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Nausea and Vomiting in Cancer Patients: Topic Review

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Abstract

Nausea and vomiting are known side effects for cancer therapy. The prevalence is around 40-80%. The level of emetoginicity varies based on different factors. The potential receptors involved in emesis pathway are dopamine receptors, 5-hydroxytryptamine type 3 receptors and neurokinin receptors. The main guidelines for prevention of nausea and vomiting are ASCO, NCCN, MASCC/ESMO. These guidelines recommend three antiemetic drugs for highly emetic chemotherapy and two antiemetic drugs for moderately emetic chemotherapy. While for low risk regimens single antiemetic might be used and for minimal risk regimens antiemetic is not routinely recommended. Non pharmacological therapy might be considered as well. There are different tools for assessment of nausea and vomiting such as EORTC-QLQ-C30 and FACT-G. The Multinational Association of Supportive Care in Cancer (MASCC) tool individually address both acute and delayed nausea and vomiting, available in different languages and has iPhone/iPad application. Proper prevention of this side effect is highly recommended to improve patient quality of life, to avoid further complications as dehydration, electrolyte imbalance and to ensure continuation of treatment plan.

Keywords: Nausea; Vomiting; Chemotherapy; Cancer; Anti-emetic; Radiotherapy; Drugs

Introduction

Nausea and vomiting (N&V) are common side effects cancer patients might suffer from. Despite the new anti-emetic agents available in the market, the incidence of N&V varies between 40-80%. This side effect induced by chemotherapy, radiotherapy and some medications as opioids. N&V prevention is still underestimated. Chemotherapy induced nausea and vomiting are classified as acute and delayed. Acute N&V occur within 24 hours after chemotherapy and delayed N&V occur 24 hours after treatment. Guidelines for prevention of N&V have been developed by National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and the Multinational Association for Supportive Care in Cancer (MASCC)/ European Society of Medical Oncology (ESMO). These guidelines are classified according to the risk of emesis into high emetic risk, moderate, low and minimal risk. Drugs from different pharmacological classes are recommended for prevention of N&V such as 5-hydroxytryptamine antagonist, steroid, Neurokinin 1 antagonist and dopamine receptor antagonist. Combination or single drug regimen might be used based on the level of emetogenicity. The prevention key factor is the proper control of N&V since the first course of chemotherapy to avoid exposing patients to unpleasant experience. Untreated nausea and vomiting might adversely affect the plan of chemotherapy continuation and patients' quality of life.

Emetogenic Pathway

The potential related receptors have been identified at the Chemoreceptor Trigger Zone (CTZ) such as dopamine receptors, several serotonin receptors (5-hydroxytryptamine type 3 (5HT3) has the most interest) and neurokinin receptors type 1 (NK1). Other important receptors involved are histamine, muscarinic acetylcholine (AChM), endorphins, gamma-aminobutyric acid and cannabinoids [1-3].

Nausea and Vomiting Assessment Tools

There are different tools available such as EORTC-QLQ-C30 and FACT-G [3]. The Multinational Association of Supportive Care in Cancer (MASCC) antiemesis tool (MAT) is a very useful and accessible tool that individually addressed both acute and delayed N&V. It is available in eleven languages, has iPhone/iPad application for cancer patients receiving chemotherapy [4].

Etiology of N&V

Classification of N&V in cancer is etiology based and might be induced by one of the following [5,6].

Cancer treatment

I-Chemotherapy: Nausea and vomiting induced by chemotherapy are common side effects of cancer treatment despite the advanced anti-emetic drugs available in the markets. Nausea is still considered by cancer patients as the most feared chemotherapy side effect [7,8]. The incidence and severity of emesis depend on many variables. Chemotherapy related factors as the particular drug used, its level of emetogenicity, dose, schedule, route of administration, and the prescribed chemotherapy regimen, single agent versus combination. Patient related factors as age, gender and prior experience during pervious chemotherapy courses. Younger age and female gender are at higher risk to have N&V. On the other hand chemotherapeutic drugs level of emetogenicity is classified based on risk of emesis. The classification schema divided into four categories: highly emetic, moderately emetic, low emetogenicity and minimally emetic. Table 1 represents the classification schema for intravenous anticancer agents

and Table 2 represents the classification schema for oral anticancer agents [9-12]. In case of combination regimen level of emetogenicity is determined by identifying the emetic level of the most emetic agent in addition to the relative contribution of other agents. A combination of cyclophosphamide and anthracycline regimen has been reclassified as highly emetic in the updated antiemetic ASCO guidelines [12,13].

Emetic risk	Chemotherapeutic Agent		
High risk > 90%	Carmustine Cisplatin Cyclophosphamide ≥ 1.5g/m2	Dactinomycin Mechlorethamine Streptozotocin	Dacarbazine
Moderate risk > 30% - 90%	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine	Cyclophosphamide < 1500mg/m2 Cytarabine > 1gm/m2 Daunorubicin Doxorubicin Epirubicin,	Idarubicin Ifosfamide Irinotecan Ooxaliplatin
Low risk 10% - 30%	Bortezomib Catumaxumab Cetuximab Cytarabine ≤ 1gm/m2 Docetaxel Doxorubicin liposomal Etoposide	5-fluorouracil Gemcitabine Ixabepilone Methotrexate Mitomycin Mitoxantrone Paclitaxel	Panitumumab Pemetrexed Trastuzumab Temsirolimus Topotecan
Minimal risk < 10%	Asparaginase Bevacizumab Bleomycin Busulfan	2-Chlorodeoxyadenosine Fludarabine Rituximab	Vinblastine Vincristine Vinorelbine

Table 1: Classification of intravenous anticancer agents level of emesis.

Level of emesis (%)	Chemotherapeutic Agents	
> 90%	Hexamethylmelanine	Procarbazine
> 30% to 90%	Cyclophosphamide	Melphalan >50 mg/m2 Vinorelbine
	Imatinib	Temozolomide
	Lomustine	
10-30%	Capecitabine	Lapatinib
	Etoposide	Lenalidomide
	Everolimus	Sunitinib
	Fludarabine	Thalidomide
<10%	Chlorambucil	Mercaptopurine
	Erlotinib	Methotrexate
	Gefitinib	Sorafenib
	Hydroxyurea	6-Thioguanine

Table 2: Classification of oral chemotherapeutic agents level of emesis.

Nausea and vomiting induced by chemotherapy classified by National Cancer Institute's Common Terminology Criteria for Adverse Events into acute, delayed and anticipatory [14]. Acute emesis occurs during the first 24-hours after the administration of chemotherapy. Delayed N&V occurs more than 24 hours after chemotherapy administration. Anticipatory N&V occurs prior to the administration of a new chemotherapy cycle due to previous experience.

II-Radiotherapy

Radiotherapy (RT) induced nausea and vomiting might occur 1-2 hours after treatment [15]. The incidence and severity depend on several factors. Treatment related factors are site and volume of radiation, single and total dose and fractionation schedule. Patient related factors are gender, age, concurrent or recent chemotherapy AND prior history of N&V. Risk of emesis has been classified by ASCO & MASCC/ESMO into four categories presented in Table 3.

High - >90%	Total body irradiation (TBI)
Moderate - 60-90%	Upper abdominal irradiation
	Hemi – body irradiation (HBI)
	Upper body irradiation (UBI)
Low - 30-60%	Cranium (all)
	Craniospinal
	Head and neck
	Lower thorax region
	Pelvis
Minimal - <30%	Other sites, including breast and extremities

Table 3: Classification of radiotherapy risk of emesis.

Nausea and Vomiting Induced by the Tumor

Brain tumor: it is the result of increased intracranial pressure.

Malignant bowel obstruction as in colorectal, ovarian and peritoneal cancer: vomiting is an early symptom in high obstruction

Metabolic: hypercalcemia, polyuria, and nocturia. Blood biochemistry will confirm the diagnosis.

Nausea and Vomiting Induced by Drugs

In addition to chemotherapeutic drugs there is non-chemotherapy medications might contribute to the development of N&V in cancer patients. During the differential diagnosis we have to exclude these factors to point the correct etiology. A careful medication history including over the counter drugs is essential. The most important medications we have to consider are narcotics, non-steroidal anti-inflammatory drugs and antibiotics/antivirals as erythromycin, tetracycline, sulfonamides, antituberculous drugs and acyclovir. Patients started on opioids initially experience N&V then tolerance to these effects tends to occur within days to weeks. Other medications might contribute to N&V are cardiovascular drugs (digoxin, antiarrhythmics, antihypertensives, beta blockers and calcium channel antagonists), diuretics, hormonal preparations (oral antidiabetics, oral

contraceptives), gastrointestinal medications (sulfasalazine, azathioprine), nicotine, central nervous system (CNS) active drugs (antiparkinsonian drugs, anticonvulsants) and antiasthmatics (theophylline). The mechanism contributes to stimulation of the chemoreceptors in the trigger zone [16,17].

Psychological Nausea and Vomiting

This type of nausea and vomiting is induced by anxiety. It is suggested by the signs and symptoms of stress, e.g. anticipatory N&V that might occur due to previous experience with N&V during prior cancer therapy.

Prevention of N&V

There are three major international anti-emetic guidelines available for prevention of nausea and vomiting. These guidelines are National Comprehensive Cancer Network (NCCN) [18], the American Society of Clinical Oncology (ASCO) [19], and the Multinational Association for Supportive Care in Cancer (MASCC)/ European Society of Medical Oncology (ESMO) Guidelines [20]. Table 4 summarizes the international recommendations for prevention of N&V induced by intravenous chemotherapy.

Emesis risk	Drug group	Drug name	Pre-chemotherapy	After chemotherapy	Comments
High	**Neurokinin 1 antagonist containing regimen**				
	5HT3 antagonist	Granisetron OR	PO: 2 mg daily OR 1 mg BID		Day 1
			IV: 0.01 mg/kg (max 1 mg)		Day 1
			TP1: 3.1 mg/24 h patch		Apply 24-48 h before chemotherapy, maximum duration of the patch is 7 days
		Ondansetron OR	PO: 16-24 mg daily		Day 1
			IV: 8-16 mg		
		Palonosetron OR	IV: 0.25 mg day 1 only		Day 1
		Dolasetron	PO: 100 mg		Day 1
	Steroid	Dexamethasone	PO or IV: 12 mg	PO or IV: 8 mg	Day 1-3 or 1-4 (if given with aprepitant)
			PO or IV: 12 mg	PO or IV: 8 mg	Day 1-3 or 1-4 (8 mg PO d2, then 8 mg BID d3-4 (if given with fosaprepitant 150 mg IV d1)
	Neurokinin 1 antagonist	Aprepitant OR	PO: 125 mg day 1	PO: 80 mg d 2-3	
		Fosaprepitant	IV: 150 mg	------	Day 1 only
Olanzapine containing regimen					
	Antipsychotic	Olanzapine	PO: 10 mg daily	PO: 10 mg daily	Day 1-4
	5HT3 antagonist	Palonosetrone	IV: 0.25 mg	-------	Day 1
	Steroid	Dexamethasone	IV: 20 mg	-------	Day 1

Table 4: Prevention of N&V induced by IV chemotherapy.

Table 5 summarizes the international recommendations for prevention of N&V related to oral chemotherapy, radiotherapy and anticipatory N&V general principles. Table 6 present comparisons between NCCN, ASCO, MASCC/ESMO guidelines [18-20].

N&V induced by oral chemotherapy				
Emesis risk	**Drug group**	**Drug name**	**Doses**	**Comments**
High to moderate	5-HT3 antagonist	Granisetron	PO: 2 m OR 1 mg BID	Daily
		Ondansetron	PO: 16-24 mg	

		Dolasetron	PO: 100 mg	
Low to minimal	5-HT3 antagonist	Granisetron	PO: 2 mg OR 1 mg BID	Daily as PRN
		Ondansetron	PO: 16-24 mg	
		Dolasetron	PO: 100 mg	
N&V induced by Radiotherapy				
Total body irradiation & upper abdomen / localized sites	5-HT3 antagonist	Granisetron	PO: 2 mg OR 1 mg BID	PO daily – start 24 h prior to radiotherapy In case of concomitant chemotherapy & RT refer to chemotherapy induced N&V
		Ondansetron	PO: 16-24 mg	
	Steroid	±dexamethasone	PO: 4 mg	
Anticipatory N&V	Benzodiazebine	Lorazepam	PO: 0.5-2 mg at night	Start the night before treatment
		Alprazolam	PO: 0.5-2 mg TID	

Table 5: Prevention of N&V induced by oral chemotherapy, radiotherapy and anticipatory N&V.

Emesis risk		Drug group	NCCN	ASCO	MASCC/ESMO
High	Option 1	Neurokinin 1 antagonist containing regimen	X	X	X
	Option 2	Olanzapine containing regimen	X	---	---
Moderate	Option 1	5HT3 antagonist (Palonosetron is preferred)	X	X	X
		+ Steroid	X	X	X
		± Neurokinin 1 antagonist *	X	X	X
	Option 2	Olanzapine containing regimen	X	---	--
Low	Option 1	5HT3 antagonist (Except palonosetron)	X	---	X
	Option 2	Steroid	X	X	X
	Option 3	Dopamine receptor antagonist	X	---	X
Minimal		Routine antimetic is not recommended	X	X	X
* Neurokinin1 antagonist recommended with AC regimen.					

Table 6: Comparison between guidelines recommendations (NCCN, ASCO, MASCC/ESMO).

Nausea and Vomiting Induced by Intravenous Chemotherapy

The antiemetic efficacy of 5HT3 antagonists is significantly improved when combined with dexamethasone. Loannidis JP and colleagues reported the benefit of addition of dexamethasone to prevent both acute and delayed emesis in a meta-analysis of 32 randomized controlled trials for patients receiving moderate or highly emetic chemotherapy. The addition of dexamethasone increased the chance of acute vomiting prevention by 25% and the risk ratio for emesis protection was 1.25 [21-25] (Table 4).

In the updated guidelines a new class Neurokinin 1 antagonist has been added to enhance the prevention of nausea and vomiting induced by chemotherapy with high emetic risk. Two different antiemetic regimens are recommended for prevention of acute and delayed emesis. Each regimen contains three drug combinations. The anthracycline and cyclophosphamide (AC) reclassified by ASCO as highly emetogenic regimen.

The first ant-emetic regimen contains 5HT3 receptor antagonist day 1 and dexamethasone day 1 through day 3 or through day 4 and neurokinin 1 (NK1) receptor antagonist day 1 through day 3 for aprepitant and day 1 only for fosaprepitant. Hesketh and colleagues compared the three drug regimen versus the standard therapy 5HT3 antagonists and dexamethasone in patients receiving high dose cisplatin, a multinational, randomized, double-blind, placebo-controlled trial. Addition of aprepitant provided superior protection versus the standard regimen in patients receiving highly emetogenic cisplatin based chemotherapy [26]. Comparing fosaprepitant versus aprepitant, Patrick L and colleagues study about the updated evidence showed that fosaprepitant is bioequivalent to aprepitant and might be

considered for patients unable to tolerate oral administration of antiemetics [27,28].

The second regimen contains olanzapine day 1 through day 4, palonosetron day 1 and dexamethasone day1. Olanzapine as antiemetic is more successful at preventing emesis than in preventing nausea, mainly delayed nausea. Navari RM and colleagues compared olanzapine versus aprepitant in addition to palonosetron and dexamethasone in each arm for the prevention of chemotherapy induced nausea and vomiting in patients receiving cisplatin or cyclophosphamide and doxorubicin. Results showed the effectiveness of olanzapine regimen at controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy and the similarity in the complete response rate in both groups [29].

To prevent N&V induced by moderately emetogenic intravenous antineoplastic agents (non cisplatin or AC chemotherapy), two drug combination of palonosetron day 1 only and dexamethsone day 1 through 3 is recommended. If palonosetron is not available first generation 5HT3 antagonists could be used. Limited evidence support adding aprepitant to the combination. Aapro MS and colleagues compared palonosetron versus ondansetron in combination with dexamethasone. Single dose palonosetron was effective as ondansetron in preventing acute CINV, its effectiveness was significantly increased over ondansetron in prevention of delayed CINV [30]. Lee Schwartzberg and colleagues pooled analysis of phase III clinical trials of palonosetron versus 5HT3 antagonists. Palonosetron is more effective than older 5HT3 antagonists for controlling delayed CINV [31,32]. Olanzapine containing regimen was recommended as an option in NCCN guidelines for prevention of moderate risk emesis [18].

For low emetic risk intravenous chemotherapy one agent 5HT3 antagonists or dexamethasone or dopamine receptor antagonist as metoclopramide might be used [18,20]. ASCO recommendation for prevention of low risk emesis was single dose of dexamethasone prior to chemotherapy [19]. In case of minimally emetogenic antineoplastic agents antiemetic should not be administered routinely before or after chemotherapy. Lorazepam and H2 blocker or proton pump inhibitor might be added to any of the regimens if needed [18-20].

Nausea and Vomiting Induced by Radiotherapy and Oral Chemotherapy

It is recommended to administer 5HT3 antagonist before each fraction with or without dexamethasone during fraction. In case of concurrent radiation and chemotherapy patients should receive antiemetic prophylaxis according to the emetogenicity of chemotherapy unless the emetic risk of radiotherapy is higher.For prevention of N&V induced by oral chemotherapy with high to moderate emetic risk start 5HT3 antagonists before chemotherapy and continue daily. In case of low to minimal emetic risk administer 5HT3 antagonists or metoclopramide or prochlorperazine or haloperidol as PRN [18-20,33] (Table 5).

Anti-emetic Drugs Pharmacology

5-HT3 receptor antagonists

First generation: Ondansetron, Granisetron, Dolasetron

Chemotherapy initiates the release of serotonin and activation of 5-HT3 receptors leading to emesis. The selective 5-HT3 receptor antagonists' have a high therapeutic index for prevention of CINV. The efficacy of 5HT3 antagonists are equal at the recommended doses and further dose escalation is not recommended. The oral route of administration is equally efficacious as the intravenous route even with highly emetogenic chemotherapy. A single dose prior to chemotherapy is therapeutically equivalent to a multiple dose schedule. They also share common side effects as constipation, headache and transient rises in liver transaminases [34-39].

Granisetron is available as IV and oral formulation. Recently a new formulation transdermal patches granisetron has been approved by FDA. Each patch contains 34.3 mg of granisetron, 3.3 mg of the drug will be released every day. This will maintain an average plasma concentration of 2.2 ng/ml over 6 days, similar to the level obtained after administering 2 mg of oral granisetron every day. Efficacy and tolerability of transdermal granisetron for the control of CINV associated with moderately and highly emetogenic multi-day chemotherapy have been evaluated in a randomized, double blind, phase III study. The results showed that granisetron transdermal is as effective as oral granisetron [40-42].

FDA issued a warning about QTc prolongation in patients treated with ondansetron. This side effect is a class effect and dose dependent specifically with IV dose of 32 mg, accordingly the revised label recommendation is to limit ondansetron initial IV dose to maximum of 16 mg and subsequent IV doses must not exceed 8 mg. ECG monitoring is recommended in patients with hypokalemia, hypomagnesemia, heart failure, bradyarrythmias, elderly and in patients having other drugs that increase the risk of QTc prolongation [43-45]. Dolasetron injection form is contraindicated as prophylaxis in CINV (FDA Drug Safety recommendation) due to the risk of QTc prolongation from increased drug exposure. The risk of abnormal heart rhythm development with oral dolasetron is less than the injection form but the potential risk is still there [46].

Second generation: Palonosetron

Palonosetron compared to first generation 5HT3 antagonists, it has higher affinity to 5HT3 receptors (30-100 fold), has significantly longer half life (40 hours). In trials of palonosetron it has been shown to be at least equivalent to the first generation 5HT3 receptor antagonists in preventing acute emesis and appears to be superior in preventing delayed emesis. In a meta-analysis Y. Jin and colleagues compared palonosetron with 5HT3 receptor antagonists in nine randomized controlled clinical trials. They investigated the outcome in a total of 3463 cases. The cumulative incidences of emesis were significantly reduced in the patients treated with palonosetron on the first day, from 2 to 5 days and the overall five days. Also palonosetronr has no reports about QTc prolongation. Palonosetron is preferred and recommended in the three guidelines for management of emesis for patients who receive moderately emetic chemotherapy [47-49].

Neurokinin-1 receptor antagonists (NK1): Aprepitant, Fosaprepitant are neurokinin-1 receptor antagonist that cross the blood brain barrier and block the emetic effects of substance P. Fosaprepitant is prodrug of aprepitant. It is effective as one-day treatment while aprepitant was approved as 3 days treatment. Both drugs are clinically effective to prevent both acute and delayed N&V induced by highly and moderately emetogenic chemotherapy. Grunberg S and colleagues compared a 3-day oral aprepitant schedule to a single dose of the intravenous fosaprepitant in three drug regimen. Results showed no inferiority between the two drugs either in acute or delayed phase of nausea and vomiting. The benefit / risk assessment of

Emand® IV (fosaprepitant) is similar to that of Emand® oral (aprepitant). NK1 receptor antagonists are considered as moderate inhibitors of the cytochrome P450 enzyme CYP3A4 which is essential in drug metabolism. Caution should be considered [50-53].

Dopamine receptors antagonists: Phenothiazines (as prochlorperazine), metoclopramide, butyrophenones. These agents have lower efficacy in management of moderately to highly emetogicity compared to 5HT3 receptors antagonists and glucocorticoids. Phenothiazines could be used to prevent N&V induced by low risk emetic chemotherapy, if glucocorticoid is contraindicated [54].

Benzodiazepines: Lorazepam

It is considered as valuable adjuncts to other antiemetic agents in the prevention of anticipated N&V due to stress but does not demonstrate intrinsic antiemetic activity as single agent [54].

Antipsychotic: Olanzapine

Olanzapine is an antipsychotic in the thienobenzodiazepine drug class. It blocks multiple neurotransmitters as dopamine 1,2,3,4 receptors, serotonin at 5HT3, 6, 2a, 2c receptors, catecholamines at alpha-1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors. Studies shown the effectiveness of olanzapine as antiemetic combined with 5HT3 receptor antagonists and glucocorticoid. It controls acute and delayed N&V in patients receiving moderately or highly emetogenic chemotherapy. Sedation is the only dose limiting toxicity for olanzapine [55-58].

Non Pharmacological Therapy

The cornerstone of non pharmacological therapy is to avoid any environmental triggers as crowded places, odors (e.g. food, perfume) and heat. Cold food is better tolerated than hot food because has less odor. Avoid fatty food, eat small and frequent meals. Apply behavioral approaches as relaxation and exercises.

Conclusion

Nausea and vomiting are still a common side effect fearing cancer patients and underestimated by oncologists. Prevention and management using structured approach is essential to avoid complications as dehydration, electrolyte imbalance. Proper prevention improve patient quality of life and ensure continuation of cancer treatment plan and patient adherence to medication.

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