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Chemotherapy-Induced Nausea and Vomiting

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Abstract

Chemotherapy-induced nausea and vomiting is a common adverse effect in cancer patients that not only impacts quality of life, but also treatment outcomes. The prevalence of nausea and vomiting is related to several factors, including the emetogenicity of the chemotherapy regimen, the dose and rate of administration of the chemotherapy agents, various environmental triggers and patient-related factors. The pathogenesis involves multiple organ systems, central nervous system, gastrointestinal tract and neurotransmitters. Clinical management should include a complete assessment of nausea and vomiting to investigate the possible etiology and the pharmacologic approach should involve agents that target each of these pathways and neurotransmitters. Various national guidelines provide recommendations for the prevention and management of CINV and combining these evidence-based strategies into clinical practice is crucial to improve morbidity and quality-of-life outcomes among cancer patients.

Keywords: nausea, vomiting, chemotherapy, radiotherapy, risk of emesis, management

1. Introduction

Nausea and vomiting (N/V) represents a primary issue in oncology requiring effective management for both prevention and treatment. Although in cancer patients several causes, such as opioid medications, can induce N/V, it is mainly related to antitumoral therapy. Chemotherapy-induced nausea and vomiting (CINV) is the most common and intolerable adverse event with negative impact on quality of life and treatment's adherence and efficacy. It is important to notice that large literature is available about N/V related to standard chemotherapy and little literature about new antitumoral therapies such as tyrosine kinase inhibitors, monoclonal antibodies and immunotherapeutic agents, instead. Management of N/V in cancer patients should begin with a complete assessment including evaluation of intensity and timing of appearance. To determine whether N/V is related to treatment (chemotherapy, radiation) or is independent of cancer treatment should be the second step. Various national and international antiemetic guidelines have been developed for the prevention of chemotherapy- and radiotherapy-induced nausea and emesis. The prevention of CINV is crucial to improve patients' confidence and compliance to treatments and the clinical management include both pharmacologic and nonpharmacologic therapies. This chapter addresses the epidemiology, clinical features, risk factors, mechanisms, and management of CINV.

2. Epidemiology

CINV involves about 60–80% of patients with cancer increasing the risk of patients' discomfort and chemotherapy's discontinuation [1]. The prevention of CINV is mainly important in reducing morbidity and total healthcare costs, as well as increasing the quality of care in patients receiving emetogenic chemotherapy. Patients experiencing CINV may refuse treatment, request or require dose reductions or seek alternative therapy options. Acute CINV may be prevented in 50% to 90% of patients using effective preventive strategies [2]. In a large European observational study, 1000 patients who had received guideline antiemetic treatment had significantly better CINV control than those who did not receive guideline treatment. The complete control rates were 60% versus 51%, respectively; however, the overall adherence to guidelines was just 29% [3].

Radiotherapy-induced nausea and vomiting (RINV) is one of the most common side effects during radiation, from which about 50% to 80% of the patients undergoing radiotherapy will suffer [4].

3. Clinical presentation

Cancer patients often experience N/V together but not necessarily. It is possible to experience nausea without emesis or emesis without nausea. The events of nausea and vomiting are generally protecting reflexes to rid intestine and stomach of toxic substances.

Nausea is described as a subjective and diffuse feeling of unease and discomfort often perceived as an urge to vomit. It can be considered a prodromal phase to the act of vomiting. It is characterized by sickness in the stomach, epigastrium and/or throat. Vomiting or emesis means the expulsion of stomach contents beyond the mouth and is accompanied by shivering and salivation.

The use of single agent cisplatin led to classify CINV into five types: acute, delayed, anticipatory, breakthrough and refractory according to the timing of appearance and in the absence of effective antiemetic prevention [5]. Acute CINV occurs within 24 hours of the chemotherapy administration, while delayed CINV occurs after 24 hours and could persist for 2–3 weeks after the administration of chemotherapy. Chemotherapeutic agents such as cisplatin, carboplatin, cyclophosphamide, anthracyclines are generally related to delayed CINV [6]. Anticipatory CINV involves patients who had already experienced N/V and occurs prior to the impending administration of chemotherapy triggered by the just thinking of it through a sensorial way (sight, smell). The incidence of anticipatory CINV has decreased in recent years because of the improved strategies for controlling acute and delayed emesis. Breakthrough CINV is vomiting and/or nausea that occurs within five days of chemotherapy administration after the use of guideline directed prophylactic antiemetic agents. This type of CINV usually requires immediate treatment or requires “rescue” with additional antiemetics. Refractory CINV is defined as vomiting and/or nausea occurring after chemotherapy in subsequent chemotherapy cycles after guideline directed prophylactic antiemetic agents have failed in earlier cycles (**Table 1**).

Patients with CINV should be assessed with a visual analog scale (0 to 10, with 0 no nausea and 10 maximum nausea). The frequency, severity, time of appearance and any associated activities (meals, drugs) should be requested. Recent treatment with chemotherapy and/or radiation therapy should then be noted with evaluation of single agent or combination of chemotherapy. The physical examination should include a complete assessment of the abdomen in order to identify a possible

Clinical presentation and physiopathology	
Acute CINV	Within 24 hours of initial administration of chemotherapy. Mainly by 5-HT3 release from the enterochromaffin cells
Delayed CINV	After 24 hours of initial administration of chemotherapy to 2–3 weeks. Mainly by substance P release, disruption of the blood–brain barrier and disruption of the gastrointestinal motility.
Anticipatory CINV	After a previous cycle of chemotherapy. Triggered by taste, smell, sight, thoughts of a previous CINV.
Breakthrough CINV	Within 5 days of initial administration of chemotherapy.
Refractory CINV	After chemotherapy despite prophylactic antiemetic agents

Table 1.
Clinical presentation and physiopathology of CINV.

organic cause of the emesis such as gastritis, bowel obstruction, an inflammatory process. A complete neurologic examination should also be performed to determine the search focal neurologic signs suggesting intracranial hypertension or meningeal carcinosis. Weight loss, appetite, anorexia, and/or cachexia should be evaluated to investigate the possible etiology of N/V and to help the differential diagnosis.

4. Risk factors

The occurrence of CINV can depend on several factors. The risk factors for CINV are both patient- and treatment-related. The most common patient-related risk factors are age, gender, previous motion sickness and/or pregnancy-related N/V and previous CINV. Patients younger than 50 years, females, patients with a history of previous motion sickness and/or pregnancy-related N/V have a greater

High-risk of emesis (>90%)	Moderate-risk of emesis (30–90%)	Low-risk of emesis (10–30%)	Minimal-risk of emesis (<10%)
Carmustine	Procarbazine	Bortezomib	Bevacizumab
Cisplatin	Carboplatin	Cetuximab	Bleomycin
Cyclophosphamide	Cyclophosphamide	Docetaxel	Busulfan
Dacarbazine	Cytosine arabinoside	Etoposide	Capecitabine
Mechlorethamine	Doxorubicin	5-fluorouracil	Chlorambucil
Streptozotocin	Epirubicin	Gemcitabine	Fludarabine
	Ifosfamide	Lapatinib	Vinblastine
	Irinotecan	Methotrexate	Vincristine
	Oxaliplatin	Mytomicin	Vinorelbine
	Melphalan	Mitoxantrone	
		Paclitaxel	
		Pemetrexed	
		Topotecan	
		Trastuzumab	

Table 2.
Classification of antitumoral therapy according to the risk of emesis.

risk of experiencing CINV. Instead, a previous history of high alcohol consumption is associated with a lower risk of CINV [7–9].

Treatment-related factors and emetogenicity of chemotherapeutic regimens are also relevant. Chemotherapeutic agents are related to various risk of emesis depending on mechanism of action, dose, route and administration in single or combined way. The intrinsic emetogenicity of chemotherapy is the crucial factor to guide the choose of antiemetic treatment. In 2004 an expert consensus conference proposed a classification of chemotherapeutic agents in four categories according to emetogenic potential: high, moderate, low and minimal risk [10]. In the high-risk category, more than 90% could experience CINV without an antiemetic prophylaxis. In the moderate-risk category the potential experience of CINV involves 30–90% of patients. In the low- and minimal risk less than 30% and 10% respectively of cancer patients experience CINV (**Table 2**) [11].

5. Physiopathology

The mechanisms of emesis are not well defined. The physiopathology of CINV includes both central nervous and peripheral system pathways and it is different in acute, delayed and anticipatory setting. The mechanisms inducing CINV have gradually been investigated over the past 60 years. In the 1950s the first hypothesis by Wang and Borison was the existence of a central site called ‘vomiting center’ located in the medulla processing all the afferent impulses to generate emesis [12]. The presence of some neuronal areas located within medulla coordinating the emetic reflex is now a more realistic hypothesis. All the neuronal cells involved in the series of events occurring during CINV have been called ‘central pattern generator’ [13]. Three primary components have been found out in the physiopathology of CINV: chemoreceptor trigger zone (CTZ), abdominal vagal afferents and neurotransmitters. After exposure to chemotherapy, the emetic reflex involves two primary sources of afferent input to neuronal areas: abdominal vagal afferents and area postrema, a structure located in the caudal end of the fourth ventricle [14, 15]. 5-hydroxytryptamine 3 (5-HT₃), neurokinin-1 (NK₁) and cholecystokinin-1 receptors located in the terminal ends of the vagal afferents are close to enteroendocrine cell into the gastrointestinal mucosa of the proximal small intestine. Chemotherapeutic agents stimulate enteroendocrine cells to release some mediators such as 5-hydroxytryptamine, substance P and cholecystokinin which bind to the specific receptors on the close vagal fibers. The afferent impulse reaches the dorsal brain stem through the nucleus of the solitary tract. Among the various receptors, 5-HT₃ are considered the most active in acute emesis. In summary, in acute CINV chemotherapeutic agents release free radicals stimulating enterochromaffin cells in the peripheral gastrointestinal tract with subsequent release of serotonin. Serotonin binds 5-HT₃ receptors through intestinal vagal afferent nerves and nucleus of the solitary tract and reaches the central nervous system. In delayed CINV the physiologic way is similar but involves less frequently 5-HT₃ and more frequently NK₁ receptors respectively. In delayed CINV chemotherapeutic agents induce the release of substance P from the neuronal cells in the central and peripheral nervous system. Substance P binds NK₁ receptors in the nucleus of solitary tract and led the afferent impulse to central nervous system.

The second pathway potentially involved in the emetic reflex include area postrema. In this region of the brain the blood–brain barrier is more permeable so it is accessible to afferent impulses in either blood or cerebrospinal fluid. This area has commonly been called ‘chemoreceptor trigger zone’. This region has afferent and efferent connections with underlying structures, the subnucleus gelatinosus and

nucleus of solitary tract, receiving vagal afferent fibers from the gastrointestinal mucosa. Metabolites and peptides released under the effect of chemotherapeutic agents can also induce emesis binding at this site.

The clinical role of neurotransmitters has been longer investigated in the past 30 years. The first interest was focused on dopamine, more recently on 5-HT and substance P. Dopaminergic antagonists are the first investigated antiemetic agents [16]. The 5-HT₃ receptor antagonists are currently the single most effective class of antiemetics for prevention and treatment of acute CINV. These receptors are located both in central sites such as area postrema and nucleus of solitary tract and in peripheral sites such as vagal afferents. The blockage of 5-HT₃ receptor is the most effective mechanism of antiemetic treatment. NK1 receptors are also located both in area postrema and nucleus of solitary tract and in the gastrointestinal mucosa. This evidence suggests that NK1 receptor antagonists plays a central role in prevention and treatment of CINV similar to 5-HT₃ receptor antagonists. Endocannabinoids have been more recently investigated as relevant neurotransmitters inducing N/V. The endogenous cannabinoids are agonistic antiemetic agents. Synthetic cannabinoids have been recently evaluated to treat refractory CINV.

Anticipatory CINV occurs as a response to a previous experience of CINV. A sensory feeling related to the first administration of chemotherapy led the patient to associate that feeling with N/V. Subsequent exposure to that feeling triggers the response of N/V. Anticipatory CINV can be effectively avoided with an adequate prevention of acute and delayed CINV [7, 17–19].

6. Management

Antiemetic guidelines are published by all the cancer organizations including American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO) and the Multinational Association of Supportive Care in Cancer (MASCC). There are some differences among the guidelines particularly in the choice of the preferred 5-HT₃ receptor antagonist and the use of cannabinoids. The general scheme for antiemetic protocols is similar for the various guidelines.

Prevention of CINV is the primary treatment to avoid subsequent episodes of CINV and anticipatory CINV. Due to physiopathology of CINV, 5-HT₃ and NK1 receptor antagonists are the main classes of drugs. Management include also both pharmacologic and nonpharmacologic agents such as steroids, dopamine antagonists, benzodiazepines, cannabinoids, antipsychotics. The primary issue is the prevention and treatment of moderately and highly emetogenic chemotherapy.

6.1 5-HT₃ antagonists

Selective 5-HT₃ receptor antagonists have revolutionized the management of CINV. They are indicated in preventing and treating N/V induced by chemotherapy with moderate and high emetic potential. The 5-HT₃ receptor antagonists include both first-generation drugs such as ondansetron (Zofran), dolasetron (Anzemet) and granisetron (Kytril) with half-life between 3–9 hours and second-generation drugs such as palonosetron (Aloxi) with half-life of approximately 40 hours. According to their half-life they are used in different indication with more use in acute CINV for first-generation drugs and delayed CINV for second-generation drugs. The first-generation antiemetic drugs are equivalent in efficacy [20–22] and they have few adverse events. The most common adverse events of 5-HT₃ receptor antagonist include headache, constipation, transient high levels of hepatic enzymes

and QT prolongation [23]. The oral and intravenous formulation are therapeutically equivalent [24]. The first-generation drugs are more active in acute CINV and appear little active and modest active in delayed N/V induced by cisplatin and moderately emetogenic chemotherapeutic agents, respectively. The second-generation 5-HT₃ receptor antagonist has a longer half-life and a greater binding affinity for the specific receptor. Three randomized prospective trials compared palonosetron with a first-generation antiemetic drug in patients receiving moderately and highly emetogenic chemotherapy. The noninferiority of palonosetron in term of complete response was demonstrated [25–27]. Some international guidelines consider palonosetron the preferred 5-HT₃ antagonist for moderate emetogenic chemotherapy regimens but there are no prospective trials demonstrating the superiority of palonosetron compared to first-generation agents.

6.2 NK1 antagonists

In the past 10 years, antiemetic treatment has greatly advanced with the availability of NK1 receptor antagonists. The NK1 receptor antagonists are the most recent class of antiemetic agents and include aprepitant (emend) fosaprepitant (ivemend), rolapitant (varuby) and netupitant (akynzeo). Aprepitant was the first approved agent in the class and is formulized as oral drug. In acute CINV the NK1 receptor antagonists are usually administered in combination with a 5-HT₃ receptor antagonists and dexamethasone. 3-days aprepitant can also be administered in delayed CINV [28]. Three randomized prospective trials compared the combination of ondansetron plus dexamethasone plus aprepitant versus ondansetron and dexamethasone in patients receiving highly emetogenic chemotherapy. Aprepitant was administered before chemotherapy and continued along with dexamethasone. The addition of aprepitant led to an approximate 50% reduction in the risk of emesis or need for rescue medications [29–31]. These evidences underline the crucial role of aprepitant in the management of CINV induced by highly emetogenic chemotherapy. A randomized prospective trial investigated the use of aprepitant in moderately emetogenic chemotherapy in almost a thousand of patients with breast cancer. A significantly higher rate of complete response in the aprepitant group was reported [32]. Fosaprepitant is an intravenous NK1 receptor antagonist. In is a water-soluble phosphoryl prodrug of aprepitant converted to aprepitant within 30 minutes after administration. A randomized double-blind study reported that a single dose of fosaprepitant after ondansetron and dexamethasone was noninferior to a standard aprepitant 3-days regimen in preventing CINV in more than 2 thousand patients receiving cisplatin [33]. This evidence suggests that a single dose of fosaprepitant enhances the antiemetic effects provided by conventional 5-HT₃ receptor agonists and corticosteroid therapy over conventional therapy alone and may provide a level of efficacy similar to that of the recommended 3-days aprepitant regimen. Rolapitant is a highly selective competitive long-acting NK-1 receptor antagonist demonstrating efficacy in randomized phase III trials. A single oral dose of rolapitant was effective in preventing delayed CINV compared with placebo, when each was used in combination with a 5-HT₃ receptor antagonist plus dexamethasone in patients receiving highly or moderately emetogenic chemotherapy [34]. Netupitant is formulated with palonosetron in a fixed-dose combination. Complete response rates during the acute and delayed CINV were significantly higher with single-dose netupitant plus palonosetron than with single-dose palonosetron in highly and moderately emetogenic chemotherapy in phase II and III trials [35].

The most common adverse events of NK1 receptor antagonists are fatigue, hiccups, dyspepsia and diarrhea. The use of aprepitant requires the evaluation of potential drug interaction due to its mechanism of action moderately inhibiting

cytochrome CYP3A4. In particular, aprepitant is related to an increase of plasma dexamethasone levels. Dexamethasone dose should be reduced when used in combination with aprepitant. Some antitumoral agents are also metabolized by CYP3A4 with the risk of increased toxicity when administered in combination with aprepitant. Aprepitant is also a weak inducer of the cytochrome CYP450. In patient receiving warfarin in combination with aprepitant the international normalized ratio (INR) decreases by 15% [36]. Rolapitant is well tolerated and its most common adverse events include neutropenia and dizziness. It inhibits CYP2D6 and it is metabolized by CYP3A4 so CYP3A4 inducers can reduce rolapitant blood levels and efficacy. The most common adverse events of netupitant include asthenia, dyspepsia, erythema and neutropenia. It is contraindicated in patients with severe renal and hepatic failure and it is an inhibitor of CYP3A4 as aprepitant [37–40].

6.3 Steroids

The antiemetic use of corticosteroids dates to the 1980s although the mechanism of efficacy is not yet clear. Dexamethasone is the most effective corticosteroid and it is widely used in combination with other antiemetic drugs both in acute and delayed CINV. In N/V induced by low emetogenic chemotherapy it could also be effectively used as single antiemetic agent (**Table 3**).

6.4 Other antiemetic treatments

A lot of agents including dopamine receptor antagonists, phenothiazines, cannabinoids, olanzapine are currently used to treat CINV induced by low emetogenic potential. Dopamine receptor antagonists such as metoclopramide and butyrophenones were most commonly used in past years and they could still be administered in combination with other antiemetic agents or in low-risk CINV. The efficacy of metoclopramide improves with increasing doses. Dopamine antagonists exhibit many adverse events and the most serious is represented by extrapyramidal symptoms. Dopamine antagonists may be considered when breakthrough CINV occurs. Currently breakthrough CINV is managed with an agent from a drug class that was not used in the prophylactic regimen. The phenothiazines are rarely administered in CINV and mainly in CINV induced by low emetogenic effect or as salvage therapy in breakthrough emesis. Antipsychotics such as olanzapine are sometimes prescribed in CINV not responding to conventional antiemetics. Olanzapine antagonizes several neurotransmitter receptors involved in the antiemetic reflex and it has been reported effective in preventing both acute and delayed CINV. No robust data comparing olanzapine with other antiemetic agents is available [41, 42]. In clinical practice olanzapine is often added to the standard three-drugs combination but it does not replace any of them. Olanzapine may be considered for the treatment of breakthrough and refractory CINV in addition to a change in the prophylactic antiemetic regimen. The most common adverse events of olanzapine include fatigue, sedation, headache, dry mouth, hyperglycemia, diarrhea.

In CINV with low and moderate emetic potential, synthetic cannabinoids have been recently evaluated. The two known cannabinoid receptors are CB1 and CB2. Blocking of CB1 and CB2 results in emesis. Cannabinoids act as an agonist on the CB1 receptors, resulting in their pharmacologic effect [43]. The use of these agents with a lower therapeutic index is not recommended as first-line treatment for prevention of CINV and should be reserved for patients refractory to or intolerant of standard antiemetics. Evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer who receive chemotherapy or radiation therapy.

Antiemetic agent	Dose	
	Acute CINV	Delayed CINV
Ondansetron	8 mg or 0.15 mg/kg day 1 (intravenous) 24 mg day 1 for high-risk (oral) 8 mg twice daily day 1 for moderate-risk (oral)	8 mg twice daily days 2–3 (oral)
Dolasetron	100 mg or 1.8 mg/kg day 1 (intravenous) 100 mg day 1 (oral)	100 mg days 2–3 (oral)
Granisetron	1 mg or 0.01 mg/kg day 1 (intravenous) 2 mg day 1 (oral)	1 mg twice daily days 2–3 (oral)
Palonosetron	0.25 mg day 1 (intravenous)	
Aprepitant	125 mg day 1 (oral)	80 mg days 2–3 (oral)
Fosaprepitant	115 mg day 1 (intravenous)	80 mg days 2–3 (oral)
Rolapitant		
Netupitant		
Dexamethasone	12 mg day 1 (intravenous) with aprepitant 12 mg day 1 (oral) with aprepitant	8 mg days 2–4 for high risk (oral) with aprepitant 8 mg days 2–3 for moderate-risk (oral) with aprepitant
	20 mg day 1 for high-risk (intravenous) without aprepitant 8 mg day 1 for moderate-risk (intravenous) without aprepitant 20 mg day 1 for high-risk (oral) without aprepitant 8 mg day 1 for moderate-risk (oral) without aprepitant	8 mg twice daily days 2–4 for high risk (oral) without aprepitant 8 mg days 2–3 for moderate-risk (oral) without aprepitant
Metoclopramide	1–2 mg/kg day 1 (intravenous)	1–2 mg/kg 2 hours after chemotherapy (intravenous) 0.5 mg/kg every 6 hours days 2–4 (oral)
Prochlorperazine	5–10 mg day 1 (intravenous) 5–10 mg day 1 (oral)	5–10 mg every 6 hours (oral)
Dronabinol	5 mg/mq (oral)	5 mg/mq every 2–4 hours (oral)
Nabilone	1–2 mg (oral)	1–2 mg twice daily (oral)
Olanzapine	5 mg for 2 days before chemotherapy (oral) 10 mg day 1 (oral)	10 mg days 2–4 (oral)

Table 3.
Management of CINV.

Two commercial forms of synthetic cannabinoids have been approved by Food and Drug Administration (FDA) with CINV indication: nabilone and dronabinol in 2005 and 2016, respectively. Studies with dronabinol and nabilone were performed in the 1970s and 1980s, before the approval of 5-HT3 receptor antagonists, and often included a placebo arm. Tramer et al. published a meta-analysis on the use of cannabinoids for CINV control. The investigators analyzed data from 30 randomized controlled studies from 1975 to 1997; 16 studies were with nabilone, 13 with dronabinol, and 1 with intramuscular levonantradol. Of the 30 studies,

10 used a placebo as the comparator, and prochlorperazine was prescribed in 12 trials. Other antiemetic controls included metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride. The authors found that cannabinoids were more effective with moderately emetogenic chemotherapy regimens than all of the active controls, but were not more effective with very high or low emetogenic regimens. More side effects were associated with the cannabinoid treatment, and patients were more likely to withdraw from therapy [44]. A 2015 meta-analysis evaluated the role of cannabinoids in chemotherapy-induced nausea and vomiting. 51 trials included in the analysis were conducted between 1975 and 1991 and none involved comparisons with current antiemetic regimens. The authors concluded that cannabis-based medications may be useful for treating refractory CINV. However, methodological limitations of the trials limit any conclusions [45]. Nabilone and dronabinol are orally active synthetic cannabinoid approved for the treatment of CINV in patients who have not experienced adequate response to conventional antiemetic treatments. The restriction is related to the side effects spectrum of this agents. Some of these adverse events are seen as beneficial to the patient. Events such as a feeling of being high or euphoria and drowsiness are seen as potentially beneficial side effects of this agent. Other side effects that are not considered beneficial and are more problematic include ataxia, anxiety, disorientation, hallucinations, depression, and psychosis. Adverse events may persist for a variable and unpredictable period, with adverse psychiatric reactions persisting 48 to 72 hours after the last dose. Orthostatic hypotension has been reported. Use of synthetic oral cannabinoids should be limited to the management of breakthrough and refractory CONV and they have no place as a first-line treatment for CINV.

In the anticipatory CINV benzodiazepines are the treatment of choice due to their antianxiety property [17]. Lorazepam or alprazolam are the most used agents in the prevention and management of anticipatory emesis in combination with standard antiemetic strategies.

Alternative treatments should also be considered particularly for the anticipatory CINV. Behavioral approaches include hypnosis, muscle relaxation, music therapy, acupuncture or acupressure [46]. Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure and other complementary or alternative therapies for the prevention of nausea and vomiting in patients with cancer. The role of ginger in the prevention of CINV has been evaluated in two trials and a meta-analysis. The first trial compared powdered ginger plus standard of care versus standard of care alone in 60 patients treated with anthracycline-based chemotherapy experienced severe CINV during previous cycles. Patients in the ginger arm reported less severe nausea and fewer vomiting episodes on days 2, 3, and 5. No adverse events were attributable to ginger [47]. The second trial compared three doses of ginger versus placebo in more than 500 patients receiving a 5-HT₃ inhibitor and dexamethasone. The two lower doses of ginger produced the largest reductions in nausea intensity [48]. A 2013 systematic review evaluated four trials and reported that ginger did not have a significant effect on the incidence of acute nausea, acute vomiting, or delayed vomiting [49].

The use of acupuncture has been evaluated in 70 patients who were randomly assigned to receive acupuncture in cycle 1 and ondansetron in cycle 2, or the reverse. All patients also received dexamethasone for 3 days. Complete response from 0 to 24 hours was similar with the two treatments, but acupuncture produced higher complete response rates from 24 to 120 hours. Constipation and insomnia were less common with acupuncture than with ondansetron [50]. Two trials evaluated acupressure wristbands and found no significant benefit against nausea and

vomiting when wristbands were added to standard antiemetic treatment among patients treated with chemotherapy [51, 52].

6.5 Radiotherapy-induced N/V

Few randomized controlled clinical trials have evaluated the prevention or treatment of N/V associated with radiotherapy. As for CINV, RINV is classified according to the emetogenic risk of radiation (**Table 4**).

Patients experiencing high-emetic-risk radiation therapy should be received a two-drug combination of a 5-HT3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction if radiation therapy is not planned for that day. Optimal frequency and duration of prophylactic 5-HT3 receptor antagonist therapy and prophylactic dexamethasone therapy for high-emetic-risk single-fraction or multiple-fraction radiation are unclear. Previous studies administered prophylactic 5-HT3 receptor antagonist therapy for durations longer than, equal to, and shorter than the duration of radiation therapy. Randomized studies comparing these approaches are lacking [53, 54].

Patients receiving moderate-emetic-risk should be treated with a 5-HT3 receptor antagonist before each fraction, with or without dexamethasone before the first five fractions. Optimal frequency and duration of prophylactic 5-HT3 receptor antagonist therapy for moderate-emetic-risk, single-fraction or multiple-fraction radiation therapy are unclear. Guidelines recommend prophylaxis before each fraction with careful monitoring of patients during radiation therapy schedules that span multiple weeks to detect symptoms experienced during interspersed days when radiation therapy and prophylaxis are not administered and to balance the benefits and toxicities of prolonged 5-HT3 receptor antagonist therapy. A study that involved moderate-emetic-risk radiation therapy demonstrated a benefit for a number of secondary end points by adding prophylactic dexamethasone therapy to prophylactic 5-HT3 receptor antagonist therapy before the first five fractions [55].

Patients treated with low- and minimal-emetic-risk radiation therapy should receive rescue therapy with a 5-HT3 receptor antagonist, dexamethasone, or a dopamine receptor antagonist.

Patients who are treated with concurrent radio-chemotherapy should receive antiemetic therapy that is appropriate for the emetic risk level of antineoplastic agents, unless the risk level of the radiation therapy is higher [56].

One trial evaluated the addition of fosaprepitant to palonosetron and dexamethasone among women who received low-emetic-risk pelvic radiation and concurrent weekly cisplatin.³⁶ The other trial compared fosaprepitant with olanzapine—each given with palonosetron and dexamethasone—among patients with head and neck or esophageal cancers who received radiation therapy and concurrent cisplatin and fluorouracil.

A systematic review of RINV reported that the clinical trial designs varied considerably in the methodologies, endpoints, and outcome measures employed with

High-risk of emesis (>90%)	Moderate-risk of emesis (30–90%)	Low-risk of emesis (10–30%)	Minimal-risk of emesis (<10%)
Total body irradiation	Upper abdomen, craniospinal irradiation	Brain, head and neck, thorax, pelvis irradiation	Extremities, breast irradiation

Table 4.
Classification of radiotherapy according to the risk of emesis.

great difficult to conclude definitive recommendations [57]. Most of the patients will be suggested to take the antiemetic by the international antiemetic guidelines. A MASCC/ESMO consensus systematic review recently evaluated 18 publications. The only fully published randomized studies in prevention of RINV were two negative studies in acupuncture and green tea, respectively. No data to support new recommendations for antiemetic prophylaxis in RINV was available. The serotonin receptor antagonists are still the corner stone in antiemetic prophylaxis of nausea and vomiting induced by high and moderate emetic risk radiotherapy. The emetogenicity of craniospinal radiotherapy was reclassified from low to moderate emetic level along with some other minor changes [58]. Further investigations are warranted to explore RINV prophylaxis in single fraction, multiple fractions and concomitant chemo-radiotherapy.

Although the mechanisms of acupuncture are not completely clear yet, a plenty of high-quality clinical trials have been conducted to evaluate the efficacy and safety of this therapy and reported that acupuncture could reduce nausea and vomiting induce by chemotherapy and radiotherapy with less side effects [50, 59, 60]. Neural mechanism like stimulating the secretion of endogenous opioid endorphin has been proved one of mechanisms of acupuncture therapeutical effect, but for RINV relative neural mechanisms have not been found yet [61].

7. Conclusions

CINV represents a common adverse event of chemotherapy with potentially significant negative impact on quality of life for patients and their families. Prevention and management of CINV is crucial to increase patients' compliance and adherence to antitumoral treatments.

7.1 High-risk of emesis

The combination of a 5-HT₃ receptor antagonist, dexamethasone and aprepitant before chemotherapy is currently the recommended strategy for chemotherapy with high- and moderate-risk of emesis. More robust data is available for cisplatin-based chemotherapy and anthracycline plus cyclophosphamide regimen, less robust data is available for other agents. Approximately 90% of patients receiving cisplatin-based chemotherapy and anthracycline plus cyclophosphamide regimen develop delayed emesis. These patients should receive a regimen with one of 5-HT₃ receptor antagonists plus 3-days oral aprepitant plus dexamethasone on days 2 to 4 to avoid delayed emesis.

7.2 Moderate-risk of emesis

For moderate-risk agents different from and anthracycline plus cyclophosphamide regimen, a combination of a 5-HT₃ receptor antagonist and dexamethasone should be administered before chemotherapy. Patients with moderate risk of emesis have moderate potential for delayed emesis. These patients should be treated with a 5-HT₃ receptor antagonist or dexamethasone alone on days 2 and 3.

7.3 Low-risk of emesis

For patients receiving chemotherapy with low-risk of emesis, a single dose of dexamethasone or a dopaminergic before chemotherapy is currently recommended. No routine prevention for delayed emesis is recommended.

Risk of emesis		Antiemetic strategy	
		Acute CINV	Delayed CINV
Minimal		None	None
Low		Dexamethasone or dopamine antagonist	None
Moderate	Anthracycline plus cyclophosphamide	5-HT3 receptor antagonist plus dexamethasone plus aprepitant	Dexamethasone days 2–4 plus aprepitant days 2–3
	Other regimens	5-HT3 receptor antagonist plus dexamethasone	5-HT3 receptor antagonist or dexamethasone days 2–3
High		5-HT3 receptor antagonist plus dexamethasone plus aprepitant	Dexamethasone days 2–4 plus aprepitant days 2–3

Table 5.
Management of RINV.

7.4 Minimal-risk of emesis

No routine prevention for acute and delayed CINV is generally indicated for chemotherapy with minimal-risk of emesis (**Table 5**).

Strategies to prevent and manage CINV represents a major challenge. In the last 20 years, more effective and well-tolerated antiemetic agents have been introduced in the clinical practice. Selective 5-HT3 receptor antagonist, NK1 antagonist receptors and steroids are currently the most effective combination. This antiemetic strategy achieved an excellent control of CINV in over 80% of patients with an excellent side-effect profile. The further goal should be the management of patients with refractory CINV impacting on therapeutic adherence.

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