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Original Study

EFFECT OF 5-HT$_3$ ANTAGONIST WITH CORTICOSTEROID IN THE TREATMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

Objectives: Chemotherapy-induced nausea and vomiting (CINV) are major adverse effects of cancer chemotherapy. Inadequate control CINV can have a significant negative impact on quality of life and can compromise adherence to chemotherapy treatment. The aim of this prospective clinical trial was to evaluate the antiemetic effect of ondansetrone combined with dcexamethasone against CINV produced by high and moderate emetogenic chemotherapy in Iraqi patients.

Materials and methods: A prospective clinical trial was conducted. Patients completed 5-day daily diaries beginning on the day of single-day chemotherapy and for one to three chemotherapy cycles, the symptoms diary was designed to collect data regarding patient's demographic characteristics, cancer type, chemotherapy regimen to patient receive ondansetrone combined with dexamethasone for the treatment of CINV.

Results: A total of 52 patients were enrolled in this study, with age range of 18-63 year (41.4±17.3; Mean ±SD) of both sexes (57.7% male and 42.3% female), 65.38 % of the patients classified as receiving high emetogenic chemotherapy, whereas 34.61% of the patients receiving moderate emetogenic chemotherapy. All the patients received ondansetrone combined with dcexamethasone for the treatment of CINV, the incidence of acute nausea in patients receiving high emetogenic chemotherapy (HEC) was 41.17% compared to 22.22% in patients receiving moderate emetogenic chemotherapy (MEC); The incidence percent of delayed nausea was 35.29% in patients receiving HEC compared to 22.22% in patients receiving MEC; the effect of administered antiemetics on the incidence of acute vomiting was 35.29% in patients receiving HEC compared to 22.22% in patients receiving MEC; unexpectedly, the incidence of delayed vomiting was only 11.76% in patients receiving HEC compared to 22.22% in patients receiving MEC.

Conclusion: the results of this study demonstrate that administration of Ondansetrone combined with dexamethasone regimen against CINV produced accepted antiemtic level compared to data reported internationally; this study highlights the need for efficient translation of standard guidelines of antiemetic to clinical practice.

Keywords: Antiemetic, chemotherapy, nausea, vomiting, ondansetrone, dexamethasone.

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are major adverse effects of cancer chemotherapy that can negatively affect a patient's quality of life as well as adherence with scheduled chemotherapy, leading to delay or sometimes to discontinue potentially beneficial treatment regimens. If poorly controlled, these adverse effects can give rise to medical complications, including poor nutrition, weight loss, dehydration, and electrolyte imbalances that complicate cancer management [(1)]. Therefore, control of CINV is a crucial factor in ensuring that patients undergoing cancer chemotherapy can get the full benefit of therapy [2].

CINV can be classified under three distinct categories: acute onset, delayed onset, and anticipatory [3]. Acute CINV occurs within the first 24 hours following chemotherapy administration, whereas delayed CINV is defined as nausea and vomiting occurring after the first 24 hours and up to 5 days after chemotherapy is given. Delayed CINV can often be worse than acute symptoms because it is more likely to occur in a patient's home, away from immediate medical assistance. Anticipatory CINV arises secondary to a history of poorly controlled nausea and vomiting during prior chemotherapy. A distinct clinical syndrome that may develop with administration of chemotherapy is known as breakthrough CINV that occurs when, despite the best prophylaxis used, the patient still experiences nausea and vomiting [4].

The chemotherapeutic drugs have been classified into four emetic risk categories: high where 90% of patients will experience emesis without prophylaxis, moderate where 30%–90% of patients will experience emesis without prophylaxis, low where10%–30% of patients will experience emesis without prophylaxis, and minimal where10% of patients will experience emesis without prophylaxis [5]. Cisplatin represents the main example of a chemotherapeutic drug with a high emetogenic potential; doses greater than 50 mg/m^2 cause CINV in more than 90% of patients if no prophylaxis is used [6].

While several evidence-based consensus guidelines for preventing chemotherapy-induced nausea and vomiting (CINV) are published and regularly updated [7], studies suggest that the clinical uptake of antiemetic guidelines is often suboptimal, and CINV is a persistent problem for patients receiving chemotherapy [8]. Patients who experience CINV may be discouraged from completing their chemotherapy regimen; Moreover, patients with emesis may require emergency care or hospitalization, adding to the economic burden of cancer care [9].

There are a number of shared principles in the major CINV guidelines from the American Society of Clinical Oncology (ASCO) [10], the Multinational Association for Supportive Care in Cancer (MASCC) [11], and the National Comprehensive Cancer Network (NCCN) [12]. These principles include the following: (1) the goal of CINV treatment is to *prevent* nausea and vomiting, not to treat them once they have occurred; (2) the risk period for CINV with MEC and HEC is *at least* 4 days, and patients must be protected for the entire risk period; (3) oral formulations and IV formulations of 5-HT3 receptor antagonists are considered essentially equally effective; (4) selection of an antiemetic or antiemetic regimen should be based on

the emetic risk of chemotherapy, a patient's prior antiemetic experience, and other patient factors; and (5) prophylactic antiemetic treatment should be used whenever the risk of CINV is 10% or greater.

Although there are many observational studies evaluating the effectiveness of different antiemetic regimens and the optimal means of implementing antiemetic guidelines in practice, but the effect of guideline adherence in preventing CINV still represents the substantial issue in this area. The aim of this prospective clinical trial was to evaluate the antiemetic effect of ondansetrone combined with dcexamethasone against CINV produced by high and moderate emetogenic chemotherapy in Iraqi patients.

Patients and Methods

A prospective clinical trial was conducted from April 2013 to November 2013 at the specialized oncology hospital in Baghdad-Iraq; male and female outpatients (aged ≥ 18 years) who were scheduled to receive at least two cycles of single-day were eligible for inclusion in the study. Patients were excluded from the study if they received chronic systemic corticosteroid therapy, concurrent abdominal or pelvic radiation therapy; other key exclusion criteria were the presence of brain metastases or vomiting in the 24 h before chemotherapy.

The study was approved by the scientific and ethics committee at Alkindy College of Medicine, University of Baghdad, and patients gave written informed consent. Patients completed 5-day daily diaries beginning on the day of single-day chemotherapy and for one to three chemotherapy

cycles, the symptoms diary was designed to facilitate collection of data regarding patient's demographic characteristics, cancer type, chemotherapy regimen, antiemetic medication prescribed in addition to incidence of CINV according to standard methods utilizing standard form [13]; medical oncologists were asked to complete a questionnaire form regarding the incidence of nausea and emesis after administration of chemotherapy, assessments of the incidence rates of nausea and emesis were requested for the acute (Day 1) and delayed (Days 2–5,or ≥24hrs) phases were reported.

Descriptive statistics were used to summarize patient demographics and study responses. Mean estimated incidence rates of nausea and emesis with 95% confidence intervals (95% CI) were reported.

Results:

The questionnaire was completed by one physician for 52 patients with age range of 18-63 year (41.4±17.3; Mean ±SD) of both sexes (57.7% male and 42.3% female), with duration of disease ranging from 1 -5years while the duration of chemotherapy treatment ranging between 1 -5 years. The main types of cancer were Non-Hodgkin Lymphoma, brain tumor, Ca-rectum, Ca-bronchus, Ca-ovary, testicular tumor, Hodgkin Lymphoma and other types, 65.38 % of the patients classified as receiving high emetogenic chemotherapy were given cisplatin containing chemotherapy, whereas 34.61% of the patients receiving moderate emetogenic chemotherapy were given regimens containing Oxaliplatin, Carboplatin, Cyclophosphamide and Adriamycin, Table 1.

* Emetogenic risk of chemotherapeutic agents classified according to the guidelines of the American Society of Clinical Oncology [14].

Antiemetic therapy consistent with standard guidelines was used in the treatment of these patients. All the patients received ondansetrone combined with dcexamethasone for the treatment of CINV.

Despite the administration of antiemetic therapy, the incidence of acute nausea in patients receiving high emetogenic chemotherapy (HEC) was 41.17% compared to 22.22% in patients receiving moderate emetogenic chemotherapy (MEC), figure 1.

Table 1: Patients' Details.

Variable	Details	Value
Age	Range	18-63 (year)
	Mean±SD	41.4 ±17.3 (year)
Sex	Male	57.7%
	Female	42.3%
Type of cancer	Non-Hodgkin Lymphoma	19.23%
	Brain tumor	19.23%
	Ca rectum	15.38%
	Ca bronchus	11.53%
	Ca ovary	11.53%
	Testicular tumor	7.69%
	Hodgkin Lymphoma	7.69%
	Others	7.69%
Type of chemotherapy	High emetogenic Chemotherapy	65.38%
	Moderate emetogenic Chemotherapy	34.61%
Duration of disease		1 -5 years
Duration of chemotherapy treatment		1 -5 years

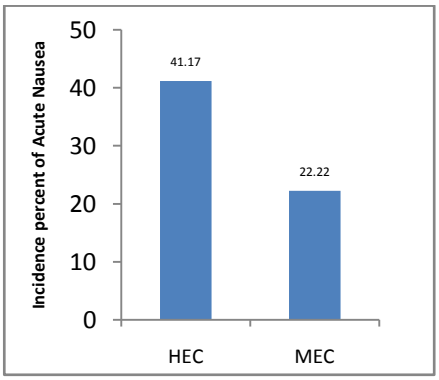

Fig.1: Effect of Ondansetrone combined with dexamethasone on the incidence of acute nausea in patients receiving high emetogenic chemotherapy (HEC) and moderate emetogenic chemotherapy (MEC).

The incidence percent of delayed nausea after administration of ondansetrone combined with dcexamethasone was 35.29% in patients receiving high emetogenic chemotherapy (HEC) compared to 22.22% in patients receiving moderate emetogenic chemotherapy (MEC), figure 2.

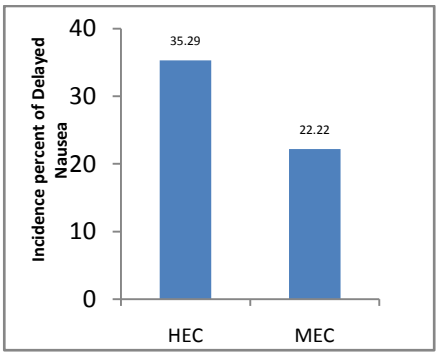

Fig.2: Effect of Ondansetrone combined with dexamethasone on the incidence of delayed nausea in patients receiving high emetogenic chemotherapy (HEC) and moderate emetogenic chemotherapy (MEC).

The effect of administered antiemetics on the incidence of acute vomiting was 35.29% in patients receiving high emetogenic chemotherapy (HEC) compared to 22.22% in patients receiving moderate emetogenic chemotherapy (MEC), figure 3.

Unexpectedly, the incidence of delayed vomiting (the most important entity among CINV that face both patient and clinicians) was only 11.76% in patients receiving high emetogenic chemotherapy (HEC) compared to 22.22% in patients receiving moderate emetogenic chemotherapy (MEC), figure 4.

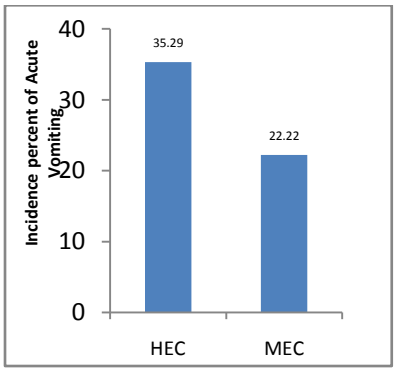

Fig.3: Effect of Ondansetrone combined with dexamethasone on the incidence of acute vomiting in patients receiving high emetogenic chemotherapy (HEC) and moderate emetogenic chemotherapy (MEC).

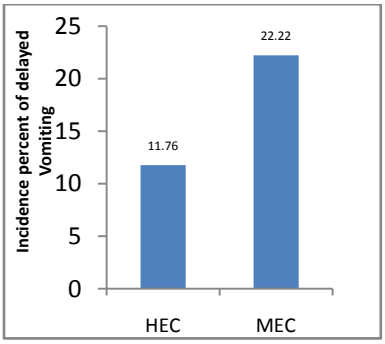

Fig.4: Effect of Ondansetrone combined with dexamethasone on the incidence of delayed vomiting in patients receiving high emetogenic chemotherapy (HEC) and moderate emetogenic chemotherapy (MEC).

DISCUSSION

Pharmacological interventions for CINV are recommended based on the type of nausea and/or vomiting and the emetogenicity of the chemotherapy. Treatment guidelines for the prevention of acute and delayed CINV have been developed by a number of cancer societies ASCO [15], MASCC/ESMO [16] and NCCN [17].

For acute emesis, the updated MASCC/ESMO guidelines recommend triple therapy with a 5-HT_3-Receptor Antagonist, corticosteroid (dexamethasone) and NK1- Receptor Antagonist for HEC regimens. Triple therapy is also recommended for anthracycline plus cyclophosphamide containing regimens. In other MEC regimens, the updated MASCC/ESMO guidelines recommend the double therapy with a 5-HT_3-RA (palonosetron preferred) and a corticosteroid (dexamethasone). For delayed emesis, the updated MASCC/ESMO guidelines recommend in patients receiving HEC, a combination of a corticosteroid (dexamethasone) and NK1-RA. For AC-based regimen, aprepitant as a monotherapy should be given. In other MEC regimens, a corticosteroid (dexamethasone) or a 5-HT_3- RA alternatively, when palonosetron was not part of the primary prophylactic treatment, are the agents of choice [18].

Despite the availability of treatment guidelines, there is evidence that adherence to and implementation of treatment recommendations are less than optimal [19] and that actual clinical practice is lagging behind current guidelines for the use of prophylactic antiemetics [20].

The 5-HT_3RAs are without doubt the most effective antiemetics in the prophylaxis of acute CINV. The different 5-HT_3RAs appear to be interchangeable. The lowest fully effective once daily dose for each agent should be used. Dexamethasone plays a major role in the prevention of acute and delayed CINV and is an integral component of almost all antiemetic regimens [21].

The results of this study showed that although there is a good adherence to the current guidelines for antiemetic use, 63.39% of patients experience acute nausea post chemotherapy treatment (41.17% for HEC and 22.22% for MEC); moreover, 57.51% of patients experience delayed nausea post chemotherapy treatment (35.29% for HEC and 22.22% for MEC type), furthermore, results of this study reported that the incidence of acute vomiting was 57.51% (35.29% for HEC and 22.22% for MEC type), compared to the incidence of delayed vomiting which is 33.98% (11.76% for HEC and 22.22% for MEC type); although the incidence of delayed vomiting due to administration of HEC which is the most important target was lower than that produced due administration of MEC, the results indicate that CINV remained a substantial problem for patients receiving chemotherapy, these results are comparable with other results obtained by different studies [22,23].

In conclusion, the results of this study demonstrate that administration of Ondansetrone combined with dexamethasone regimen against CINV produced accepted antiemtic level compared to data reported internationally; this study highlights the need for efficient translation of standard guidelines of antiemetic to clinical practice.

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