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Review Article

RECENT UPDATES IN THE MANAGEMENT OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

The leading factor that has an impact on cancer patients' quality of life and their adherence to treatment is chemotherapy induced nausea and vomiting (CINV). Better understanding of the physiology of CINV and the identification of risk factors can be beneficial in improving the treatment outcomes. A number of antiemetic agents are currently available including 5-hydroxytryptamine receptor antagonists ($5HT_3$RAs), neurokinin receptor antagonists (NK_1RAs), dopamine receptor antagonists, benzodiazepines and cannabinoids. These agents can be used in the effective management of CINV according to the various antiemetic guidelines like NCCN (National Comprehensive Cancer Network) guidelines, ASCO (American Society of Clinical Oncology) guidelines and MASCC (Multinational Association of Supportive Care in Cancer) guidelines. Even though CINV can be prevented to a great extent with these agents, some patients still experience nausea and vomiting. In order to attain the ultimate goal of complete control of CINV, more effective therapies are greatly needed. This review focuses on the pathophysiological aspects of CINV, antiemetic agents, current guidelines for management of CINV, their comparative evaluation and recent trends in management of CINV.

Keywords: Chemotherapy induced nausea and vomiting, ASCO antiemetic guidelines, NCCN antiemetic guidelines, 5 hydroxytryptamine receptor antagonists (5HT3RAs), neurokinin receptor antagonists (NK1RAs), olanzapine.

INTRODUCTION

Chemotherapy is one of the prime therapeutic regimens for treating cancer. The most common and distressing adverse effect which continues to be a significant problem in patients receiving chemotherapy is nausea and vomiting [1].CINV can affect a patient's quality of life. They can occur within the first 24 hours of starting chemotherapy (acute), or persist for 24 hours or more or begin 24 hours afterchemotherapy (delayed) or before patients actually receive their next chemotherapy because of the negative past experience with chemotherapy (anticipatory), occur despite prophylactic treatment (breakthrough) and can arise due to the failure of antiemetic therapy in the previous cycles (refractory) [2,3]. Chemotherapy induced nausea and vomiting can have a number of clinical implications for patients, including non-compliance with treatment, unwillingness or inability to eat and /or drink and nutritional deficits[4].If there is any deficiency in antiemetic prophylaxis, patients receiving chemotherapy may experience nausea and/or vomiting. Therefore, effective management of CINV represents an extremely important part of patient's overall care plan [5]. The purpose of this article is to review the current understanding of CINV and different approaches for its safe and effective management.

RISK FACTORS FOR CINV

The severity of CINV depends on many factors. Some patients have a higher risk for developing CINV. Risk factors for developing CINV can be grouped into two basic categories like *Treatment-related factors* {type of chemotherapy (highly or moderately emetogenic drugs, dosage of the chemotherapeutic agents} and *Patient-related factors* {age and sex, prior history of CINV, emesis during pregnancy or motion sickness, alcohol use, anxiety}. In addition, cancer itself is a risk factor, with the level of risk related to the cancer stage and location [6, 7].

Emetogenic Potential of Chemotherapeutic Agents

With regard to their emetogenic potential, the drugs for chemotherapy can be categorized into four major categories: highly emetogenic (>90%), moderately emetogenic (30-90%), low emetogenic (10-30%) and minimally emetogenic (<10%) respectively [8, 9, 10].

Chemotherapy drugs vary in their emetogenicity (ability to induce vomiting). Cisplatin is considered to be the most emetogenic drug [7].Other commonly used drugs with high emetogenic potential include cyclophosphamide, lomustine and dacarbazine. Emetogenicity can also be increased through combination of individual drugs with lesser potential to cause CINV [combination of low emetogenic agents like methotrexate (>100 mg/m2) and cytarabine (<1mg/m2) results in moderate emesis], or higher doses of single agents in an individual patient (cyclophosphamide when given at doses of >1500 mg/m2 is highly emetogenic whereas at doses below 1500 mg/m2 will induce only moderate emesis). Understanding the emetogenic potential of a chemotherapeutic agent or combination is important in prescribing the appropriate prophylactic regimen [11, 9, 10]. The level of emetogenicity[9] of various chemotherapeutic agents experienced by the patients receiving chemotherapy is shown in Table 1.

Table1: Emetogenic risk of antineoplastic agents

High risk (>90%)	Moderate risk (30–90%)	Low risk (10–30%)	Minimal risk (<10%)
Carmustine	Carboplatin	Bortezomib	Bevacizumab
Cisplatin	Cyclophosphamide	Cetuximab	Bleomycin
Cyclophosphamide	(≤1.5 g/m^2)	Cytarabine(<1g/m^2)	Busulfan
(>1.5 g/m^2)	Cytarabine (>1 g/m^2)	Docetaxel	Chlorambucil
Dacarbazine	Daunorubicin	Etoposide	Cladribine
Dactinomycin	Doxorubicin	5-Fluorouracil	Fludarabine
Mechlorethamine	Epirubicin	Gemcitabine	Vinblastine
Streptozocin	Idarubicin	Ixabepilone	Vincristine

Lomustine	Ifosfamide Irinotecan Mitoxantrone (>12mg/m^2) Oxaliplatin	Lapatinib Methotrexate(>100mg/m^2) Mitomycin Mitoxantrone(<12mg/m^2) Paclitaxel Pemetrexed Teniposide Thiotepa Temsirolimus Topotecan Trastuzumab	Vinorelbine

PATHOPHYSIOLOGY OF CINV

Nausea and vomiting induced by chemotherapy are two distinct components and must be assessed independently. Nausea is defined as a sensation of unease and discomfort in the upper stomach with an involuntary urge to vomit. It often, but not always, precedes vomiting. Nausea is the most difficult symptom to assess due to its subjective nature[12].Vomiting is the forceful expulsion of the contents of the stomach through the mouth and sometimes through the nose. Vomiting is mediated by vomiting centre in brain which comprises of three main components (the area postrema, the nucleus tractus solitaries, and the dorsal vagal complex) that integrate the emetic responses.Various scales like CTCAE (Common Terminology Criteria for Adverse Events) are often used (Table 2) so that patients can indicate their level of distress and the nausea and vomiting can be graded [13, 14].

Table 2: Grading of CINVas per CTCAE guidelines

Grade	Nausea
0	None
1	Able to eat
2	Oral intake decreased
3	No significant intake
	Vomiting
0	None
1	1 episode in 24 hours
2	2-5 episodes in 24 hours
3	≥ 6 episodes in 24 hours
4	Require hospitalization

Although multiple neurotransmitters are involved in emetic pathways, dopamine, 5-HT3, substance P, and their corresponding receptors play a key role in the onset of CINV. Receptors for these transmitters are found in high numbers in the dorsal vagal complex, area postrema, and gastrointestinal tract. Chemotherapy damages the gastrointestinal tract and activates abdominal vagal afferents. Under drug stimulus, the enterochromaffin cells of the gastrointestinal mucosa release 5-HT3, which binds to its receptor on the vagal afferent neurons. The binding between 5-HT3 and its receptor stimulates two specific areas in the central nervous system both located in the medulla: the chemoreceptor trigger zone (CTZ) and the vomiting center (VC). The CTZ is activated via blood or cerebrospinal fluid and initiates the release of various neurotransmitters, which stimulate the VC. Once activated, the VC modulates the efferent transmission to the respiratory, vasomotor, and salivary centers as well as to the abdominal muscles, diaphragm, and esophagus, resulting in emesis. Chemotherapy may also induce vomiting through the direct interaction of the drug with the area postrema also [15].

ANTIEMETIC AGENTS

Nausea and vomiting forced up to 20% of patients to postpone or refuse their chemotherapy treatment. The goal of each antiemetic therapy is to abolish nausea and vomiting. Prior to the introduction of ondansetron (FDA approved in 1991), nausea and vomiting were common adverse events of certain types of chemotherapy. Various researches over the past years have led to steady improvements in the control of chemotherapy induced nausea and vomiting. The development of the 5-HT3-receptor antagonists (5HT3RAs) was one of the most significant advances in the chemotherapy of cancer patients. Another group of antiemetics, the NK1-receptor antagonists (NK1RAs), have recently been developed, and the first drug in this class, aprepitant (FDA approval in 2003) was incorporated into the antiemetic guidelines of CINV [16].

A wide variety of antiemetic agents are available for the management of CINV. The key to effective control of nausea and vomiting is to prevent it before it occurs, whenever possible. Hence these medications are always administered prior to chemotherapy. Antiemetic drugs may be used alone or in combination. Agents used for controlling nausea and vomiting include 5-HT3 receptor antagonists, NK1 receptor antagonists, corticosteroids, dopamine receptor antagonists, benzodiazepines and cannabinoids[3] .

5- HT3 RECEPTOR ANTAGONISTS

The 5-HT3 RAs are the class of agents that act as selective receptor antagonists, at the 5-HT3 receptor, blocking serotonin both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone. These drugs have been the most widely used antiemetics for the management of CINV for many years. Mainly five 5-HT3 RAs are currently available.

Eg:- (a) First generation - ondansetron, dolasetron, granisetron tropisetron.
(b) Second generation- palonosetron

The first generation agents are the most commonly used ones in the chemotherapy induced nausea and vomiting. They are especially effective in controlling the acute emesis, occurring in the first 24 hours following chemotherapy. They are given 30 minutes before highly or moderately emetogenic chemotherapy and continued for a few days to prevent further CINV. The most common side effects are headache and constipation. Palonosetron has a prolonged half-life of about 40 hours and greater binding affinity for the 5-HT3 receptor than the first generation agents and hence a more effective antiemetic action[17].It is usually given in doses of 0.25 mg thirty minutes prior to chemotherapy. It is mainly indicated in prevention of acute emesis caused by highly emetogenic agents as well as acute and delayed emesis caused by moderately emetogenic agents. Headache, dizziness and constipation are the most commonly reported adverse effects [18].

For chemotherapy, these drugs should be used only on a scheduled basis and not on “as needed” basis, since the use of this drug is only in the prevention of nausea and vomiting and not in the rescue of CINV. The FDA has notified healthcare professionals that ondansetron hydrochloride (Zofran®) 32 mg single premixed IV doses in sodium chloride or dextrose will no longer be marketed because of the potential for QT prolongation, which can lead to torsade de pointes, a potentially fatal abnormal heart rhythm. The currently approved dose is 0.15mg/kg every 4 hours for 3 doses. No single dose administration should exceed 16 mg[19].

NEUROKININ 1 (NK1) RECEPTOR ANTAGONISTS

NK1 receptors are located in the gastrointestinal tract and in the brain stem. These receptors act as the binding sites for substance P [20].Aprepitant is the first member of this class which is the most

commonly used drug of all the NK1 receptor antagonists. It exerts its antiemetic action through the inhibition of substance P in the emetic pathways in both the central and peripheral nervous systems.[3,8]It augments antiemetic activity of 5-HT3RAs and corticosteroids to inhibit both acute and delayed phases of CINV, when given in combinations. Aprepitant (Apretero®) is available commercially as capsules of 80 mg and 125 mg. The recommended dose of aprepitant is 125 mg 30 minutes prior to chemotherapy on day 1, followed by 80 mg once daily on day 2 & day 3 in combination with a 5-HT3RA on day 1 & dexamethasone on days 1-4 for highly emetogenic chemotherapy (HEC) but for moderately emetogenic chemotherapy (MEC) 125 mg of the drug is given only on day 1 in combination with 5-HT3RA and dexamethasone. The main reported side effects of aprepitant are constipation, fatigue and diarrhoea[21].

Fosaprepitantdimeglumine (Emend®) approved in 2008 by FDA, a prodrug of aprepitant, was developed to provide a parenteral alternative to the orally administered aprepitant. Fosaprepitant is rapidly converted to aprepitant via the action of ubiquitous phosphatases [8, 17].The antiemetic properties of fosaprepitant are attributable to aprepitant, which is a selective neurokinin 1(NK1) receptor antagonist with low affinity for NK2 and NK3 receptors . It penetrates the brain and occupies central NK1 receptors for a sufficient duration to inhibit both acute and delayed phases of CINV. This could be administrated on day 1 (150 mg) with other antiemetics 30 minutes beforeintravenous chemotherapy and then on days 2 and 3 the treatment is continued with oral aprepitant as above. Fosaprepitant is useful in conditions like patients with severemucositis or dysphagia or gastrointestinaldisturbance that would make oral therapy problematic [22].

CORTICOSTEROIDS

Corticosteroids can be used in cancer patients to control chemotherapy induced nausea and vomiting. Dexamethasone is the most commonly used corticosteroid and is an integral component of almost all antiemetic regimens used in the prevention of acute and delayed CINV.It is commonly administered in combination with 5-HT3 receptor antagonists. It acts on intestinal mucosa thereby decreases inflammation, blocking 5-HT3 release, and by decreasing the permeability of blood-brain barrier. All the antiemetic guidelines recommend the use of dexamethasone for the acute emesis. For delayed emesis, dexamethasone is recommended in combinationwith aprepitant for highly emetogenic chemotherapy. It is administered orally, I.M or I.V in the dose range of 8 mg to 40 mg (pediatric dose: 0.25–0.5 mg/kg). Insomnia, indigestion and hyperglycemia are the most common side effects with short term use [10].

DOPAMINE RECEPTOR ANTAGONISTS

Dopamine receptor antagonists were widely used as antiemetic agents before the introduction of 5-HT3 receptor antagonists. This includes metoclopramide, domperidone, haloperidol, chlorpromazine, and prochlorperazine. Among these drugs metoclopramide is the prototype agent. Even though metoclopramide was proven to be effective when combined with steroids in the prevention of delayed CINV, it is not much in use now because of its low therapeutic index and its use is generally reserved for agents with low emetogenic potential or in patients intolerant or refractory to the first line antiemetics.[23] It produces antiemetic effect by blocking dopamine receptors and also serotonin receptors in chemoreceptor trigger zone of the CNS. Metoclopramide is given as 1-2 mg/kg 30 minutes before chemotherapy as an IV dose and the dosage should be repeated every 2 hours for 2 doses and every 3 hours for 3 doses. Side-effects include acute dystonic reactions, akathesia, and sedation. Domperidone does not cause dystonia as it does not cross the blood brain barrier. Haloperidol is rarely used in children for CINV because of the risk of arrhythmias. [8]

BENZODIAZEPINES

Benzodiazepines such as lorazepam, midazolam, and alprazolam have become recognized as valuable adjuncts in the prevention and treatment of anxiety and the symptoms of anticipatory nausea and vomiting (ANV) associated with chemotherapy, especially with the highly emetogenic regimens. [3] Benzodiazepines have not demonstrated intrinsic antiemetic activity as single agents. Therefore, their place in antiemetic prophylaxis and treatment is adjunctive to other antiemetic agents. They act on higher CNS structures, the brainstem, and spinal cord and exert its action. Lorazepam produces antiemetic effect at doses of 0.5-2 mg every 4-6 hours as needed either orally/ I.V. The major side effects reported are confusion, visual disturbances and sedation. Alprazolam has been shown to be effective when given in combination with metoclopramide and methylprednisolone.[24]

CANNABINOIDS

Cannabinoids are active against the neurotransmitter systems involved in nausea and vomiting reflexes. Two oral formulations, Dronabinol and Nabilone were approved by the US Food and Drug Administration in 1985 for use in CINV. CB1 type cannabinoid receptors are present throughout the central nervous system, and CB2 receptors are localized in the periphery, primarily on immunocytes and mast cells and also present on brainstem neurons. Through either of the above receptors, cannabinoids directly and indirectly affect the neurotransmitters like serotonin, neurokinin and dopamine which play a critical role in mediating CINV. In the gastrointestinal tract, cannabinoids act on enterochromaffin cells thus diminishing the vagal excitation by the serotonin release. Cannabinoids have overlapping modulatory activity with NK1 inhibitors, and dopamine receptor antagonists in the brain stem. [25]

Dronabinol and Nabilone are both well absorbed orally but they differ with regard to their formulation and pharmacokinetics. Dronabinol is formulated with sesame seed oil and hence contraindicated in patients with hypersensitivity to sesame seed oil whereasnabilone is a synthetic cannabinoid. Both dronabinol and nabilone are available as capsules for oral administration. For CINV dorabinol is usually taken orally in a dose of 5 mg/m2 1 to 3 hours before chemotherapy and then 5 mg/m2/dose every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day. Dose may be increased up to a maximum of 15 mg/m2/dose if needed.Treatment with nabilone should begin orally at doses of 1-2 mg twice daily (maximum of 6 mg divided in 3 doses daily). It can be administered 2 or 3 times per day during the entire chemotherapy course and can be continued up to 48 hours after the last chemotherapy dose. A dose of 1-2 mg in the night before chemotherapy may also be beneficial.[26, 27]Adverse effects like dysphoria, drowsiness, dizziness, and dry mouth have slowed the adoption of cannabinoids into clinical practice.[28, 29, 23]

GUIDELINES FOR TREATMENT OF CINV

A number of guidelines are available for the management of chemotherapy induced nausea and vomiting. NCCN (National Comprehensive Cancer Network) guidelines, ASCO (American Society of Clinical Oncology) guidelines and MASCC (Multinational Association of Supportive Care in Cancer) guidelines are the major important standard references in the treatment of CINV.[30,31]

MASCC guidelines are based on the Perugia Consensus Conference on Antiemetic Therapy June 2009 and later updated in April 2011 and January 2013. ASCO guidelines were published in 1999 and later updated in 2006 and 2011 respectively. National Comprehensive Cancer Network updated antiemetic guidelines were published by the NCCN in 2007.The updates were based on the 2004 Perugia International Antiemetic Consensus Conference of the Multinational Association of Supportive Care in Cancer. All the guidelines recommend a dosing schedule for the safe and effective management of nausea and vomiting induced by chemotherapy.[32]

Table 3: Drug combinations recommended for CINV as per ASCO, MASCC and NCCN guidelines

Groups	ASCO	MASCC	NCCN
HIGH RISK			
Acute	5-HT_3RA + Dexamethasone + Aprepitant /Fosaprepitant	5-HT_3RA + Dexamethasone + Aprepitant /Fosaprepitant	5-HT_3RA + Dexamethasone + Aprepitant / Fosaprepitant ± Lorazepam
	Dexamethasone +		Dexamethasone + Aprepitant ± Lorazepam
Delayed	Aprepitant	Dexamethasone + Aprepitant (Dexamethasone only if Fosaprepitant used on day 1)	
MODERATE RISK			
Acute	Palonosetron +Dexamethasone	*1.Anthracycline/ Cyclophosphamide* 5-HT_3RA +Dexamethasone + Aprepitant/Fosaprepitant *2. Other than Anthracycline/ Cyclophosphamide* Palonosetron+Dexamethasone	5-HT_3RA + Dexamethasone ± Aprepitant / Fosaprepitant ± Lorazepam
Delayed	Dexamethasone	*1.Anthracycline/ Cyclophosphamide* Aprepitant/ None (if Fosaprepitant used on day 1) *2. Other than Anthracycline/ Cyclophosphamide* No routine prophylaxis	5-HT_3RA/Dexamethasone / Aprepitant / Fosaprepitant (if used on day 1) ± Dexamethasone ± Lorazepam
LOW RISK			
Acute	Dexamethasone	Dexamethasone/ 5-HT_3RA /Dopamine receptor antagonist	Dexamethasone /Prochlorperazine / Metoclopramide
Delayed	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis
MINIMAL RISK			
Acute	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis
Delayed	No routine prophylaxis	No routine prophylaxis	No routine prophylaxis

Table 4: Dosages of antiemetic agents as per NCCN, MASCC and ASCO guidelines

Drugs	Route	NCCN	MASCC	ASCO
5-HT_3RAs				
Dolasetron	I.V	-	-	-
	PO	100 mg	100 mg	100 mg
Granisetron	I.V	0.01 mg/kg	1 mg or 0.01 mg/kg	0.01 mg/kg or 1 mg
	PO	1 mg or 2 mg (days 2-3) 8 -24 mg	1 mg or 2 mg	2 mg
Ondansetron	I.V	16-24 mg(days2-3)	8 mg or 0.15 mg/kg	8 mg or 0.15mg/kg
	PO	0.25 mg	16 mg	8 mg
Palonosetron	I.V	-	0.25 mg	0.25 mg
	PO	Not included	0.50 mg	0.50 mg
Ramosetron	I.V	Not included	Not included	0.3 mg
	PO	Not included	Not included	-
Tropisetron	I.V	Not included	5 mg	5 mg
	PO		5 mg	5 mg
NK_1 RAs				
Aprepitant	I.V	125 mg (day 1)	125 mg (day 1)	125 mg (day 1)
	PO	80 mg (days 2-3)	80 mg (days 2-3)	80 mg (days 2-3)
Fosaprepitant	I.V	150 mg (day 1)	150 mg (day 1)	150 mg (day 1)
CORTICOSTEROID				
Dexamethasone	I.V	12 mg (day 1)	20 mg / 12 mg once daily 8 mg bid (days 3-4)	12 mg (day 1) 8 mg (day 2-4)
	PO	8 mg (days 2-4)	8 mg once daily	
*OTHER AGENTS**				
Lorazepam	I.V/PO	0.5 – 2 mg (days 1-4) every 4 hours	Not included	Not included
Metoclopramide	I.V/PO	10-40 mg (day 1)	Not included	Not included
Olanzapine	PO	2.5-5 mg bid (3-7 days)	Not included	Not included
Prochloperazine	PO	10 mg PO/IV	Not included	Not included

* **NCCN guidelines recommend that these can be used for breakthrough nausea and vomiting**

COMPARISON OF ANTIEMETIC GUIDELINES

MASCC, NCCN and ASCO guidelines are the three guidelines which are commonly used for management of CINV and can be summarized as follows. The various guidelines suggest somewhat similar regimens with minor variations for highly emetogenic, moderately emetogenic, minimally emetogenic and low emetogenic agents.

FOR HIGHLY EMETOGENIC CHEMOTHERAPY

ACUTE CINV & DELAYED CINV

All three guidelines suggest a combination of 5-HT3RA, dexamethasone and aprepitant/ fosaprepitant within the first 24 hours for acute CINV with highly emetogenic chemotherapy. But a combination of dexamethasone and aprepitant are suggested for delayed CINV with highly emetogenic chemotherapy in all the three guidelines. NCCN guidelines also recommend the use of lorazepam in combination with dexamethasone and aprepitant for the treatment of delayed emesis caused by highly emetogenic chemotherapy.

MODERATELY EMETOGENIC CHEMOTHERAPY

ACUTE CINV & DELAYED CINV

For acute CINV the ASCO and MASCC guidelines recommend the triple combination of a 5-HT3RA, dexamethasone and aprepitant, for patients receiving the combination of anthracycline and cyclophosphamide based regimens whereas the NCCN guidelines suggest the use of aprepitant in selected patients receiving other chemotherapies of moderately emetogenic risk like carboplatin, epirubicin, ifosfamide and irinotecan.

For delayed CINV, dexamethasone is the preffered agent for moderately emetogenic agents. As per MASCC & ASCO guidelines if aprepitant is used for prevention of acute CINV then it should also be used for the prophylaxis of delayed CINV. The NCCN guidelines suggest aprepitant with or without dexamethasone for this. A 5-HT3RA can be used as an alternative.

LOW EMETOGENIC CHEMOTHERAPY

Both MASCC and ASCO guidelines recommend the use of a steroid alone in the first 24 hours and no prophylaxis beyond 24 hours for acute CINV with low emetogenic chemotherapy. As per the recommendations of NCCN guidelines prochlorperazine or metoclopramide can be used as alternative drugs to dexamethasone.

MINIMALLY EMETOGENIC CHEMOTHERAPY

For patients treated with minimal emetogenic risk, no routine prophylaxis is suggested by all the three guidelines.

ASCO guidelines suggest the use of ramosetron for CINV whereas this agent is not included in NCCN and MASCC guidelines.NCCN guidelines recommend that various agents like olanzapine, lorazepam, metoclopramide and prochlorperazine in the treatment of break through nausea and vomiting caused by chemotherapy .

RECENT ADVANCES IN ANTIEMETIC THERAPY

During the last two decades there have been considerable achievements regarding the management of chemotherapy induced nausea and vomiting. Due to the influence of these adverse effects in the overall quality of life of the cancer patients various researches that focus on CINV continues. Recent developments including the use of second generation serotonin receptor antagonists like palonosetron, neurokinin receptor antagonists like aprepitant, fosaprepitantetc has controlled CINV to a great extent. However no drugs can so far achieve a complete control of CINV. Hence there are many ongoing trials on various agents.

Olanzapine, an atypical antipsychotic agent works by blocking multiple neurotransmitters; serotonin at 5 HT2a, 5 HT2C, 5 HT3 and 5 HT6 receptors, dopamine at D1, D2, D3 and D4 receptors, catecholamine at alpha1 receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors. Due to this multiple blocking effect, particularly at D2 and 5 HT3 receptors, this drug has got potential to be used as an antiemetic agent and may be useful as an adjuvant to chemotherapy. Tan et.al. [33] reported that the drug can be used in combination with ondansetron and dexamethasone for prevention of chemotherapy induced nausea and vomiting in cancer patients receiving highly and moderately emetogenic chemotherapeutic drugs safely and effectively. As per the results of various studies olanzapine is included in the MASCC and NCCN guidelines for the treatment of refractory and breakthrough emesis. [34, 13] It is usually given orally 10 mg once daily for 3-5 days beginning on day 1 of chemotherapy or 5 mg once daily for 2 days before chemotherapy followed by 10 mg once daily (beginning on the day of chemotherapy) for 3-8 days.

Olanzapine can cause hyperglycemia and hence should be used with caution in diabetic patients. But this does not seem to be a problem in case of CINV as it is a short term therapy. Even though there are no specific recommendations, close monitoring is necessary when olanzapine is given in patients with hepatic impairment. This drug can also cause anticholinergic effects like constipation, blurred vision, urinary retention etc and hence should be used with caution in patients with decreased gastrointestinal motility, paralytic ileus, urinary retention and visual problems. Fasting lipid profile, fasting blood glucose, periodic assessment of hepatic transaminases (in patients with hepatic disease), waist circumference, orthostatic blood pressure, mental status, extrapyramidal symptoms (EPS) etc. should be monitored.[33]

CONCLUSION

Nausea and vomiting associated with cancer chemotherapy can result in significant morbidity, adversely affect a patient's quality of life, and lead to poor compliance with the treatment regimen. Updated guidelines from ASCO and NCCN recommend that all patients receiving chemotherapy should be treated preferentially with antiemetic regimens containing agents like 5-HT3 receptor antagonists, corticosteroids, and NK1 receptor antagonists. These agents should be used in accordance with the recommended doses both before and after chemotherapy. [19] Despite all these facts, uncontrolled vomiting and inadequately controlled nausea are the major problems in many patients receiving chemotherapy. [16] However future trials should focus on the complete prevention of CINV.

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