Original Article

Effectiveness of Fosaprepitant in Combination with 5-HT3 Receptor Antagonist and Dexamethasone in Management of Chemotherapy Induced Nausea and Vomiting

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ABSTRACT

Introduction: Chemotherapy-induced nausea and vomiting (CINV) is one of the common side effects of cancer chemotherapy, that affects patient's physical and psychological aspects, decreasing patients quality of life and compliance with therapy. CINV can be acute, delayed or anticipatory. This study assessed effectiveness of fosaprepitant (NK-1 receptor antagonist) in combination with 5-hydroxytryptamine-3 receptor antagonist (5-HT3 RA) plus dexamethasone in prevention and management of nausea and vomiting in patients receiving broad range of chemotherapy regimens.

Materials and methods: The current study is prospective study conducted on randomly selected 72 patients during first and second cycle of standard chemotherapeutic regimens. During 144 cycles of chemotherapy patients were randomly assigned in two different anti emetic regimen; triplet regimen (aprepitant, 5-HT3 RA, dexamethasone) and duplet regimen (5-HT3 RA, dexamethasone). All the patients were interviewed using MASCC antiemesis tool (MAT) for incidence of nausea and vomiting. Nausea and vomiting was assessed for 5 days following 1st day of each chemotherapy cycle.

Results: During the period of study, duplet regimen was administered in 68 cycles and triplet regimen was administered in 76 cycles of chemotherapy. Most of the chemotherapy regimen were platinum based compounds (61%). In duplet regimen 76.6 % (52/68) and 72.1% (49/68) patients had acute and delayed vomiting respectively whereas in triplet regimen 7.9% (6/76) and 5.3% (4/76) patients had acute and delayed vomiting respectively. Complete response in triplet regimen were achieved in 89 % of chemotherapy cycles which were significantly low in duplet regimen 10 % only.

Conclusions: This study concludes that addition of fosaprepitant in combination with 5-HT3 RA and dexamethasone prevents CIMV in cancer patients receiving chemotherapy.

Keywords: Diclofenac, Tramadol, Analgesia.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the well known side effect of cancer chemotherapy. Lorusso, et al., (2017) has mentioned that nausea and vomiting is the most common adverse effect anticipated as well as experienced by patients receiving chemotherapy.[1] Poorly controlled nausea and vomiting significantly impairs daily functioning, compromises the quality of life and reduces work productivity of patients receiving chemotherapy.[2] Apart from physical impairment due to dehydration, electrolyte imbalance and malnutrition due to nausea and vomiting, CINV also has significant impact on psychological aspects leading to poor adherence to chemotherapy.[3]

On the basis of study on emesis occurring following cisplatin administration CINV is classified as acute

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emesis which is observed typically within 24 hours and delayed emesis, observed after 24 hours of chemotherapy.[4] On further study of emesis in cancer patients by Neese et al., (1980), it was observed that patients experienced vomiting as a conditioned reflex which was precipitated by anticipation of unpleasant experience from previous treatment, previous experience of emesis or the smell of the clinic and was described as anticipatory emesis.[5]

Chemotherapeutic agents through direct mucosal or blood born mechanism, stimulate enteroendocrine cells in gastro-intestinal cells, and peripheral mononuclear cells in blood to release mediators like 5- Hydroxytryptamine (5-HT), substance P and cholecystokinin, which then mediate the afferent impulse to central nervous system, initiating emetic response.[6,12,13] Therefore, drugs like granisetron, dexamethasone and aprepitant have definite role in management of chemotherapy induced nausea and vomiting.[7,8] Glucocorticoids inhibit the release of emetic mediators from gastrointestinal tract and peripheral blood cells, interact with serotonin receptors, inhibit nucleus tractus solitarius and they also reduce pain, thereby reducing concomitant use of opioids, which in turn reduces opioid-related nausea and vomiting.[9,10]

NK1 receptor antagonist prevent both acute and delayed chemotherapy induced nausea and vomiting by action at receptors within central nervous system blocking their activation by substance P released as unwanted consequence of chemotherapy.[11] Aprepitant, the first NK1 receptor antagonist was approved in 2003 by FDA in prevention of CINV.[12] To improve the compliance of anti emetic therapy, instead of aprepitant which is administered orally for 3 days (125 mg on Day 1, 80 mg on Day 2 and 3), intravenous prodrug of aprepitant, fosaprepitant was formulated.[13] A phase 3 trial showed that single 150 mg intravenous dose of foaprepitant could block 90% of NK-1 receptors, and was non inferior to 3 days oral aprepitant.[14]

This study assessed effectiveness of NK-1 receptor antagonist, fosaprepitant in combination with 5-hydroxytryptamine-3 receptor antagonist (5-HT_3 RA) plus Dexamethasone in prevention and management of nausea and vomiting in patients receiving broad range chemotherapy regimens.

Material & Methods

The current study is prospective study of 72 patients receiving standard chemotherapeutic regimens for various tumor types. The inclusion criteria were biopsy proven case of various carcinoma planned for 1st cycle standard multiagent chemotherapeutic regimens. Patients with upper GI malignancy who had nausea and vomiting prior to chemotherapy and patients who did not give consent were excluded from the study.

During the period of 6 months 72 patients receiving first cycle chemotherapy were selected randomly and were followed up in second cycle chemotherapy. In total 144 cycles of chemotherapy was administered and during each cycle patients were randomly assigned in duplet and triplet anti emetic regimen. In dupet regimen patient received Granisetron 3 mg intravenous and Dexamethasone 8mg intravenous in each day of chemotherapy, while in triplet regimen patients received Fosaprepitant 150 mg diluted in 500 ml of normal saline infused intravenously over 2 hours on first day along with intravenous Granisetron 3 mg and Dexamethasone 8 mg on each day of chemotherapy. All the patients were interviewed using MASCC antiemesis tool (MAT) for incidence of nausea and vomiting. Nausea and vomiting was assessed for 5 days following 1st day of each chemotherapy cycle. Similarly experience of nausea in both phase was reported and scored between 0 -10. Acute nausea and vomiting was defined as nausea and vomiting in first 24 hours after chemotherapy. Similarly delayed nausea and vomiting was defined as nausea and vomiting occurring after 24 hours after chemotherapy to 4 days after chemotherapy. Complete response (CR) was defined as no vomiting or no rescue therapy during evaluation period.

Results

The study included seventy two patients who were diagnosed with cancer. All the patients included in the study were scheduled for first cycle chemotherapy and were followed up in second cycle chemotherapy. Median age of patients included in study was 49 years (range 16-75) with female predominance (56.94 %) During the period of study, duplet regimen was administered in 68 cycles and triplet regimen was administered in 76 cycles of chemotherapy. Most of the chemotherapy regimen contained platinum based compounds (61%) (Table 1).

Table 1 Clinical characteristics of patients

Characteristics	Number (%)
Age (Years)	
Maximum	75
Minimum	16
Median	49
Sex	
Male	31(43.05)
Female	41(56.94)
Type of Malignancy	
Lung	15 (20.83)
Breast	12 (16.66)
Head and Neck	11 (15.27)
Gynecological	10 (13.88)
Genitourinary	9 (12.5)
Colorectal	9 (12.5)
others	6 (08.33)
Cisplatin based chemotherapy regimen	
Yes	44 (61.11)
No	28 (38.88)

In duplet regimen 76.6 % (52/68) and 72.1% (49/68) patients had acute and delayed vomiting respectively. Similarly in triplet regimen 7.9% (6/76) and 5.3% (4/76) patients had acute and delayed vomiting respectively (Table 2). The differences were statistically significant. Incidence of acute and delayed nausea were also statistically lower in triplet regimen compared to duplet regimen (25% and 11.8% vs 83% and 82.4%). CR in triplet regimen was achieved in 89 % of chemotherapy cycles which were significantly low in duplet regimen 10 % only. Further analysis revealed that mean frequency of vomiting and nausea score both in acute and delayed phase were lower in triplet regimen compared to duplet regimen (Table 3). Among triplet regimen, infusion site reactions were observed in 4 (5.26%) patients and were managed conservatively.

Table 2 Percentage of patients with Vomiting and Nausea

	Vomiting			Nausea	
Regimen	**Complete Response**	**Acute**	**Delayed**	**Acute**	**Delayed**
Triplet	89.47	7.9	5.3	25	11.8
Duplet	10.53	76.6	72.1	83	82.4
Triplet Regimen: Fosaprepitant + 5-HT3RA + Dexamethasone					
Duplet regimen : 5-HT3RA + Dexamethasone					

Table 3 Mean score of Vomiting and Nausea (N)

	Mean frequency of Vomiting		Mean score of Nausea	
Regimen	**Acute**	**Delayed**	**Acute**	**Delayed**
Triplet	.10	.13	.69	.43
Duplet	1.8	1.76	2.94	3.16
Triplet Regimen: Fosaprepitant + 5-HT3RA + Dexamethasone				
Duplet regimen : 5-HT3RA + Dexamethasone				

Discussion

CINV is established adverse drug reactions of different chemotherapeutic agents. Some chemotherapeutic drugs are highly emetic where as other are least emetic. But CINV has direct impact on patients daily life and is also a indicator of good quality of life of cancer patients. Antiemetic therapy is always aimed to minimize the incidence of CINV. Our study clearly demonstrates that during chemotherapy with moderate to higly emetic drugs, a NK-1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone can prevent CINV more effectively. Our findings are in consistent with other studies, suggesting addition of fosaprepitant in combination with other antiemetic drugs lowers CINV.[18,19] Adverse reactions observed with intravenous fosaprepitant are leukopenia, anorexia, constipation, vomiting, diarrhea, hiccups and asthenia.[14,15] A study has shown that coadministration of fosaprepitant with anthracyclin based chemotherapy was associated with higher incidence (67%) of infusion site reaction compared to chemotherapy without anthracyclin (16%).[16] Venous toxicity of fosparepitant include pain, erythema, swelling, extravasation and phlebitis.[17] Similarly, higher incidence of infusion site reaction when administered with the combined cyclophosphamide and doxorubicin was higher in fosaprepitant (34.7%) as compared to aprepitant (2.3%).[18] Nevertheless this current study showed infusion site reactions were observed in 5.26% patients with NK-1 receptor antagonist. These NK-1 receptor antagonist are also known to alter cytochrome P450 activity, thus the potential for a drug reaction with these agents should be considered when selecting anti emetic therapy.[19]

The emetogenic potential of chemotherapeutic agents are classified as: minimal risk (<10%), low risk (10 % - 30 %), moderate risk (30% - 90%) and high risk (>90%).[6] Chemotherapeutic drugs with minimal emetogenic risk include Bevacizumab, Bleomycin, Fludarabine,

Vinblastin, Vincristine, whereas Bortezomib, Cetuximab, Cytrabine <100mg/m^2, Docetaxal, Etoposide, Flurouracil, Gemcitabine, Methotrexate, Mitoxantrone, Paclitaxel, Pemetrexed, Transtuzumab are classified as low emetogenic risk drugs, similarly moderate risk drugs are Carboplatin, Cyclophosphamide ≤ 1.5g/m^2, Cytarabine>1g/m^2, Daunorubicin, Idarubicin, Oxaliplatin, Irinotecan, Ifosfamide and drugs like Carmustin, Cisplatin, Cyclophosphamide >1.5g/m^2, Dacarbazine, Streptozocin are classified as highly emetogenic drugs.[6]

The updated ASCO clinical practice guidelines on anti emetic drugs recommends use of following anti emetics: a NK-1 receptor antagonist, a serotonin receptor antagonist, dexamethasone, and olanzapine during high emetic-risk antineoplastic agents, a serotonin receptor antagonist, and dexamethasone with or without NK-1 receptor antagonist during moderate emetic-risk antineoplastic agents, and a single dose of a serotonin receptor antagonist or a single 8 mg dose of dexamethasone during low emetic-risk antineoplastic agents.[20] The same guideline also recommends that adult patients treated with minimal emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis.

Several risk factors like age, gender, history of alcohol intake, anxiety or history of emesis during pregnancy are identified in regard with CINV.[21] However in present study risk factors interpretation was not done. Anticipatory emesis was also not included in current study.

Conclusions

CINV is one of the distressing adverse effect of chemotherapy. Use of anti emetic regimen in accordance with emetogenic potential of chemotherapeutic agents could reduce patients morbidity and improve compliance. The present study concludes that addition of NK-1 receptor antagonist with dexamethasone and 5-HT$_3$ receptor antagonist has beneficial results in context of Nepalese patients as well in prevention of chemotherapy induced nausea and vomiting.

Conflict of interest: None

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