Review Article

PORTO BIOMEDICAL JOURNAL
WHERE SCIENCE MEETS KNOWLEDGE

OPEN

Portuguese consensus on the prevention and treatment of nausea and vomiting induced by cancer treatments

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Abstract

Chemotherapy-induced nausea and vomiting (CINV) and radiotherapy-induced nausea and vomiting (RINV) strongly affect the quality of life of patients with cancer. Inadequate antiemetic control leads to the decline of patients' quality of life, increases rescue interventions, and may even compromise adherence to cancer treatment. Although there are international recommendations for controlling CINV and RINV, these recommendations focus mainly on pharmacological management, with scarce information on additional measures that patients may adopt. Moreover, the prophylaxis and management of CINV/RINV are not always applied. Thus, we identified the need to systematize the strategies for preventing and managing CINV/RINV and the associated risk factors to implement and promote effective prophylactic antiemetic regimens therapy in patients with cancer. This review sought to create a set of practical recommendations for managing and controlling CINV/RINV, according to the current international recommendations for antiemetic therapy and the main risk factors. Conclusively, we intended to produce a patient-centered guidance document for health care professionals focused on the awareness, monitoring, and treatment of CINV/RINV.

Keywords: nausea, vomiting, antiemetics, chemotherapy, radiotherapy

Introduction

Despite the enormous advances in antineoplastic therapies, chemotherapy-induced nausea and vomiting (CINV) and radiotherapy-induced nausea and vomiting (RINV) represent one of the most common adverse events (AEs) that substantially affect patients with cancer.[1-3] Nausea is characterized by an unpleasant, subjective, and painless sensation that causes the desire to vomit and may be accompanied by symptoms such as tachycardia, dizziness, and weakness. It is considered more disabling and difficult to control than vomiting,[1,3] defined as a central nervous system response where the abdominal muscles and diaphragm contraction occurs, causing expulsion of the gastric contents.[3,4] The pathophysiology of nausea and vomiting is not yet fully defined. It has been described that emesis associated with chemotherapy (CT) and radiotherapy (RT) has similar pathophysiological mechanisms,[5] resulting from a complex interaction of neural pathways, neurotransmitters, and the gastrointestinal system.[6,7]

Types of emesis

Nausea and vomiting can be divided into five categories, according to their intensity and the period in which they occur[3,6,8-11]—(1) *acute*: occurring in the first 24 hours post-CT, with an intensity peak 5–6 hours after CT; (2) *late*: occur after the first 24 hours after CT administration, with a peak in intensity generally in 48–72 hours after treatment; (3)

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.portobiomedicaljournal.com).

Porto Biomed. J. (2023) 8:5(e234)

Received: 4 May 2023 / Received in final form: 8 August 2023 / Accepted: 1 September 2023

http://dx.doi.org/10.1097/j.pbj.0000000000000234

anticipatory: resulting from a conditioned response to certain stimuli after previous CT rounds, are assumed to have an emotional origin, and to present as psychosomatic symptoms; (4) *breakthrough*: occurring regardless of the administration of antiemetic prophylaxis and may require rescue therapy; and (5) *refractory*: occurring in subsequent cycles of CT when antiemetic prevention and/or rescue therapy was not effective in previous cycles.

Emetogenic risk: patient and antineoplasic regimen–intrinsic factors

Given the high incidence of nausea and vomiting in the oncology setting (CT: 70%–80% of patients, 20% of which moderate to severe; RT: 50%–80% of patients),[12] identifying associated risk factors is critical for its management and prevention.

The risk for CINV and RINV has a multifactorial nature, including multiple intrinsic characteristics of the patient and the associated cancer treatment regimen. The patients' emetogenic risk factors are young age, female sex, history of pregnancy-associated emesis/morning sickness, emesis in previous CT treatments, the expectation of CINV, anxiety, smoking, and low alcohol consumption.[3,13] Treatment-related risk factors relate to the type and scheme of CT/RT. Table 1 presents the emetogenic potential of various drugs and CT regimens.

The emetogenic potential of CT is based on the drug with the highest emetogenic risk of a given regimen. It is categorized according to the percentage of patients presenting with acute vomiting within 24 hours of drug administration: (1) *high risk* (occurs in ≥90% of patients, with the risk remaining beyond three days after the last dose of CT); (2) *moderate risk* (occurs in 30%–90% of patients, with the risk remaining beyond three days after the last dose of CT); (3) *low risk* (occurs in 10%–30% of patients); and (4) *minimal risk* (occurs in <10% of patients).[14-16]

Similarly, RT presents different levels of emetogenic risk according to the dose, irradiated location, and association with CT: (1) *high risk* (occurs in >90% of patients; in total body irradiation treatments), (2) *moderate risk* (occurs in 30–90% of patients; upper abdomen and craniospinal irradiation), (3) *low risk* (occurs in 10%–30% of patients; brain, head and neck, chest irradiation), and (4) *minimal risk* (occurs in <10% of patients; breast and extremities irradiation)[12,17] (Table 1).

Previous assessment of the emetogenic potential associated with the CT/RT regimen is crucial for optimizing the therapeutic strategy, avoiding nausea conditioning, increasing therapeutic adherence, and the loss of quality of life (QoL) of the patient with cancer.

Management and control strategies of CINV and RINV

After the evaluation of the emetogenic risk, the preventive/prophylactic treatment of emesis associated with CT or RT is mainly based on the pharmacologic agents widely reported in the literature.[11,18] Antiemetic agents include corticosteroids, cannabinoids, ginger consumption, and some neurotransmitter receptor inhibitors/antagonists (serotonin, dopamine, and neurokinin-1 receptor antagonists).[19] Despite the less scientific evidence, some nonpharmacological approaches have also shown benefits, including specific diets, acupuncture, acupressure, music therapy, and massage/relaxation exercises.[20] Adopting combined and adequate strategies, monitored by the clinical team, is crucial in correctly managing and controlling CINV/RINV.

Recommendations for CINV and RINV prevention and treatment

The decade of 1990 represented an essential milestone in developing antiemetic drugs with greater effectiveness in antiemetic control. In 1999, the *American Society of Clinical Oncology* (ASCO, 1999) published the first *guidelines* on antiemetics.[7,21] Since then, several guidelines for the prevention and control of CINV/RINV have been published, namely by ASCO,[14,21] the National Comprehensive Cancer Network (NCCN),[22] the Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO),[8] the *Sociedad Española de Oncología Médica* (SEOM),[9] and by other expert groups, including the expert meetings in India,[23] Japan,[6] and multinational groups.[14,24]

The ASCO and NCCN guidelines share fundamental recommendations, with some differences from those of MASCC/ESMO (the main differences and similarities between policies are described in Table 2). Although the recommendations for treating CINV/RINV in patients with cancer under protocols with high and moderate emetic risk are similar, the consensus is lower for treatments with low or minimal emetic risk.[7,8,10,25] Similarly, the current guidelines still do not fully acknowledge the role of adjuvant and nonconventional treatments in preventing CINV/RINV.

The latest guideline update included olanzapine in the quadruple therapy for high emetic potential regimens, combined with 5HT3-RA (selective serotonin receptor antagonists), NK1-RA (neurokinin-1 receptor antagonists), and dexamethasone. This change follows the publication of a phase III study with 380 patients treated with an anthracycline-cyclophosphamide (AC)–based CT regimen.[26] Because the publication of this study occurred after the last update of the MASCC/ESMO guidelines,[8] these suggest olanzapine only for breakthrough CINV. However, the AEs of olanzapine, including sedation, justify caution in its generalization.

While the abandonment of dexamethasone on days 2–4 after AC-based CT represents another change adopted by ASCO in 2021,[21] it was maintained in the other recommendations for this CT regimen and others with high emetic potential (Table 2). MASCC/ESMO guidelines propose administering aprepitant (NK1-RA) or dexamethasone on days 2 and 3, thus considering the possibility of a corticosteroids-free regimen, to avoid AEs such as insomnia, agitation, dyspepsia, appetite, weight changes, and acne (Table 2).[8]

For treatment with cisplatin, MASCC/ESMO guidelines recommend using dexamethasone and aprepitant or dexamethasone and metoclopramide at days 2–4 (Table 2).[8]

Regarding carboplatin AUC >4 mg/mL/min (moderately emetic regimen), all guidelines now suggest adding an NK1-RA, based on the results of clinical trials with rolapitant, fosaprepitant, and aprepitant (Table 2).[27-29] The recommendations for treating acute emesis in low emetogenic risk regimens mostly agree on using only one antiemetic, except for ASCO, which, in 2017, included a 5HT3-RA. Finally, owing to limited evidence, the different guidelines do not provide any recommendations for delayed emesis associated with low or minimal-risk emesis regimens (Table 2).

Concerning treatment and prevention of RINV, the ASCO, NCCN, and MASCC/ESMO guidelines present similar recommendations (Table 3), including prophylaxis with 5HT3-RA in patients considered at high and moderate risk. However, even in this group of patients, the advice for additional prophylactic dexamethasone does not follow an identical pattern in the three guidelines (Table 3). This difference stems from a randomized study including 211 patients at moderate risk of RINV, which showed a modest benefit from the

Table 1.

Emetogenic risk of current oncological therapeutic approaches based on chemotherapy and radiotherapy

Emetogenic risk	Endovenous chemotherapy	Oral chemotherapy	Radiotherapy (treated area)
High	Cisplatin; cyclophosphamide (>1500 mg/m^2); dacarbazine; doxorubicin + cyclophosphamide; epirubicin + cyclophosphamide; carmustine (>250 mg/m^2); streptozocin; carboplatin AUC ≥4; doxorubicin ≥60 mg/m^2; epirubicin >90 mg/m^2; ifosfamide ≥2 g/m^2; melfalan ≥140 mg/mg^2	—	Total body irradiation
Moderate	Actinomycin D; aldesleukin >12-15 million IU/m^2; alemtuzumab; amifostine (≥300 mg/m^2); azacitidine; bendamustine; busulfan (>4 mg/day); carboplatin; carmustine (≤250 mg/m^2); clofarabine; cyclophosphamide (≤1500 mg/m^2); citarabine (>200 mg/m^2, >1000 mg/m^2); daunorrubicin; doxorubicin <60 mg/m^2; epirubicin <90 mg/m^2; idarrubicin; ifosfamide <2 g/m^2; IFN-α (≥10 million IU/m^2); irinotecan; liposomal irinotecan; melfalan (<140 mg/m^2); methotrexate (≥250 mg/m^2); oxaliplatin; temozolomide; tiotepa; trabectidine; trastuzumab deruxtecan; arsenic trioxide	Abemaciclib; bosutinib >400 mg/day; busulfan ≥4 mg/day; cabozantinib; ceritinib; crizotinib; ≥100 mg/m^2/day, enasidenib; etoposide; imatinib >400 mg/day; lenvatinib; lomustine; midostaurin; niraparib; procarbazine; temozolomide; ribociclib; rucaparib; selinexor; trifluridine-tipiracil; temozolomide; vinorelbine	Upper abdomen Craniospinal irradiation[21]
Low	Aflibercept; amifostin (<300 mg); axicabtagene ciloleucel; blinatumomab; bortezomib; brentuximab vedotin; cabazitaxel; carfilzomib; cetuximab; citarabine (100–200 mg/m^2); decitabine; docetaxel; pegylated liposomal doxorubicin; etoposide; eribulin; 5-fluorouracil; gemcitabine; gemtuzumab ozogamicin; IFN-α (5-10 million IU/m^2); methotrexate (50–250 mg/m^2); mitomycin C; mitoxantrone; nab-paclitaxel; nelaribine; paclitaxel; panitumumab; pemetrexed; pentostatin; pertuzumab; temsirolimus; tisagenlecleucel; trastuzumab emtansine (TDM-1); topotecan	Acalabrutinib; afatinib; alectinib; alpelisib; axitinib; bexacarotene; brigatinib; capecitabine; chlorambucil; cobimetinib; dabrafenib; dacomitinib; dasatinib; duvelisib; encorafenib; entrectinib; erdafitinib; erlofinib; stramustine; etoposide; everolimus; fludarabine; gefitinib; gilteritinib; glasdegib; hydroxyurea; ibrutinib; idelalisib; ivosidenib; ixazomib; lapatinib; larotrectinib; lenalidomide; lorlatinib; melfalan; methotrexate; neratinib; nilotinib; olaparib; osimertinib; palbociclib; panobinostat; pazopanib; pomalidomide; ponatinib; regorafinib; ruxolinitib; sonidegib; sorafenib; sunitinib; thalazoparib; tegafur-uracil; 6-thioguanine; thalidomide; topotecan; trametinib; vandetanib; vemurafenib; venetoclax; vismodegib; vorinostat; zanubrutinib; bosutinib ≤400 mg/day; busulfan <4 mg/day; cyclophosphamide <100 mg/m^2/day; imatinib ≤400 mg/day	Brain Head and neck[21] Thorax Pelvis
Minimum	L-asparaginase; avelumab; bevacizumab; bleomycin; cemiplimab; cladribine; daratumumab; durvalumumab; fludarabine; ipilimumab; IFN-α (≤5 million IU/m^2); nivolumab; obinutuzumab; ofatumumab; pembrolizumab; pixantron; polatuzumab vedotin; cytarabine (<100 mg/m^2); methotrexate (≤50 mg/m^2); ofatumumab; peginterferon; ramucirumab; rituximab; siltuximab; trastuzumab; vinblastine; vincristine; vinorelbine vindesin; denileukin diftitox; pegaspargase; valrubicin; liposomal vincristine	Mercaptopurine; tretinoin	Breast Extremities

AUC = area under the curve; IFN = interferon; IU = international units.

combination of dexamethasone and ondansetron (5HT3-RA) in the first five fractions of RT.[30]

As previously mentioned regarding the recommendations for CINV prevention and control, the most significant discrepancy between the guidelines for RINV is seen in the prophylaxis and treatment of low-risk and minimal-risk patients, essentially because of the scarcity of studies in this population. While NCCN guidelines do not provide information in this context,[12] the others indicate the possibility of rescue (or prophylaxis in the case of the MASCC/ESMO guidelines) with 5HT3-RA, with dopamine receptor antagonists or with dexamethasone (Table 3). There is no evidence to support a higher or lower degree of recommendation for these categories of drugs. The well-described benefits of some medications used for CINV prevention, including olanzapine or NK1-RA, are not present in any of the guidelines RINV-related because of the lack of evidence. Noteworthy, there is a consensus on adopting the treatment and prophylaxis of CINV for patients with concomitant chemoradiotherapy.

The correct management of CINV/RINV, adequately adjusted to the emetic potential of the therapy, increases the possibility of carrying out all the planned treatments, improving patients' response rate, survival, and QoL.[31] Thus, it is critical to foster the continuous training of health professionals on antiemetic support measures, promote the implementation of the existing guidelines,

Table 2.

Description of the main aspects of ASCO, NCCN, and MASCC/ESMO guidelines

	CT/emesis type	ASCO (2020)	NCCN (2021)	MASCC/ESMO (2016)
Emetogenic risk				
Minimum	All regimens/acute (D1) or delayed (D2-3) emesis		No routine prophylaxis	
Low	All regimens/acute emesis (D1)	5HT3-RA; DEX	DEX; METO; PROC; 5HT3-RA	DEX; 5HT3-RA; METO
	All regimens/delayed emesis (D2-3)		No routine prophylaxis	
Moderate	No carboplatin/acute emesis (D1)	5HT3-RA + DEX	DEX + 5HT3-RA ± NK1-RA; OLA + PALO + DEX	5HT3-RA + DEX
	No carboplatin/late emesis (D2-3)	DEX	OLA; APR ± DEX; DEX + 5HT3-RA	DEX (for drugs associated with delayed moderate emesis) or no prophylaxis
	Carboplatin AUC≥4 (mg/mL)/min/acute emesis	5HT3-RA + NK1-RA + DEX	5HT3-RA + DEX; PALO + DEX + OLA; 5HT3-RA + NK1-RA + DEX	5HT3-RA + NK1-RA + DEX
	Carboplatin AUC≥4 (mg/mL)/min/late emesis	DEX (D1 only)	5HT3-RA or DEX (D2 and D3); OLA (D2 and D3); APR ± DEX (D2 and D3)	APR (if APR has been used for acute emesis control) or no prophylaxis
	Carboplatin/acute emesis treated with NK1-RA	APR + FOS + NET; PALO + FOS; PALO + ROLA	APR + FOS + NET; PALO + ROLA	APR + FOS + NET; PALO + ROLA
High	Cisplatin or other high emetogenic risk agents/acute emesis (D1)	NK1-RA + 5HT3-RA + DEX + OLA	OLA + NK1-RA + 5HT3-RA; PALO + DEX + OLA; 5HT3-RA + NK1-RA + DEX	NK1-RA + 5HT3-RA + DEX + OLA
	Cisplatin or other high emetogenic risk agents/delayed emesis (D2-4)	APR + DEX + OLA	OLA + APR + DEX; OLA; APR + DEX	APR + DEX + OLA
	AC/acute emesis (D1)	NK1-RA + 5HT3-RA + DEX + OLA	5HT3-RA + DEX; PALO + DEX + OLA; NK1-RA + 5HT3-RA + DEX	NK1-RA + 5HT3-RA + DEX
	AC/delayed emesis (D2-D4)	APR + OLA	5HT3-RA; DEX; OLA; APR + DEX	APR (if APR has been used for acute emesis control) or no prophylaxis
	AC/acute emesis treated with NK1-RA	D1: NK1-RA + 5HT3-RA + DEX + OLA D2-4: APR + DEX + OLA	APR + FOS + NET; PALO + ROLA	APR + FOS + NET; PALO + ROLA

5HT3-RA = 5-HT3 receptor antagonists; AC = anthracycline + cyclophosphamide; APR = aprepitant; DEX = dexamethasone; AUC = area under curve; FOS = fosaprepitant; FOSN = fosnetupitant; METO = metoclopramide; NET = netupitant; NK1-RA = neurokinin-1 receptor antagonists; OLA = olanzapine; PALO = palonosetron; PROC = prochlorperazine; ROLA = rolapitant.

foment work in multidisciplinary teams, and in-depth acknowledgment of the symptoms reported by patients.

In this study, the authors reviewed the most recent literature and the international guidelines on treating CINV/RINV, encompassing the most critical evidence between 2018 and 2022, aiming to create an updated, straightforward guidance document to use and apply in clinical practice. The presented work emphasizes the critical pharmacological aspects outlined in international guidelines and strongly focuses on non-pharmacological interventions, encompassing self-care techniques such as physical exercise, dietary habits, and massages. While acknowledging the importance of patient engagement and active involvement, existing publications often fail to consolidate all these aspects into a single comprehensive document. Therefore, this document serves as a digest of the latest clinical guidelines and highlights the significance of self-care and patient-centered measures in effectively managing CINV and RINV.

Methodology

This article results from a project conceived and developed by AICSO (*Associação de Investigação de Cuidados de Suporte em Oncologia*). In addition to designing the study, AICSO was also responsible for selecting the working group comprising a multidisciplinary group of Portuguese specialists. The Portuguese Society of Oncology (SPO) nominated a representative to participate as an expert in this project.

A literature search was performed in PubMed using the following keywords: "emesis," "vomit," "nausea," "chemotherapy," "radiotherapy," "cancer," "lymphoma," and "leukaemia" for the period between 2018 and 2022. The time interval chosen is

Table 3.

ASCO, NCCN, and MASCC/ESMO guidelines for prevention and prophylaxis of RINV

Emetogenic risk	ASCO (2020)	NCCN (2021)	MASCC/ESMO (2016)
Minimum	No routine prophylaxis	—	No routine prophylaxis
Bass		—	Prophylaxis or rescue with DEX or dopamine receptor antagonist or 5HT3-RA
Moderate	5HT3-RA (all fractions of RT) + DEX (in the five initial fractions)	5HT3-RA + optional DEX	5HT3-RA + optional DEX
High	5HT3-RA + DEX	5HT3-RA + optional DEX	5HT3-RA + DEX

5HT3-RA = 5-HT3 receptor antagonists; DEX = dexamethasone; RT = radiotherapy.

justified because the previously published guidelines included literature up to 2018. The search results included systematic reviews, meta-analyses, clinical trials, and clinical studies. Articles were analyzed according to the publication type and CT/RT regimen under analysis.

Specifically, concerning the management of nausea and vomiting in the multidisciplinary treatment of cancer disease, it is essential to include CT and RT: CT has a wide range of emetogenic potential depending on the agent, route of administration and dosage, and RT is generally indicated in about half of the patients at least once during the cancer disease treatment.[32]

Although studies on nonpharmacological prevention and treatment strategies are still scarce, they are essential in managing and controlling CINV and RINV because they represent complementary and self-care measures. Patients with cancer have a high nutritional risk, with a prevalence of malnutrition between 20%-70%, depending on the cancer location.[33] Factors related to tumors, and treatments contribute to malnutrition, such as nausea and vomiting, causing food and nutritional imbalances. Thus, the adoption of an appropriate nutritional strategy, achieved through changes in the patient's diet, in the nutritional and dietary composition of meals (including dietary strategies to control nausea and vomiting), and the prescription of nutritional supplements, may constitute a tool for the management and control of CINV/RINV.[34]

Other nonpharmacological strategies include physical relaxation practices, such as yoga, massage, aromatherapy with essential oils, and acupuncture.[35]

Literature on hematological neoplasms was also reviewed, given the high incidence of late emesis associated with the high emetogenic potential of CT generally administered[36] and the inexistence of international guidelines in this field.

Critical review of the literature related to CINV and RINV

The literature search regarding nausea and vomiting induced by CT, RT, and associated with the treatment of hematological neoplasms identified a total of 109 relevant publications between 2018 and 2022, described in Supplementary Tables 1 to 10 (http://links.lww.com/PBJ/A34), encompassing clinical trials, systematic reviews, and meta-analyses for pharmacological and nonpharmacological treatments (Fig. 1).

Pharmacological management and control of CINV

The literature search identified 36 clinical studies, five meta-analyses, two systematic reviews, and four systematic reviews with meta-analyses on pharmacological strategies for preventing and treating nausea and vomiting during CT (Supplementary Tables 1 and 2, http://links.lww.com/PBJ/A34).

The analyzed drugs in the identified clinical studies (Supplementary Table 1, http://links.lww.com/PBJ/A34) were olanzapine (9 studies), NEPA (combination of NK1-RA netupitant and 5HT3-RA palonosetron; seven studies), and aprepitant (seven studies). The remaining 13 studies analyzed other drugs/pharmacological combinations, such as granisetron, fosaprepitant, fosnetupitant, and gabapentin. The systematic reviews and meta-analyses in this domain (Supplementary Table 2, http://links.lww.com/PBJ/A34) assessed clinical studies comparing the efficacy of triple (NK1-RA + 5HT3-RA + corticosteroids) vs double conventional (5HT3-RA + corticosteroids; four trials) antiemetic regimens and the use of olanzapine alone or in combination (three trials). The remaining four publications evaluated the use of NEPA in patients on CT with cisplatin or AC, the safety profile of a new formulation of surfactant-free aprepitant (HTX-019), a comparison of the efficacy of administering palonosetron and dexamethasone alone on day one vs day 1–3, and finally a comparison of different combinations of antiemetic agents for highly emetogenic CT regimens. The overall analysis of these studies concluded that in CT regimens with high emetogenic risk, triple combinations are superior in the acute and late phases, and the inclusion of an NK1-RA in prophylactic regimens is recommended. In addition, concerning triple prophylactic regimens based on NK1-RA and associated with CT with high emetogenic risk, including olanzapine, is beneficial because it potentiates the improvement of nausea, vomiting, and QoL—noteworthy, the 5 mg dose is associated with less sedation and a better safety profile, compared with a 10 mg dose.[37] It was also concluded that the combination of NEPA and dexamethasone effectively prevent CINV in highly emetic regimens, improving the QoL of patients and promoting therapeutic adherence. A triple regimen (dexamethasone + 5HT3-RA + NK1-RA) is recommended to prevent CINV associated with carboplatin-based combinations.

Our analysis leads to the conclusion that, in general, the available pharmacological treatment is effective and safe in the treatment and prophylaxis of nausea and vomiting associated with CT and that the choice should be made according to the profile of the CT regimen. Adequate management in the prevention of nausea and vomiting is a critical factor for the success of CT.

Pharmacological management and control of CINV—other agents

Ten articles were identified regarding the pharmacological treatment of nausea and vomiting using other pharmacological agents, corresponding to four clinical studies, three systematic reviews, and three meta-analyses (Supplementary Tables 3 and 4, http://links.lww.com/PBJ/A34). Regarding cannabinoids (medical cannabis, THC: CBD), their use has demonstrated efficacy, especially in nausea.[38-40] However, it is essential to consider the potential AEs arising from their use, namely

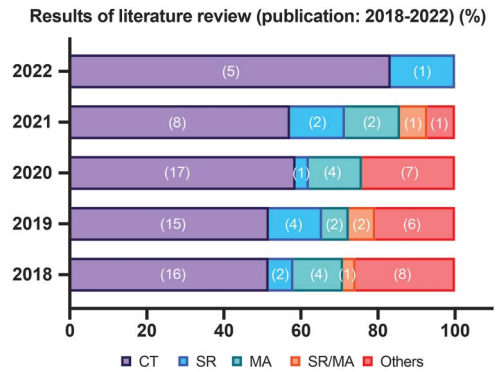

Figure 1. Scientific publications in antiemetic management and control in oncology therapy, published between 2018 and 2022. A total of 109 scientific publications were obtained through a literature search in the PubMed/Medline database, including CT (clinical trials), SR (systematic reviews), MA (meta-analyses), SR/MA (systematic reviews with meta-analysis), and others (guidelines, opinion, and literature review articles). Inside the brackets is indicated the number of found publications.

dysphoria, euphoria, and sedation (two clinical studies[38,39] and one meta-analysis[40]).

Because the effect of ginger and its derivatives (gingerol and shogoal) on emetic control has been evaluated in different studies in the context of different types of neoplasia, their heterogeneity does not allow a robust conclusion. The various presentations and dosages of these compounds (capsule, powder, liquid) seem to mitigate nausea in the acute phase but not in the late stage, with improvements in QoL (two clinical studies,[41,42] two systematic reviews,[43,44] and two meta-analyses[45,46]).

Nonpharmacological management and control of CINV

The literature search identified nine clinical studies and five systematic reviews and meta-analyses on nonpharmacological antiemetic treatments for patients on CT (Supplementary Tables 5 and 6, http://links.lww.com/PBJ/A34). Analyses of the articles show that yoga or acupuncture positively reduces the incidence and severity of CINV.[47-50] The NCCN guidelines[22] recommend yoga, acupuncture, and relaxation practices, including aromatherapy and music therapy, to control anticipatory nausea and vomiting (seven clinical studies and six systematic review/meta-analysis articles).

Regarding the impact of nutritional intervention on the control of CINV, although the available information is limited, dietary education and protein-boosting seem to have a positive effect (two clinical studies and one systematic review). As the NCCN recommended,[51] including a nutritionist experienced in oncology in the multidisciplinary team accompanying these patients is fundamental.

Pharmacological management and control of RINV

Regarding the pharmacological treatment of RINV, only three articles were identified, corresponding to one clinical study, one systematic review, and one meta-analysis (Supplementary Tables 7 and 8, http://links.lww.com/PBJ/A34). Considering the analyzed studies, we found that in preventing acute RINV in moderate-risk and high-risk treatments, 5HT3-RA is superior to placebo and other active drugs, such as dopamine receptor antagonists, rescue therapy, or dopamine receptor antagonists with dexamethasone (Supplementary Table 7, http://links.lww.com/PBJ/A34). In preventing and treating RINV in patients undergoing palliative RT at moderate risk, ondansetron has been found to promote superior control of nausea and vomiting compared with 5HT3-RA. In addition, the combination of aprepitant + granisetron, because of its efficacy and safety, also represents a valuable option in preventing RINV in patients undergoing palliative RT at moderate risk of RINV (Supplementary Table 8, http://links.lww.com/PBJ/A34).

The lack of results on this topic reflects an underestimation, underreporting, and underanalysis of RINV. Although the existing guidelines are relatively homogeneous, it is vital to continue promoting their knowledge and implementation in clinical practice.

Management and control of CINV in hematological neoplasms

Regarding articles focusing on CINV control in hematological neoplasms, 12 clinical studies and one systematic review were identified (Supplementary Tables 9 and 10, http://links.lww.com/PBJ/A34).

The literature in this theme demonstrates the efficacy of the triple 5HT3-RA + NK1-RA + dexamethasone (e.g. ondansetron + aprepitant + dexamethasone) antiemetic regimen in the main prehematopoietic progenitor transplant–conditioning regimens (three clinical studies and one systematic review). In this context, NEPA may also be an option, given the advantage of conventional single-dose administration (one study) or even multiple doses, which is equally effective in managing and controlling CINV (two studies). In addition, palonosetron should be considered in preventing CINV in patients with lymphoma treated with highly emetogenic ABVD-type CT regimens (one study). The administration of olanzapine should also be encouraged, given that it promotes clinical improvement of nausea and vomiting in the context of hematopoietic transplantation and intensive CT (two studies). Finally, it should be noted that in the context of managing and controlling CINV in hematological malignancies, besides the high therapeutic heterogeneity, there is also a high under-prophylaxis because of poor adherence to guidelines on antiemetic therapy in clinical practice.

Drug interactions in anti-CINV/RINV therapy

Because patients with cancer are subject to concomitant medication, there is an increased risk of drug interactions, sometimes harmful to the organism and compromising the desired therapeutic effect.[52] These interactions may result in the induction or inhibition of the CYP enzyme complexes, primarily present in the liver, responsible for the metabolism of xenobiotics.

NK1-RA are generally well-tolerated and without AEs, being associated with some episodes of headache, constipation, and hiccups. Intravenous administration of fosaprepitant has been associated with some local hypersensitivity reactions, a possible consequence of the surfactant PS80. Still, these may be attenuated with HTX-019 (aprepitant i.v. without surfactant) or NEPA (netupitant + palonosetron).[53] Intravenous rolapitant has been discontinued because of the high number of anaphylactic reactions reported.[54] Drug interactions related to NK1-RA have been investigated and described in the metabolisation profile: while aprepitant and netupitant are mainly metabolized by CYP3A4, rolapitant is metabolized by CYP2D6. This difference results in a distinct drug interaction profile with other substrates

Table 4.

Principles of prevention and prophylaxis for CINV/RINV

	Principles of CINV/RINV management and control
1	The clinical team should consider the international recommendations for CINV/RINV and implement strategies that all its members adopt in the clinical practice
2	Prophylaxis is the primary goal of antiemetic therapy in patients with cancer undergoing CT/RT.
3	Any oncology patient undergoing CT/RT with an emetogenic risk >10% should receive prophylaxis for nausea and vomiting
4	The antiemetic therapy selection should consider the emetogenicity of CT/RT and the patient's risk factors
5	The antiemetic therapy should cover the entire period of emetogenic risk derived from the administered oncological treatment
6	Patient monitoring should be continuous and real-time to record all symptoms and signs between consultations and treatments
7	It is essential to explain to patients the importance of keeping the prophylactic treatment as prescribed (medical adherence) and the existing therapeutic approaches (self-care and pharmacological nature)

Table 5.

Practical guidelines for prevention and prophylaxis of CINV/RINV

Antiemetic therapy	Recommendations	MASCC level of scientific confidence	ESMO level of evidence/grade of recommendation
Therapeutic approach			
CT with high emetogenic risk (i.v.)	• Recommended prophylaxis for acute and late phase: triple regimen 5HT3-RA + NK1-RA + DEX	High	I/A
	• NEPA + DEX: Single-dose NEPA facilitates therapeutic adherence and improves patients' QoL	—	I/A
	• Inclusion of OLA 5 mg: consider in case of recurrent nausea and vomiting	Moderate	I/A
	• Acute emesis: 5HT3-RA + DEX		II/B
CT with moderate emetogenic risk (i.v.)	• PALO is the most suitable 5HT3-RA	—	II/B
	• The inclusion of OLA or NK1-RA may be considered	—	II/B
	• Acute emesis on carboplatin-based CT: recommendation for triple regimen 5HT3-RA + NK1-RA + DEX	Moderate	II/B
	• Late emesis: no routine prophylaxis, except when CT/RT regimen is typically associated with late emesis	No confidence possible	IV/D
CT of low/minimum emetogenic risk (i.v.)	• Acute emesis: regimen with a single antiemetic agent (5HT3-RA or DEX or DOP-RA)	No confidence possible	II/B
	• If CINV/RINV persist: consider prophylactic antiemetic treatment in subsequent cycles with the therapeutic regimen associated with the moderate emetogenic risk level	No confidence possible	IV/D
	• Late emesis: no recommendation	No confidence possible	IV/D
CT (oral)	• High to moderate emetogenic risk: 5HT3-RA	—	II/B
	• Low to minimal emetogenic risk: DOP-RA	—	II/B
Breakthrough Emesis	• If emesis becomes refractory to antiemetic treatment: adjust the regimen at the next CT cycle to that associated with a higher emetogenicity level	—	V/C
	• Rescue therapy: OLA or benzodiazepines	Moderate	II/B
Anticipatory Emesis	• The best solution is to ensure that acute and delayed emesis is controlled in advance	Moderate	III/A
	• Benzodiazepines: helpful in reducing anxiety	Moderate	II/B
RT	• High emetogenic risk: 5HT3-RA ± DEX	High (for the addition of DEX: moderate)	II (for the addition of DEX: III)
	• Moderate emetogenic risk: 5HT3-RA ± DEX (DEX for short periods)	High (for the addition of DEX: moderate)	II (for the addition of DEX: III)
	• Low emetogenic risk: prophylaxis or rescue with 5HT3-RA or DEX or DOP-RA	Low	IV
	• Minimal emetogenic risk: no routine prophylaxis, but in case of breakthrough emesis, administer 5HT3-RA or DOP-RA	Low	IV
	• RINV prevention: ONDA, PALO, or APR + GRAN		
Chemoradiotherapy	• Adjust for CT emetic potential unless the risk of RT-induced emesis is high	Low	IV
Self-care	• Yoga, relaxation therapies (aromatherapy, music therapy), relaxation massage, and acupuncture positively reduce CINV/RINV.	—	II/A
	• Oral cannabinoids: effective in controlling antiemetics but with AEs (sedation, dysphoria, and euphoria) that require special attention and monitoring	*	*
	• Ginger and derivatives (gingerol and shogoal): promising use, but no conclusive results yet for therapeutic recommendation	*	*
	• Nutritional intervention, dietary education, and protein supplementation: seem to have a positive impact on antiemetic management and control, although studies are still scarce	*	*
	• NCCN recommendation: monitoring by an experienced oncology nutritionist for the dietary management of symptoms and optimization of the nutritional status of patients with cancer	*	*

ESMO levels of evidence (I to V) and Grades of Recommendation (A to D) are given according to the ESMO-adapted version of the grading of the Infectious Disease Society of America. The MASCC Levels of Scientific Confidence were classified as—high: repeated, randomized trials that were appropriately sized and well conducted; moderate: at least one randomized trial, supported by well-conducted, phase II trials, or possibly several well-conducted phase II studies; low: formal clinical trials of a level less than that expressed above; very low: a clinical impression only; —: no confidence possible.

* Despite lacking a degree of evidence on the available MASCC or ESMO Guidelines, these therapies/interventions have all been shown to be effective in controlling anticipatory emesis and should, therefore, be considered for the prevention and treatment of CINV and RINV.

5HT3-RA = 5-HT3 receptor antagonists; APR = aprepitant; CT = chemotherapy; DEX = dexamethasone; DOP-RA = dopamine receptor antagonists; GRAN = granisetron; i.v. = intravenous; NEPA = oral combination of the NK1-RA, netupitant, and the 5-HT3-RA, palonosetron; NK1-RA = neurokinin-1 receptor antagonists; OLA = olanzapine; ONDA = ondansetron; PALO = palonosetron; QoL = quality of life; RT = radiotherapy.

of these enzymes. For example, dexamethasone is a substrate of CYP3A4 and is metabolized less by CYP3A4 when conjugated with netupitant by competition (requiring dexamethasone dosage reduction to avoid overexposure).[55] Notably, the drug interactions of netupitant with other CYP3A4 substrates, including chemotherapeutic agents such as paclitaxel, vimblastine, vincristine, and vinorelbine, are under investigation for their relevance in the efficacy of antineoplastic therapy.[56] Similarly, the interaction between aprepitant/fosaprepitant and the anticoagulant agent warfarin, often prescribed to patients with cancer to prevent venous thromboembolism and blood hypercoagulation, is described.[57] This interaction stems from the metabolisation of

Table 6.

Recommended dosages of antiemetic agents

Agent	Dosage	MASCC level of scientific confidence	ESMO level of evidence/grade of recommendation
NK1-RA			
APR or FOS (acute emesis)	CT day: APR 125 mg, single oral dose, or FOS 150 mg, i.v. single dose	Moderate	II/A
APR or FOS (delayed emesis)	D2-D3 post-CT: APR 80 mg daily oral or FOS 150 mg i.v	Moderate	II/B
ROLA	Day of CT: 180 mg, single oral dose	High	I/A
NET/NEPA	CT day: 300 mg NET +0.5 mg PALO, oral single dose	Moderate	II/A
5HT3-RA			
ONDA			
HEC-induced acute emesis	i.v.: 8 mg or 0.15 mg/kg; oral: 24 mg	High	I/A
MEC-induced acute emesis	i.v.: 8 mg or 0.15 mg/kg; oral: 16 mg	Moderate; High	III/B; I/A
GRAN			
HEC-induced acute emesis	i.v.: 1 mg or 0.01 mg/kg; oral: 2 mg	High	I/A
MEC-induced acute emesis	i.v.: 1 mg or 0.01 mg/kg; oral: 2 mg	High	I/A
DOLA			
HEC-induced acute emesis	i.v.: 100 mg or 0.18 mg/kg; oral: 100 mg	High; Moderate	I/A; I/A
MEC-induced acute emesis	i.v.: 100 mg or 0.18 mg/kg; oral: 100 mg	Moderate	II/A
TROP			
HEC-induced acute emesis	i.v. or oral: 5 mg	Moderate	I/A
MEC-induced acute emesis	i.v.: 5 mg; oral: 5 mg	Moderate; Low	III/B; III/B
PALO			
HEC-induced acute emesis	i.v.: 0.25 mg; oral: 0.5 mg	Moderate	II/A
MEC-induced acute emesis	i.v.: 0.25 mg; oral: 0.5 mg	Moderate	II/A
DEX			
HEC			
Acute emesis	20 mg, single dose	High	I/A
Late emesis	8 mg, taken 2×/day for 3–4 days	Low	III/A
MEC			
Acute emesis	8 mg, single dose	Moderate	II/A
Late emesis	8 mg, daily dose for 3–4 days	Low	III/C
LEC			
Acute emesis	4–8 mg, single dose	No confidence possible	II/B

ESMO levels of evidence (I to V) and Grades of Recommendation (A to D) are given according to the ESMO-adapted version of the grading of the Infectious Disease Society of America. The MASCC Levels of Scientific Confidence were classified as: high: repeated, randomized trials that were appropriately sized and well conducted; moderate: at least one randomized trial, supported by well-conducted, phase II trials, or possibly several well-conducted phase II studies; low: formal clinical trials of a level less than that expressed above; very low: a clinical impression only; —: no confidence possible.
5HT3-RA = 5-HT3 receptor antagonists; APR = aprepitant; CT = chemotherapy; D = day; DEX = dexamethasone; DOLA = dolasetron; FOS = fosaprepitant; GRAN = granisetron; HEC = highly emetogenic chemotherapy; i.v. = intravenous; MEC = moderately emetogenic chemotherapy; NET = netupitant; NEPA = netupitant and palonosetron; NK1-RA = neurokinin-1 receptor antagonists; ONDA = ondansetron; PALO = palonosetron; ROLA = rolapitant; TROP = tropisetron.

warfarin by CYP2C9 and its stimulation by aprepitant/fosaprepitant, resulting in a clinically relevant decrease in prothrombin time/INR (International Normalized Ratio).[58,59] Consequently, patients with cancer on chronic warfarin therapy should be frequently monitored.

Concerning 5HT3-RA, there are few descriptions of AEs, with reported drug interactions with amiodarone, amisulpride, apomorphine, and bosentan.[60]

Principles and practical guidelines for the management and control of CINV and RINV

Based on the critical literature analysis, a set of principles and systematized guidelines for health professionals assisting patients with cancer was developed. These should be individually implemented to ensure effective and correct management and control of CINV and RINV and improve QoL and therapeutic efficacy (Tables 4-6).

Funding

This project was supported/funded by CSL Vifor, Portugal. Support for third-party medical writing assistance for this manuscript, furnished by Evidenze, was provided by CSL Vifor.

Acknowledgements

The authors would like to acknowledge AICSO and Evidenze Portugal for the support provided during the execution of this manuscript.

Conflict of interest

C.V.: consultancy/advice or reimbursement for travel expenses from Bristol Myers Squibb, Genentech/Roche, Grünenthal, Lilly, Merck Serono, MSD, Novartis, and Pfizer. R.B.: Amgen: consultancy, research funding, speakers bureau; Janssen: consultancy, speakers bureau; BMS: consultancy, research funding, speakers bureau; Takeda: consultancy, speakers bureau. The remaining authors have no conflicts of interest to disclose.

Author Contributions

C.V.: conceptualization, review of guidelines and articles on chemotherapy, writing and revising the manuscript. R.B.: conceptualization, review of articles on oncology, hematology and transplantation, writing and revising the manuscript. E.M.: review of articles on nutrition, writing and revising the manuscript. J.C.M.B.: review of articles on nausea and vomiting induced by chemotherapy, writing and revising the manuscript.

M.L.: review of articles on radiotherapy, writing and revising the manuscript. S.T.P.: review of articles on nonpharmacological interventions, writing and revising the manuscript. A.C.: review of articles on nutrition and hematology, writing and revising the manuscript. A.M.: conceptualization, review of guidelines and articles, writing and revising the manuscript. S.C.: review of articles on oncology/chemotherapy, writing and revising the manuscript.

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