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EFFICACY AND COST OF GRANISETRON VERSUS ONDANSETRON IN THE PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING AMONG CANCER PATIENTS AT KENYATTA NATIONAL HOSPITAL

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ABSTRACT: Differences in cost and similarities in the efficacy between ondansetron and granisetron have been reported in many clinical studies and prompted this study to determine whether such differences are important as Kenyatta National Hospital. Thirty-four adult cancer patients scheduled to start their consecutive three weekly cycles of cisplatin-based chemotherapy regimens, were recruited into a double-blind randomized crossover study to receive ondansetron 12 mg or granisetron 3 mg each combined with dexamethasone 8 mg as intravenous on the first day and continued on their respective oral combinations from day 2 to 4. The frequency of nausea and vomiting were recorded daily during 5 days of antiemetic treatment. Data were collected using a close ended questionnaire and statistical analysis was performed using STATA version 13 software. Statistical significance was checked using Fisher's exact test and was considered when p value was less than 0.05. Female predominance was 70.6%, while dominant age was 50-70 years at 47.1% with a mean age of 53.5 (± 11.9) years and cervical cancer was leading cancer. Complete prevention of acute and delayed vomiting/nausea was observed in about 80 % of patients receiving either of the treatments. Direct cost with granisetron based antiemetic treatment regimen was higher compared with the one with ondansetron at a ratio of approximately 10:1. Ondansetron and granisetron each combined with dexamethasone have similar efficacy; the choice of each can depend on the cost. Ondansetron should be preferred to granisetron and further research for delayed chemotherapy induced nausea and vomiting requires to be done.

INTRODUCTION: Chemotherapy induced nausea and vomiting (CINV) are two major side effects experienced by patients in cancer treatment. Inadequately controlled CINV can result in other medical complications affecting patient's quality of life [1]. These additional complications lead to the complication of medical care at elevated cost and decrease of patient's adherence to antineoplastic therapy [1, 2].

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At Kenyatta National Hospital (KNH), ondansetron and granisetron are both used depending on the availability, although granisetron is very expansive and not easily afforded by many patients.

Both granisetron and ondansetron are given as intravenous bolus directly followed by chemotherapy administration. Delayed CINVs are not controlled because patients are not prescribed oral antiemetics to take after chemotherapy administration. The two antiemetics are usually given combined with dexamethasone to boost their efficacy. There is no research that has been done in KNH addressing the above issues to find out if the two antiemetics have different or equivalent efficacy among cancer patients. Chemotherapy induced nausea and

vomiting (CINV) is divided in acute (observed in 24 h of chemotherapy administration), delayed (observed from the second day post chemotherapy administration and may persist for 5 - 7 days) or anticipatory (observed before chemotherapy administration). There are two other categories recognized as breakthrough (observed during chemotherapy administration) and refractory (type that decline antiemetic drugs) nausea and vomiting[1]. Patients starting cancer treatment have consistently claimed chemotherapy-induced nausea and vomiting as one of their greatest fears [3]. Inadequately controlled CINV impairs usual functional activity and quality of life for patients, increases the cost of health care resources, and may further compromise adherence to treatment [3, 4].

Usually the frequency of nausea and vomiting is primarily function of the emetogenic potential of the chemotherapeutic regimen used. The use of the effective antiemetic agents; potential emetogenic of cytotoxic and individual patient characteristics are the basic considerations to achieve exhaustive preventive treatment of acute and delayed nausea and vomiting. The choice of antiemetic is guided its emetogenic potential and possible substantial risk of delayed nausea and vomiting [4]. In highly emetogenic cytotoxics a combination of a 5-hydroxytryptamine-3 receptors antagonist (5-HT RA) and steroid (dexamethasone) has appeared effective and well tolerated in the prevention of CINV. In literature, many clinical data support this combination for patients receiving cisplatin-based chemotherapy to be the appropriate indicated [4, 5].

Several studies have yielded different results regarding the efficacy of granisetron and ondansetron. Stewart at al found no significant differences in efficacy between the two drugs when evaluated by comparing the degree of nausea and distress, number of emetic episodes and overall control of emesis [6]. According to Perez *et al*., the proportion of nausea and emesis free patients at 24 and 48 h using ondansetron and granisetron are approximately equivalent [7]. He also concluded that granisetron is more efficacious than ondansetron when used in combination with a steroid (dexamethasone) in to prevent both acute and delayed vomiting caused by highly emetogenic chemotherapy [7]. Ondansetron and granisetron are considered to have high effectiveness in the prophylaxis of acute CINV although granisetron has a longer half life compared to ondansetron and is claimed to be more effective in the prevention of delayed CINV.

Ondansetron at the dosage of 8mg and granisetron 3 mg, each combined with dexamethasone, demonstrated similar efficacy and tolerability in prophylaxis of cisplatin induced emesis [3]. There is no statistically significant difference observed between the two antiemetic drugs for acute and delayed emesis [6, 8]. Various studies have been published comparing the 5-HT3 RA, but convincing data on clinically significant differences are still lacking for many of them, particularly in relation to delayed emesis. A meta-analysis of randomized controlled trials (RCT) conducted to determine if the current data available show any therapeutic difference between ondansetron and granisetron concluded that both granisetron and ondansetron have similar antiemetic efficacy for prophylaxis of chemotherapy-induced nausea and vomiting [9]. The number of comparative studies that addressed the delayed nausea and vomiting scenarios were low and therefore further RCTs are still needed to confirm these results [9].

Other clinical trials have shown granisetron to be an effective and well tolerated agent for the treatment of nausea and vomiting [10]. Due to its particular pharmacokinetic properties (safe profile and minimal drug-drug interactions), granisetron is considered to be more effective and well tolerated in special populations, such as patients with refractory properties, those with hepatic or renal defections, children and elderly [10].

MATERIALS AND METHODS:

Participants: A total of 34 cancer patients (10 male and 24 female) of 18 years and older were enrolled to participate in a double blind controlled trial at KNH in different areas where cancer patients are cared. The participants were sampled using a consecutive method when are scheduled to start their 1st chemotherapy cycle on a cisplatin-based regimen. All patients were voluntary and ethically consent of research activities.

Materials: The study used a closed ended questionnaire of 8 pages and 50 questions together with consent form signed voluntarily by each study participant.

Procedure: Patients were recruited into a double-blind randomized crossover study to receive ondansetron 12 mg or granisetron 3 mg each combined with dexamethasone 8 mg mixed in 50ml of normal saline and given as 15 minutes iv infusion 30 minutes before chemotherapy administration on the first day. Form 2nd days to 5th day after all patients received oral ondansetron 8mg or granisetron 1mg each combined with dexa-methasone 4 mg twice a day. The frequency of nausea and vomiting were assessed and recorded directly from the patient (for inpatients) or through a telephone call (for outpatients) every day. Data were collected and reported as frequencies (%). Statistical analysis was performed using STATA version 13 software. Statistical significance was done using Fisher's exact test for each variable and it was termed significant when p value was less than 0.05.

TABLE 1: SUMMARY OF ANTIEMETIC DRUGS SCHEDULE AND DOSING

Antiemetic drug	Day 1	Day 2 - 5
Ondansetron	-Ondansetron 12mg IV -Dexamethasone 8mg IV	-Ondansetron 8mg PO BD -Dexamethasone 4mg PO BD
Granisetron	-Granisetron 12mg IV -Dexamethasone 8mg IV	-Granisetron 1mg PO BD -Dexamethasone 4mg PO BD

RESULTS: Out of 34 participants, 24 (70.90%) were females and 16 (47.1%) were in age category of 50-70 years with mean age of 53.5 (+/-11.9) years. Twenty-one (61.8%) patients were of normal BMI, 2 (5.9) overweight and 5 (14.7%) were underweight with a mean weight of 61.8 (+/-14.6) kg. Cervical cancer and Head and neck cancers were leading with 14 (41.2%) patients and 10 (29.4%) respectively.

Cisplatin and paclitaxel combined was the predominant regimen prescribed at 64.7% and the most frequent dose of cisplatin was 75 mg/m^2 at 79.4%. No acute nausea observed in 27(79.4%) patients on ondansetron combination and 28 (82.4%) patients with granisetron combination. One (2.9%) patient had severe nausea with ondansetron combination, but none with granisetron combination. A complete response to prevent acute vomiting was achieved in 29 (85.3%) patients on ondansetron combination and 30 (88.2%) patients on granisetron combination.

TABLE 2: EFFECT OF ANTIEMETIC TREATMENT ON ACUTE NAUSEA AND VOMITING

Response	Ondansetron + Dexamethasone	Granisetron + Dexamethasone	p value
Number of treatment cycles	34	34	
Acute nausea			
No nausea	27 (79.4%)	28 (82.4%)	0.500
Mild nausea	6 (17.6%)	6 (17.6%)	0.624
Moderate nausea	0 (0%)	0 (0%)	NA
Severe nausea	1 (2.9%)	0 (0%)	0.500
Acute vomiting			
Complete response	29 (85.3%)	30 (88.2%)	0.500
Major response	5 (14.7%)	4 (11.8%)	0.500
Minor response	0 (0%)	0 (0%)	NA
Failure	0 (0%)	0 (0%)	NA

NA: Not Applicable

No failure treatment was observed and therefore the difference in efficacy between the two antiemetics was not statistically significant. No nausea was observed in more than 50% of the patients on the second day and the percentage increased progressively up to the fifth day.

Vomiting was absent in more than half of the patients during the second day and again the number increased up to the end of follow up. Comparison between the two combinations of drugs yielded p values above 0.05 and therefore the difference in efficacy was not statistically significant between the two antiemetics in prevention of acute and delayed nausea and vomiting.

Direct cost analysis of the two antiemetics each combined with dexamethasone using KNH prices revealed that patients spent KSh 694 in five days using ondansetron combination compared to KSh 7,074 while using granisetron combination. The ratio of the cost was approximately 10:1 in favour of granisetron combination.

DISCUSSSION: Females were predominant at 70.6%, which correlates with other studies done in Kenya, Nigeria, Cameroun and USA [11, 12, 13, 14]. The leading type of cancers were cervical cancer at 41.2% and head and neck at 29.4% relative to the statement from a recent report of the ICO Information Centre on Human Papilloma Virus (HPV) and Cancer (HPV Information Centre) which ranks cervical cancer as the most common in

Kenya at incidence of 22.4% and claim an evidence of HPV to be a relevant risk factor of anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers). The most affected age category was 50-70 years with mean age of 53.5 (+/-11.9) years. These are elderly patients targeted by chronic diseases including cancer [15].

More than a half of the patients had normal body mass index (BMI), 14.7% were underweight associated with the disease later diagnosed. The most frequently used chemotherapy regimens were cisplatin/ paclitaxel since it can be used in outpatients and has demonstrated broad clinical activity in a variety of malignancies [16, 17, 18].

The most frequently prescribed dosage of cisplatin was 75 mg/m^2 as it is mostly used in cervical cancer which was the predominantly diagnosed. As the 5-HT3 antagonists perform similarly in the clinical setting, pharmacological differences do not seem to translate into therapeutic differences [19].

In this study, there was no significant difference in antiemetic efficacy in acute or delayed nausea and vomiting between ondansetron and granisetron each combined with dexamethasone among KNH cancer patients and both combinations appeared effective against CINV.

The complete response rate for acute vomiting was 88.2% with granisetron and 85.3% with ondansetron compared to the rates for delayed vomiting of 79.5% with granisetron and 78.7% with ondansetron but the difference observed was not statistically significant; similar to the trial done by Italian Group for Antiemetic Research on high emetogenic cytotoxic (HEC) [20]. The control of delayed nausea and vomiting was still less satisfactory, but better compared to the use of the either of the two antiemetic drugs alone as found in other different studies [3, 20, 21, 22].

Although the two antiemetic combinations didn't show any significant difference in the prevention of CINV there was considerable difference in the terms of their costs. The combination including granisetron was almost ten times more expensive compared to one with ondansetron during five days of antiemetic treatment, similarly to the study done in Malaysia [23].

TABLE 3: EFFECT OF ANTIEMETIC TREATMENT ON DELAYED NAUSEA AND VOMITING

Day	Response	Ondansetron + Dexamethasone	Granisetron + Dexamethasone	p value
Day 2	Delayed nausea			
	No nausea	17 (50%)	21 (61.8%)	0.231
	Mild nausea	13 (38.2%)	10 (29.4%)	0.304
	Moderate nausea	3 (8.8%)	3 (8.8%)	0.664
	Severe nausea	1 (2.9%)	0 (0%)	0.500
	Delayed vomiting			
	Complete response	19 (55.9%)	21 (61.8%)	0.403
	Major response	11 (32.4%)	10 (29.4%)	0.500
	Minor response	3 (8.8%)	3 (8.8%)	0.664
	Failure	1 (2.9%)	0 (0%)	0.500
Day 3	Delayed nausea			
	No nausea	25 (73.5%)	27 (79.4%)	0.388
	Mild nausea	7 (20.6%)	4 (11.8%)	0.560
	Moderate nausea	2 (5.9%)	2 (5.9%)	0.693
	Severe nausea	0 (0%)	1 (2.9%)	0.500
	Delayed vomiting			
	Complete response	25 (73.5%)	28 (82.4%)	0.280
	Major response	7 (20.6%)	3 (8.8%)	0.152
	Minor response	2 (5.9%)	2 (5.9%)	0.693
	Failure	0 (0%)	1 (2.9%)	0.500
Day 4	Delayed nausea			
	No nausea	30 (88.2%)	28 (82.4%)	0.367
	Mild nausea	3 (8.8%)	2 (5.9%)	0.500
	Moderate nausea	1 (2.9%)	4 (11.8%)	0.178
	Delayed vomiting			
	Complete response	30 (88.2%)	28 (82.4%)	0.367
	Major response	3 (8.8%)	2 (5.9%)	0.500
	Minor response	1 (2.9%)	4 (11.8%)	0.178
Day 5	Delayed nausea			
	No nausea	33 (97.1%)	31 (91.2%)	0.307
	Mild nausea	1 (2.9%)	1 (2.9%)	0.754
	Moderate nausea	0 (0%)	2 (5.9%)	0.246
	Delayed vomiting			
	Complete response	33 (97.1%)	31 (91.2%)	0.307
	Major response	1 (2.9%)	1 (2.9%)	0.754
	Minor response	0 (0%)	2 (5.9%)	0.246

The study showed that both antiemetic combinations (Ondansetron or Granisetron) were effective to prevent CINV but the control was better in acute compared to the delayed phase. Ondansetron and granisetron; each combined with dexamethasone have similar efficacy in prevention of cisplatin induced nausea and vomiting; determination of clinical choice between the two antiemetics should be then led by direct cost. Patients follow up should be encouraged to achieve complete prevention of CINV by putting all patients on oral antiemetic up to 5th day post chemotherapy. KNH should prefer the cost affordable antiemetic and further research is needed to find out the optimal antiemetic regimen for the delayed phase of CINV.

TABLE 4: DIRECT COST OF PREVENTING CINV AT KNH

Combination	Duration	Drug	Total quantity	Unit cost (KSh)	Total cost (KSh)
	Day1	Ondansetron 4mg iv	3	110	694
		Dexamethasone 4mg iv	2	10	
O + D		Normal saline 50ml	1	20	
	Day 2 - 5	Oral Ondansetron 4mg	26	10	
		Oral Dexamethasone 0.5mg	64	1	
	Day 1	Granisetron 3mg iv	1	1,610	7,074
		Dexamethasone 4mg iv	2	10	
G + D		Normal saline 50ml	1	20	
	Day 2-5	Oral Granisetron 1mg	8	670	
		Oral Dexamethasone 0.5mg	64	1	

O: Ondansetron, G: Granisetron, KSh: Kenyan Shillings

CONCLUSION: Both antiemetic in combination with dexamethasone are effective to control CINV and have demonstrated similar efficacy and tolerability although the control is better for acute compared to the delayed phase. The granisetron based combination has sown to be more expensive than the one based on ondansetron, thus their clinical use will be dictated by direct cost.

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