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RESEARCH ARTICLE

AUDIT OF ANTIEMETIC DRUG PRESCRIPTION AND THEIR EFFECT IN AMELIORATING NAUSEA AND VOMITING IN PEOPLE UNDERGOING CURATIVE CHEMOTHERAPY FOR THEIR CANCER: OBSERVATIONS FROM A TERTIARY CARE CENTRE

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ABSTRACT: **Background:** In the treatment of cancer with chemotherapy, the drug induced nausea and vomiting (NIV) is an important side effect and in severe conditions can hamper the therapy. In this study an attempt is made to understand the prescription pattern of the various antiemetic regimens and their efficacy in ameliorating both NIV and the quality of life. **Methods**: In the study 68 patients were initially included of which 60 completed all the proposed 6 cycles of chemotherapy. The extent of nausea and vomiting and the effect of the same on the quality of life of the patients were assessed using a questionnaire, which was filled at various time points (0, 6, 24 and 120 hrs) following the initiation of the chemotherapy. **Results**: Comparison of the mean of the various parameters showed that the mean age of the patients enrolled was 47.55 ± 9.893 with 73.3% being females and 26.78% being males. The most common type of cancer in this study was Ca breast (35%). Palonosetron was the most common antiemetic used (63.3%), followed by aprepitant, granisetron and ondansetron. Dexamethasone was prescribed to all patients. Patients who were on antiemetic regimens which didn't include aprepitant complained of acute (75%) and delayed nausea (6%), as well as acute (45%) and delayed emesis (5%). Patients who received aprepitant had complete response (no nausea, no emesis) (100%). The quality of life parameters of patients was not affected significantly. **Conclusion**: The combinations of aprepitant + palonosetron + dexamethasone and aprepitant + dexamethasone were most commonly preferred and achieved reasonable effectiveness.

KEYWORDS: cancer chemotherapy-induced nausea and vomiting, chemotherapy, anti-emetics, palonosetron, aprepitant, acute and delayed nausea, acute and delayed emesis.

INTRODUCTION:

In clinics, cancer chemotherapy is hampered by the intense nausea and vomiting induced by cytotoxic agents. This distressing symptom would hamper the continuation of the therapy and worsen the quality

Uncontrolled nausea and vomiting may even make the patient consider stopping the treatment[1, 2]. This will invariably affect the cancer cure and survival. Most of the anticancer drugs show severe nausea

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and vomiting as an integral adverse effect. Chemotherapy induced nausea and vomiting (CINV) is classified as acute, delayed, anticipatory, breakthrough and refractory phases and the right choice of anti-emetics could circumvent this problem [1, 2].Chemotherapy induced nausea and vomiting adversely affects the quality of life of cancer patients, often leading to poor compliance with the treatment regimen and serious metabolic complications [1, 2]. The recent introduction of more effective antiemetic agents has improved the quality of life significantly. However, CINV still remains a significant complication of cancer chemotherapy and requires constant medical attention [1, 2].The most important concern for patients is the nausea and vomiting associated with the cancer treatment rather than their life expectancy, leading to discontinuation of an otherwise life saving chemotherapeutic regimen [3].

The risk of CINV depends on various patient related factors and the chemotherapeutic regimen administered [1, 2]. The more of these present in the patient, the more likely is he going to experience CINV. According to The American Society of Clinical Oncology (ASCO), chemotherapeutic agents have been classified based on their emetogenic potential [1,2]. Accordingly, several classes of antiemetic drugs are also available that antagonize the neurotransmitter receptors known to be involved in the physiology of nausea and vomiting [4-6]. From a pharmacological perspective, the antiemetic drugs are classified according to their primary action (some agents affect multiple receptors) and a combination therapy is more effective in the treatment taking into consideration that multiple pathways are involved in the pathophysiology of CINV [1,2]. In this study, we proposed to understand the pattern of antiemetic regimens used in chemotherapy induced nausea and vomiting and to evaluate the efficacy of the antiemetic regimens used and on the quality of life of the patients.

MATERIALS AND METHODS:

Following approval from the institutional ethics committee, the study was conducted in the medical oncology department of Father Muller medical college, Kankanady, Mangalore. The study period was from October 2010 to September 2011.

Design: Cross sectional prospective study

Inclusion criteria: Previously untreated cancer patients (chemotherapy naïve) in the age group of 18-65 years with newly diagnosed cancer, scheduled to receive either HEC, MEC or low risk chemotherapy were included in the study.

Exclusion criteria: Patients in the pediatric and geriatric age groups; patients with brain tumors or gastrointestinal tumors (which by itself can induce emesis) were excluded from the study. Also excluded were patients who were on other emetogenic drugs.

Details of the study: All patients coming under the inclusion criteria were explained the need for doing the study. After their written informed consent was obtained, details of their chemotherapeutic and antiemetic regimens administered during each cycle was recorded in a case record form. To determine the extent of CINV and the effect of the same on the quality of life of these patients, a questionnaire was used and completed at various intervals of 0, 6, 24 and 120 hrs, considering the types of CINV (acute, delayed). The patients were followed up for six cycles of chemotherapy and during each cycle, the questionnaires were filled. Only patients who completed six cycles of chemotherapy were included in the study, in order to evaluate the efficacy of the antiemetic regimen over the six cycles, and changes if any, in the antiemetic regimens.

Statistical method used: The results obtained were tabulated and analyzed using mean, frequency, percentage, descriptive statistics, Friedman test, and

ranking. SPSS version 11.5 was used and a 'p' value<0.05 was considered significant.

RESULTS:

Table 1: Details on the clinical, anticancer and antiemetic regimen used in the study

		Frequency	Percent
Type of Cancer	Breast	21	35.0
	Lung	19	31.7
	Ovary	17	28.4
	Granulosa Cell tumor	2	3.4
	Post cricoid carcinoma	1	1.7
Type of	HEC	17	28.3
	MEC	42	70
	Low risk	1	1.7
Regimen in cycle 1	Aprepitant + Palonosetron+ Dexamethasone	10	16.7
	Aprepitant + Dexamethasone	5	8.3
	Palonosetron + Dexamethasone	38	63.3
	Granisetron + Dexamethasone	6	10
	Ondansetron + Dexamethasone	1	1.7
Regimen in cycle 6	Aprepitant+ Palonosetron+ Dexamethasone	18	30
	Aprepitant + Dexamethasone	11	18.3
	Palonosetron + Dexamethasone	24	40
	Granisetron + Dexamethasone	7	11.7
	Ondansetron + Dexamethasone	-	-

Table 2: Incidence of acute and delayed nausea and emesis in cycle 1 and 6 of chemotherapy

		Regimen	Patients	Acute (6 hrs)		Delayed (24-120 hrs)	
				Y	N	Y	N
Nausea	cycle 1	Aprepitant + Dexamethasone+/- Palonosetron	15	-	15	-	15
		Palonosetron + Dexamethasone	38	38	-	-	38
		Granisetron + Dexamethasone	6	6	-	6	-
		Ondansetron + Dexamethasone	1	1	-	-	1
		Total	60	45	15	6	54
	cycle 6	Aprepitant +Dexamethasone +/- Palonosetron	29	-	29	-	29
		Palonosetron + Dexamethasone	24	24	-		22
		Granisetron + Dexamethasone	7	7	-	4	3
		Ondansetron +Dexamethasone	-	-	-	-	-
		Total	60	31	29	6	54
Emesis	cycle 1	Aprepitant + Dexamethasone +/- Palonosetron	15	-	15	-	15
		Palonosetron+Dexamethasone	38	38	-	3	35
		Granisetron +Dexamethasone	6	6	-	3	3
		Ondansetron +Dexamethasone	1	1	-	-	1
		Total	60	45	15	6	54
	cycle 6	Aprepitant + Dexamethasone +/- Palonosetron	29	-	29	-	29
		Palonosetron + Dexamethasone	24	22	2	-	24
		Granisetron + Dexamethasone	7	7	-	4	3
		Ondansetron + Dexamethasone	-	-	-	-	-
		Total	60	29	31	4	56

Table 3: Nausea and vomiting throughout 6 cycles of chemotherapy

	Time points (Hours)	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Statistical details
Do you feel like vomiting	0	15.49	8.18	12.57	12.93	12.57	12.38	
	6	15.31	14.39	12.38	12.38	8.18	13.21	N = 60
	24	7.82	7.82	8.18	8.73	8.18	7.34	X^{2} = 518.77 Df = 18 P = 0.0001
	120	7.45	7.45	7.45	7.45	7.45	7.45	
Do you feel nausea now	0	17.84	17.84	18.06	14.73	14.73	15.18	
	6	17.84	17.40	17.40	14.06	14.73	15.18	N = 60
	24	9.40	8.73	8.95	9.40	9.62	9.40	X^{2} = 684.77 Df = 23 P = 0.0001
	120	8.06	8.29	8.95	8.06	8.06	8.06	

Data was collected from 68 cancer patients. Eight patients were lost to follow up. Sixty patients were followed up for six cycles of chemotherapy. The mean age of the patients who took part in the study was 47.55 years ± 9.9. Out of a total of 60 patients who took part in the study, 73.3% were females and 26.7% were males (Table 1). The most common type of cancer patients in the study was cancers of breast (35%), lung (31.5%), ovary (28.4%), granulosa cell tumor (3.4%) and post cricoid carcinoma patients (1.7%) (Table 1). In the study 70% patients received moderately emetogenic chemotherapy (MEC) (Table 1). In cycle 1 all patients received dexamethasone. The most common antiemetic administered was palonosetron (63.3%), followed by a combination of aprepitant and palonosetron (16.7%). (Vide table 14). In cycle 6 the number of patients on palonosetron reduced to 40%, and the number of patients on aprepitant plus palonosetron increased to 30% (Table 1).

With respect to acute & delayed nausea and vomiting in cycle 1, 75% patient complained of acute nausea; delayed nausea was seen in 10% patients. 45.4% patients had acute emesis; delayed emesis was seen in 6% patients (Table 2). In cycle 6, 55% patients complained of acute nausea; delayed nausea was seen in 10% patients. 30% patients had acute emesis; delayed emesis was seen in 6.7% patients (Table 2). The results indicated that the quality of life of 75% patients was affected during cycle 1 chemotherapy. However, after changes were made in the antiemetic regimens in some of them, the quality of life improved by the time they were receiving cycle 6 of the chemotherapy (Table 3 and 4).

DISCUSSION:

Even though a great deal of progress has been made in the last 20 years; nausea and vomiting still continue to be the major adverse effects in cancer chemotherapy. With the appropriate use of anti-emetics, cancer induced nausea and vomiting can be reduced to up to 80%. Adequately controlled CINV can improve the quality of life of patients. Our study investigated the pattern of anti-emetics prescribed in cancer chemotherapy; their efficacy over six cycle of chemotherapy, and the effect of CINV on the quality of life in these patients.

Our study had more females (73.3%) compared to males (26.7%) (Table 1).Most of the patients in the study were middle aged (mean age – 47.55 yrs). Cancer today, is one of the leading causes of death worldwide. According to the Indian Council of Medical Research, the most common cancers prevalent in India in women are breast cancer and cervical cancer, and in men, it is lung, stomach, oral and esophageal cancer[6].The most common types of cancer in our study were breast (35%), lung (31.7%) and ovary (28.4%). The least common were granulosa cell tumor (3.4%) and posterior cricoid carcinoma (1.7%) (Table 1)

Various factors for chemotherapy induced nausea vomiting have been defined, which include age, gender, history of alcohol consumption, previous exposure to chemotherapy, and various treatments administered. The most important of these factors is the emetogenic potential of the chemotherapeutic agents [7]. Our study showed that 28.3% patients received highly emetogenic chemotherapy (cisplatin based), 70% received moderately emetogenic chemotherapy (carboplatin based) and 1.7% received low risk chemotherapy (methotrexate) [7] (Table 1)

At present, five classes of pharmacologic agents are used for the prevention and treatment of CINV: dopamine antagonists, corticosteroids, serotonin antagonists, neurokinin antagonists, and cannabinoids. Earlier studies showed that dopamine antagonists such as phenothiazines and high-dose metoclopramide had either limited efficacy or high toxicity. Current guidelines state that patients must be treated with antiemetic regimens which include a combination of a 5-HT3 receptor antagonist, a corticosteroid, and an NK-1 antagonist, thus providing a high therapeutic index [8].

All patients in our study received dexamethasone in all cycles of chemotherapy. Clinical studies have shown a successful rate of 87.4% for single administration of dexamethasone, while if it is combined with ondansetron, the rate becomes 91.8% in controlling vomiting due to chemotherapy (cisplatin), especially in the delayed type of vomiting , proving that a combination regimen is better than single drug administration (The Italian group for antiemetic research, 2000). Herrstedt J, et al analyzed data combined from 2 phase III trials to assess the efficacy of a combination of aprepitant (NK1 antagonist), a 5HT3 antagonist and a corticosteroid in patients receiving chemotherapy. It was noted that patients receiving a combination of all three drugs had a 33 percentage point improvement in the complete response (no nausea, no emesis) rate when compared to patients receiving only a 5HT3 antagonist and corticosteroid[9].

In cycle 1, the most common antiemetic administered was palonosetron (63.3%), followed by a combination of aprepitant plus palonosetron (16.7%) (Table 2). The others used were aprepitant (8.3%), granisetron (10%) and ondansetron (1.7%), which was the least common. In cycle 6, the number of patients taking palonosetron reduced to 40% and the number taking aprepitant plus palonosetron increased to 30%, and patients taking aprepitant increased to 18.3% (Table 2). The number of patients taking granisetron reduced to 11.7% and patients taking ondansetron reduced to nil. Aprepitant was added to the antiemetic regimens in one patient in cycle2, one patient in cycle 3, and fourteen patients in cycle 4 following which they found complete response in nausea and vomiting. Two patients replaced aprepitant with other anti-emetics due to the high cost of the same. None of the patients whose antiemetic regimens comprised of aprepitant complained of nausea or vomiting, showing that aprepitant has a better antiemetic cover than other anti-emetics used in this study. In 36 cases of breast cancer, Hesketh et al[10] observed that in patients were treated with aprepitant, palonosetron and dexamethasone, acute and delayed no emesis rates were 97% and 94% respectively.

In cycle 1, acute emesis was seen in 75% patients, and delayed emesis in 6% patients (granisetron and ondansetron group). Patients in the palonosetron group didn't have delayed emesis (Table 2). In a study done by Eisenberg and co workers with 161 cancer patients, it was shown that palonosetron had a prolonged efficacy in preventing delayed emesis[11].

In cycle 6, the incidence of acute nausea reduced to 55% from 75%, owing to the change in antiemetic regimens by addition of aprepitant. Acute emesis also reduced to 52.6% from 75%. There were no significant changes in the incidence of delayed

nausea and emesis (Table 2). A study was done by Osorio in Australia on twenty six patients, who received various combinations of anti-emetics including aprepitant, a 5HT3 antagonist and dexamethasone. During the therapy, aprepitant was started in seven more patients in cycle 4, and one more in cycle 5. It was concluded that the addition of aprepitant was associated with improved control of nausea and vomiting [12].

In cycle 2, 3, 4 and 5, there were no significant changes and hence we have used comparisons of cycle 1 and 6 (Table 3). CINV ranks high on the list of factors most feared in cancer patients, and although it is no life threatening, it has a major impact on the quality of life in these patients. The results indicated that that the overall acute nausea was more than delayed nausea ($p<0.000$) and overall acute vomiting was more than delayed vomiting ($p<0.007$) (Table 3). We note that most patients were affected by nausea and vomiting only to a mild extent, which only means that the anti-emetics used were reasonably effective. CINV did not affect the normal routine of these patients. The presently preferred anti-emetics for CINV are aprepitant + palonosetron + dexamethasone and aprepitant + dexamethasone which afford reasonable antiemetic cover.

SUMMARY:

CINV is one of the major and most feared adverse effects in cancer patients, which could lead to discontinuation of life saving therapy and compromise quality of life. This study investigated the pattern of antiemetic usage in preventing and treating CINV. The effect of CINV on the quality of life of these patients was also evaluated. The results study indicate minimal impact on the quality of life with preferred antiemetic choices of aprepitant + palonosetron + dexamethasone and aprepitant + dexamethasone.

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