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RESEARCH ARTICLE
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EVALUATION OF EFFICACY OF PROPHYLACTICALLY USED PREMEDICATION FOR THE MANAGEMENT OF NAUSEA, VOMITING AND HYPERSENSITIVITY REACTIONS TO CISPLATIN, TAXANES AND FAC (5-FLUOROURACIL, ADRIAMYCIN (DOXORUBICIN) AND CYCLOPHOSPHAMIDE) BASED CHEMOTHERAPY:

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Abstract

To assess premedication's efficacy for managing nausea, vomiting and hypersensitivity reactions before chemotherapy. An observational prospective study was conducted at Nuclear Institute of Medicine and Radiotherapy Hospital Jamshoro, Sindh, Pakistan, from November 2020 to July 2022. The study included 180 patients, aged 18-60 years. A validated questionnaire was used to record data of patients. Most frequent reaction was Tachycardia 40% in Cisplatin, 46% in Paclitaxel and 50% in Docetaxel, Hypotension 30% in Cisplatin, 40% in Paclitaxel and 5-Flouro Uracil (5-FU) and 43% in Docetaxel, Phlebitis 44% in Paclitaxel, Flushing 57% in Docetaxel, Skin rash 57% in Paclitaxel and 63% in Docetaxel, Oral sore 40% in 5-FU, Diarrhea 40% in Cisplatin, 54% in Paclitaxel, 63% in Docetaxel while 54% in Cyclophosphamide and Doxorubicin and 40% in 5-FU. Nausea, vomiting and hypersensitivity reactions were controlled significantly by the use of premedication in Cisplatin

and FAC based chemotherapy while in taxane-based chemotherapy these reactions were observed in moderate range.

Key words: Pre Medication, Nausea and Vomiting, Hypersensitivity Reactions, Chemotherapy, Cisplatin, Taxanes, FAC

INTRODUCTION

One of the common meditating side effects of carcinoma treatment is Chemotherapy-induced nausea and vomiting (CINV), which is observed in around 40% of the patients.[1-3] Although, all antineoplastic drugs have probable adverse effects like nausea and vomiting induced by chemotherapy, and infusion reactions (IRs), these can be prevented by prophylactically used medication or premedication. Hence, it is strongly advised that oncologists must possess a deep understanding of these possible negative events and the preemptive measures required to reduce the frequency and intensity of adverse events.[4] Such type of reactions have the potential to greatly affect patients' quality of life unless treated properly. Chemotherapy-induced nausea and Vomiting (CINV) may lead to anorexia, nutritional depletion, and metabolic disorder and ultimately result in discontinuation of chemotherapeutic treatment.[5] The administration of many cytotoxic agents carries the risk of potentially hypersensitivity reactions (HSR). Hypersensitivity is characterized as an unanticipated response that cannot be accounted for by the established toxicity profile of the chemotherapy drug. Hypersensitivity reactions have been observed with the usage of various antineoplastic agents.[6]

[Due to hypersensitivity both sudden and delayed responses have been documented, leading to symptoms of skin flushing, redness, itching, hives, dyspnea, low blood pressure, bronchospasm, nausea, backache, and fever.[7]

As per the recommendation of different guidelines such as the American Society of Clinical Oncology (ASCO), Multinational Association of Supportive Care in Cancer (MASCC), European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines, the chemotherapeutic induced adverse reactions can be prevented by prophylactic use of pre-medications before infusions of chemotherapeutic agents.

RESEARCH DESIGN.

An observational prospective study was conducted at Nuclear Institute of Medicine and Radiotherapy Hospital Jamshoro, Sindh, Pakistan, from November 2020 to July 2022.

PATIENT SAMPLING.

The study was conducted by recruiting the patients who were visiting this hospital. Sampling was done by randomly selecting the sample of 180 patients who received premedication before receiving Cisplatin, Paclitaxel, Docetaxel and FAC-based chemotherapy.

ANALYSIS.

Drugs used as a premedication were recorded and compared with recommended guidelines and the efficacy of these prophylactically used premedication against nausea, vomiting, and hypersensitivity reaction were observed during chemotherapy. Patients' medication record file was used to obtain patients' demographic data, diagnose, and information of therapeutic. A validated questionnaire was used to record feedback of patients.

ETHICAL CONSIDERATION

After the approval from the authorities of hospital, the study was conducted and before participation the participants were informed and their consent was taken.

RESULTS

Prophylactically premedication is a widely used practice before chemotherapy infusion to prevent chemotherapy-induced nausea, vomiting and hypersensitivity reactions. Different guidelines for prophylactically used premedication drugs are available (Table. 1), based on available guidelines, premedication has been prescribed. The present study included 180 patients aged 18-60 years in which were females comprise 110 of 180 patients, 50 patients received Cisplatin for head and neck carcinoma at a dose of 50mg every week, 50 patients received Paclitaxel at a dose of 175mg/m^2 every 3 weeks, 30 patient received Docetaxel at a dose of 75mg/m^2 every 3 weeks while 50 patients received FAC-based chemotherapy for breast carcinoma at a dose of (5-fluorouracil 500mg/m^2, Adriamycin 60mg/m^2, and Cyclophosphamide 600mg/m^2) every 3 weeks as presented in table 2. A simplified pre-medication regimen was given in 15 to 20 minutes of 100ml infusion before starting chemotherapy which consisted of a dexamethasone 8mg, H1 blockers (diphenhydramine 25mg) as shown in Table 3.

TABLE1: CINV Prophylaxis Recommendations for IV Chemotherapy.

		ASCO	**MASCC/ESMO**	**NCCN**
HEC	Acute Phase	5-HT3-RA + dex + NK1-RA + olanzapine	5-HT3-RA + dex + NK1-RA +/- olanzapine	Option 1: 5-HT3-RA + dex + NK1-RA + olanzapine (preferred) Option 2: Any 5-HT3-RA + dex + NK1-RA Option 3: palonosetron + dex + olanzapine
	Delayed Phase	Non-AC: dex days 2-4 + oral aprepitant (if used on day 1) days 2–3 + olanzapine days 2–4 AC: aprepitant (if given on day 1) + olanzapine	Non-AC: dex days 2–4 AC: aprepitant (if used on day 1) or dex days 2–3 +/- olanzapine. Note: no further prophylaxis if fosaprepitant (Emend for injection), netupitant (Akynzeo), or rolapitant used on day 1	Olanzapine days 2–4 + aprepitant po days 2–3 (if used on day 1) + dex days 2–4 Olanzapine days 2–4 Aprepitant po days 2–3 (if used on day 1) + dex days 2–4
Carboplatin	Acute Phase	5-HT3-RA + dex + NK1-RA, when dosed at AUC ≥ 4	5-HT3-RA + dex + NK1-RA	Same as HEC above
	Delayed Phase	No prophylaxis	Aprepitant days 2 and 3 if used on day 1	Same as HEC above
MEC	Acute Phase	5-HT3-RA + dex	5-HT3-RA + dex	Option 1: 5-HT3-RA + NK1-RA + dex Option 2: 5-HT3-RA + dex Option 3: Olanzapine + palonosetron + dex
	Delayed Phase	Dex only if patients receiving therapies with known potential	Dex only if patients receiving therapies with known	5-HT3-RA or dex or olanzapine (on days 2 and 3

		for delayed CINV (i.e., oxaliplatin, anthracycline, cyclophosphamide)	potential for delayed CINV (i.e., oxaliplatin, anthracycline, cyclophosphamide)	only if given on day 1) Aprepitant (if given on day 1) +/- dex on days 2 and 3
LEC	Acute Phase	5-HT3-RA or dex	Dex or 5-HT3-RA or dopamine RA	Dex or metoclopramide or prochlorperazine or 5-HT3-RA
	Delayed Phase	None	None	None
Minimal	Acute Phase	None	None	None
	Delayed Phase	None	None	None

Note. ASCO = American Society of Clinical Oncology; MASCC = Multinational Association of Supportive Care in Cancer; ESMO = European Society for Medical Oncology; NCCN = National Comprehensive Cancer Network; RA = receptor antagonist; dex = dexamethasone; AUC = area under the curve; LEC = low emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; HEC = highly emetogenic chemotherapy. Information from Hesketh et al. (2020); NCCN (2021); Roila et al. (2016).

Table 2. Chemotherapeutic agent and their indication in different carcinoma

Chemotherapeutic Agent	Indication
Cisplatin	Head and Neck (H&N) Carcinoma
Paclitaxel	Breast Carcinoma
Docetaxel	Breast Carcinoma
Cyclophosphamide	Breast Carcinoma
Doxorubicin	Breast Carcinoma
5-Fluorouracil (5-FU)	Breast Carcinoma

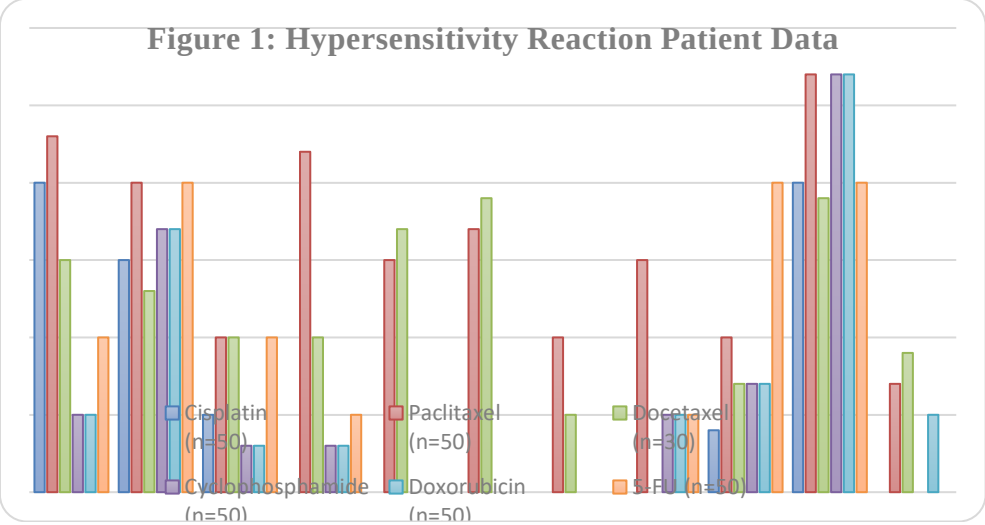
Table 3. Premedication

Prophylactically Used Premedication	Indication
Inj: Dexamethasone 8mg	To prevent nausea & vomiting and hypersensitivity reaction.
Inj: Pheniramine maleate 25mg	To prevent hypersensitivity reaction
Inj: Granisetron Hcl 3mg	To prevent nausea & vomiting

It has been observed that premedication has helped to some extent to control chemotherapy-induced Nausea Vomiting and hypersensitivity reactions. The most frequent reactions that were observed include tachycardia accounts for 40% in Cisplatin, 46% in Paclitaxel and 50% in Docetaxel , hypotension accounts for 30% in Cisplatin, 40% in Paclitaxel and 5-FU & 43% in Docetaxel while 34% in Cyclophosphamide and Doxorubicin , dyspnea accounts for 20% in Paclitaxel, Docetaxel and 5-FU , Phlebitis accounts for 44% in Paclitaxel & 33% in Docetaxel , flushing accounts for 30% in Paclitaxel & 57% in Docetaxel and skin rash accounts for 57% in Paclitaxel & 63% in Docetaxel, Urticaria accounts for 20% in Paclitaxel, Abdominal cramps also observed 30% in patients of Paclitaxel, Oral sore was frequently observed in 5-FU in 40%, Diarrhea accounts for 40% in Cisplatin, 54% in Paclitaxel, 63% in Docetaxel while 54% in Cyclophosphamide and Doxorubicin and 40% in 5-FU as shown in Table 4. Figure 1 shows the graphical representation of hypersensitivity reactions produced by different chemotherapeutic agents.

Table 4. Hypersensitivity Reaction Patient Data

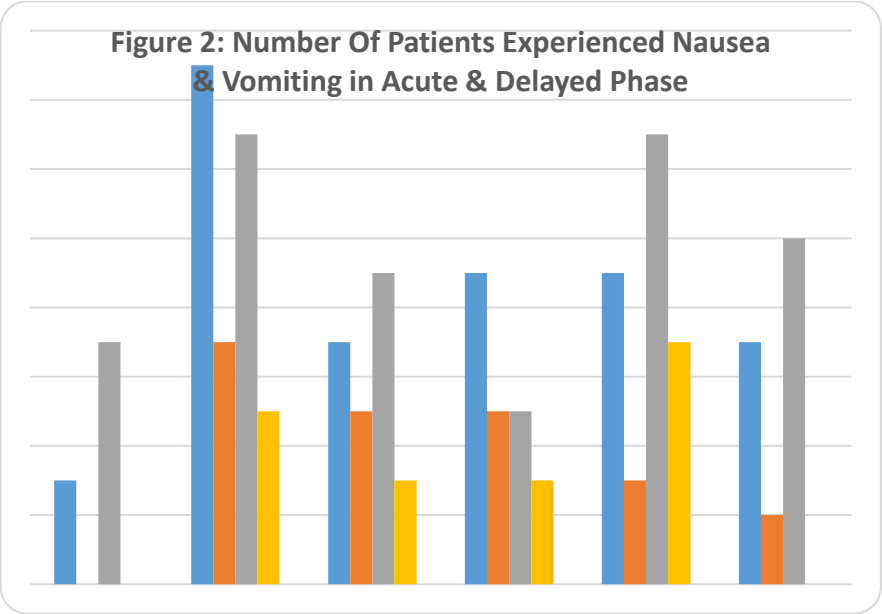
Reaction	Cisplatin (n=50)	Paclitaxel (n=50)	Docetaxel (n=30)	Cyclophosphamide	Doxorubicin	5-FU
				n=50		
Tachycardia	20	23	15	5	5	10
Hypotension	15	20	13	17	17	20
Dyspnea	5	10	10	3	3	10
phlebitis	0	22	10	3	3	5
flushing	0	15	17	0	0	0
Skin rash	0	17	19	0	0	0
Urticaria	0	10	5	0	0	0
Abdominal cramps	0	15	0	5	5	5
Oral Sore	4	10	7	7	7	20
Diarrhea	20	27	19	27	27	20
Pelvic pain	0	7	9	0	5	0



Nausea and vomiting were also reported to some extent in patients who had received Paclitaxel and Docetaxel in a frequency of 30% and 23% in the acute phase of nausea while 26% and 30% in the acute phase of vomiting. Other chemotherapeutic agents were reported to produce nausea and vomiting in less frequency as shown in Table 5. Figure 2 shows the graphical representation of nausea and vomiting of different chemotherapeutic agents.

Table 5. Number Of Patients Experienced Nausea & Vomiting

Chemotherapeutic Agent	N0. Of patients	Experienced Nausea ACUTE	DELAYED	Experienced Vomiting ACUTE	DELAYED
Cisplatin	50	3	NO	7	NO
Paclitaxel	50	15	7	13	5
Docetaxel	30	7	5	9	3
Cyclophosphamide Doxorubicin 5-FU	50	9	5	5	3
		9	3	13	7
		7	2	10	0



It has also been observed that in 1st cycles of chemotherapy most of patients were depressed and their depression become challenging towards their emotional and mental health conditions. Similarly, patients with prolong exposure of chemotherapeutic agent due to their disease at advanced stage or with metastasis are really compromised patients that affect patients over all quality of life and contribute to feeling of depression.

DISCUSSION

This study presents the efficacy and safety of prophylactically used antiemetic and antiallergic drugs to prevent nausea, vomiting and hypersensitivity reactions. Nausea, vomiting and Hypersensitivity reactions following chemotherapeutic agents were reported commonly in 1st cycle of chemotherapy or in patients who had received more cycles of chemotherapy. Hypersensitivity reaction including tachycardia was reported in the moderate range in Cisplatin and Taxane preparation (Paclitaxel and Docetaxel), hypotension and diarrhea were reported in mild to moderate range among cytotoxic agent, and flushing and skin rash were only reported in Taxane preparation, while phlebitis only reported in Paclitaxel in a moderate range. Similarly, nausea and vomiting were also well controlled by Granisetron (5-HT3 receptor antagonist).

The findings of my study correlate with the following studies significantly including Boulanger J, Boursiquot JN, et al (2014), Broyles AD, Banerji A, et al (2020), Bonamichi-Santos R, Castells M (2018), Pagani M, Bavbek S, et al (2019) reported hypersensitivity reaction to Paclitaxel and Docetaxel after premedication in 10% of the patients which include hypotension, dyspnea, flushing, chest or back pain.[8-11] Similarly, a study presented by Solimando DA, Wilson JP showed that hypersensitivity reaction produced by Doxorubicin can be prevented by Diphenhydramine or Diphenhydramine and hydrocortisone[12]. Latreille, J., Stewart, D, et al (1995) reported that by the addition of Granisetron to Dexamethasone, nausea and vomiting well controlled 24 hours after the infusion of Cisplatin in a dose greater than 50mg/m^2.[13] Another study of Italian Group for Antiemetic Research (1995) reported that Granisetron in combination of Dexamethasone can effectively control nausea and vomiting in moderate emetogenic therapy.[14] Similarly study of Ritter, H. L., Gralla, R. J.,et al (1998) showed that Granisetron can effectively prevent nausea and vomiting in multiple cycles of Cisplatin.[15]

Another study presented by Turan, T., Bozok, et al (2007) that prophylactic Antiemetic activities of Tropisetron and Granisetron were stronger than Ondansetron.[16]

CONCLUSION

Chemotherapy related side effects like nausea and vomiting were controlled significantly by the use of Granisetron (5-HT3 receptor antagonist) and dexamethasone. Hypersensitivity reactions were well controlled by Dexamethasone and Pheniramine maleate in Cisplatin and FAC-based chemotherapy while in Taxane-based chemotherapy hypersensitivity reactions were seen in moderate range. In the initial cycles, most of the patients were depressed and their depression became challenging for their emotional and mental health conditions. Similarly, patients with prolonged exposure to chemotherapeutic agents due to their disease at an advanced stage or with metastasis are compromised patients that affect patients' overall quality of life and contribute to feelings of depression. Therefore, it is very necessary to give prophylactically olanzapine as it is also recommended by ASCO, MASCC/ESMO, and NCCN guidelines.

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