	7

HEC, high emetic risk chemotherapy; MEC, emetic risk chemotherapy; LEC, low emetic risk chemotherapy; MinEC, minimal emetic risk chemotherapy.

Regarding antiemetic use for the prevention of delayed emesis, the data showed that 90% of antiemetic prescriptions were non-adherent with ASCO guidelines. Overuse of ondansetron was observed in 20% of prescriptions, lack of dexamethasone prescriptions on days 2 and 3 post chemotherapy was observed in 80% and overuse of metoclopramide was observed in 37% of prescriptions (Table 3).

The percentage of patients with complete response (no emesis or rescue therapy) over 5 days post chemotherapy was 36%. Acute vomiting was experienced by 37% of the patients and delayed vomiting by 12%, whilst acute nausea was present in 49% of the patients and delayed nausea in 14%.

## Ethical consideration

The study was approved by the Ethical committee at the Faculty of Medicine, University of Gezira. Subsequently, the study proposal was reviewed by the research committee of the Department of Oncology for feedback from physicians treating the potential participants. After identifying eligible patients and obtaining the consultant's agreement, verbal consent was obtained from each patient. The verbal consent explained the study aims, objectives and potential value, and all data were collected anonymously.

## Discussion

The current cross-sectional prospective observational study is the first study conducted to investigate the pattern of antiemetic medications prescribed for prophylaxis of CINV, their adherence to guidelines and their efficacy in patients undergoing the first cycle of chemotherapy at NCI, Gezira State, Sudan. This observational study reflects the treatment pattern in a real practice. In Sudan, antiemetic medications used for the prevention of CINV are free of charge to Sudanese citizens at governmental institutions; therefore, medication cost and clinicians trend to prescribe treatment according to reimbursement guidelines were not considered as confounding factors influencing antiemetic prescribing pattern in our setting.

CINV are adverse events that should be totally controlled to reduce morbidity and prevent premature termination of chemotherapy. The goal of clinical guidelines is mainly focused on the complete prevention of CINV rather than

on treatment. This should be achievable in the majority of patients receiving chemotherapy, even with highly emetic agents so as to improve QOL and avoid complications. Aapro et al. reported that adherence to antiemetic guidelines significantly increased the control of CINV in patients receiving highly or moderately emetogenic chemotherapy agents.<sup>13</sup> For acute emesis, the updated ASCO guidelines recommend triple therapy with NK1-receptor antagonist (NK1-RA), a 5-HT<sub>3</sub> receptor antagonist and dexamethasone for HEC regimens (including anthracycline plus cyclophosphamide containing regimens). For MEC regimens, the updated ASCO guidelines recommend palonosetron and dexamethasone or 5-HT<sub>3</sub> receptor antagonist, dexamethasone and aprepitant. In low emetogenic chemotherapy, a monotherapy with dexamethasone is recommended, and for minimal emetogenic chemotherapy, no prophylaxis is necessary.<sup>10</sup> For delayed emesis, the updated ASCO guidelines recommend in patients receiving HEC (including anthracycline plus cyclophosphamide containing regimens) a combination of a dexamethasone and NK1-RA. In other MEC regimens, 5-HT<sub>3</sub> receptor antagonist, dexamethasone or NK1-RA is recommended. In low and minimal emetogenic chemotherapy, no prophylaxis is necessary.<sup>10</sup>

Despite the availability of treatment guidelines, there is evidence that adherence to treatment recommendations is less than optimal.<sup>14,15</sup>

Our analysis revealed that most patients received prophylactic antiemetic therapy with two drugs followed by those treated with one drug and that 5-HT<sub>3</sub> receptor antagonists and glucocorticoids were the most widely used drugs for prophylactic antiemetic therapy. NK1-RA and palonosetron were not used as they are not registered for clinical use in our setting, and this could be a possible confounding factor for non-adherence to ASCO guidelines.

In this study, about 90% of pre-chemotherapy antiemetic prescriptions regimens did not adhere to the ASCO guidelines. Similar result has been reported in Saudi Arabia.<sup>16</sup> Koch et al. also reported extremely low adherence rate (3%) in 113 patients with colorectal cancer receiving MEC or LEC.<sup>17</sup> The pattern of non-adherence to ASCO guidelines in our study included overuse of ondansetron before chemotherapy regimens classified as having low or minimal emetic risk. This was inconsistent with ASCO guidelines and indicates unnecessarily high cost. Also there was a lack of prescription of dexamethasone in 16 of 80 patients receiving HEC and MEC regimens. However, ASCO guidelines recommend the use of dexamethasone for the acute prevention of highly, moderately and low emetogenic chemotherapy. This finding may be attributed to physicians' perception of steroid-related adverse events. Similarly, underuse of dexamethasone was described in a previous study from Saudi Arabia.<sup>16</sup> In 14% of patients in this study, dexamethasone was prescribed as antiemetic prophylaxis to patients already receiving prednisolone-containing chemotherapy. The steroid duplication was also described in a previous study.<sup>16</sup>

In this study, an oral 5-HT<sub>3</sub> antagonist was prescribed to all patients at discharge, regardless of the emetogenicity of the chemotherapy. Overuse of 5-HT<sub>3</sub> receptor antagonists was documented in a previous study in Brazil.<sup>18</sup> Although continuing ondansetron alone beyond 24 h has a minor role in the control of delayed CINV in patients who received HEC,<sup>19</sup> the benefit has not been as great as that seen with dexamethasone monotherapy.<sup>20</sup> Furthermore, the addition of a 5-HT<sub>3</sub> receptor antagonist beyond 24 h along with glucocorticoids did not significantly improve control of delayed emesis as compared with dexamethasone monotherapy.<sup>20</sup> Thus, the use of 5-HT<sub>3</sub> receptor antagonists to prevent delayed emesis is not recommended. This finding suggests that there is overuse of an expensive antiemetic medication in a limited resource setting where there is an economic need for the reduction of medical care expenses.

ASCO guidelines suggest prophylactic administration of dexamethasone beyond 24 h after chemotherapy as part of triple therapy for HEC or as monotherapy for LEC.<sup>10</sup> Our analysis revealed that no patient received dexamethasone on days 2 and 3 as prophylaxis for delayed emesis. The observed underuse of prophylactic dexamethasone for delayed CINV is similar to that found in previous studies.<sup>21</sup> In this study, metoclopramide was prescribed as antiemetic prophylaxis for delayed emesis in 37% of patients, which was inconsistent with the recommendation of ASCO guidelines. Recent ASCO guidelines stated that metoclopramide should be reserved for patients who are intolerant to any of the 5-HT<sub>3</sub> antagonists, dexamethasone or aprepitant.

The control of nausea was substantially lower than the control of vomiting in this study as shown in Table 4. The data suggest that, whilst delayed nausea and vomiting were well controlled, acute nausea and vomiting remain a significant problem in practice. This is in contrast to some reports that have discussed the difficulty of prevention using antiemetic guidelines for delayed CINV.<sup>22</sup> A previous survey showed underestimation of delayed CINV among medical oncologists and oncology nurses.<sup>23</sup> Despite the use of prophylactic antiemetic medications, a study has shown that 36% patients developed acute CINV and approximately 59% developed delayed CINV.<sup>24</sup> Lack of NK-1-RA was a major obstacle in our patient group who were treated with HEC and MEC regimens and could have contributed to the poor outcome our patients experienced. Therefore, introduction of NK-1 receptor antagonists could improve compliance with treatment guidelines and improve patients' outcomes. Furthermore, proper utilisation of dexamethasone as recommended by ASCO guidelines could lead to greater control of CINV.

**TABLE 4:** Comparison of the CINV frequency in this study with previous studies.

Characteristics	Molassiotis et al. <sup>25</sup> (%)	Almazrou et al. <sup>16</sup> (%)	This study (%)
Acute vomiting	15.7	9.5	37
Delayed vomiting	14.7	8.4	12
Acute nausea	37.3	37.9	49
Delayed nausea	47.1	26.3	14

Source: Almazrou & Alnaim<sup>16</sup> and Molassiotis et al.<sup>25</sup>

To improve adherence to antiemetic guidelines at the NCI, the findings of this study were presented at the department scientific meetings and inadequate adherence to antiemetic guidelines was highlighted. Furthermore, departmental training sessions regarding appropriate use of the antiemetic guidelines were implanted.

## Conclusion

We have conducted a prospective cross-sectional study to evaluate the patterns of prophylactic antiemetic use by patients with cancer during chemotherapy. Despite the availability of guidelines of antiemetic prophylaxis of CINV, this study indicated an extremely low adherence rate. Non-adherence included a trend of both underuse and overuse of indicated antiemetic medications.

## Acknowledgements

### Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

### Author(s) contributions

M.M.A.E. was the project leader. A.A.S.A.A. was responsible for data collection. M.M.A.E., M.O.M.E. and A.A.S.A.A. contributed to project design and analysis and interpretation of data analysis and manuscript writing.

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