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REVIEW

A multidisciplinary expert opinion on CINV and RINV, unmet needs and practical real-life approaches

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ABSTRACT

Introduction: A range of combination chemotherapy regimens are currently used in clinical practice. However, international antiemetic guidelines often only categorize the emetogenic potential of single agents rather than the emetogenicity of combination chemotherapy regimens. To manage the nausea and vomiting induced by antineoplastic combinations, guidelines suggest antiemetics that are appropriate for the component drug with the highest emetogenic potential. Furthermore, antiemetic guidelines generally do not consider the influence of other factors, including individual patient characteristics, on the emetic effects of cancer treatments. Similarly, the emetogenic potential of radiotherapy is stratified only according to the site of radiation, while other factors contributing to emetic risk are overlooked.

Areas covered: An Expert Panel was convened to examine unresolved issues and summarize the current clinical research on managing nausea and vomiting associated with combination chemotherapy and radiotherapy.

Expert opinion: The panel identified the incidence of nausea and vomiting induced by multi-drug combination therapies currently used to treat cancer at different anatomic sites and by radiotherapy in the presence of other risk factors. Based on these data and the clinical experience of panel members, several suggestions are made for a practical approach to prevent or manage nausea and vomiting due to chemotherapy regimens and radiation therapy.

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1. Introduction

Nausea and vomiting are among the most frequent toxicities associated with antineoplastic agents and radiation treatments used for oncological patients, with an estimated incidence rate of nearly 50% [1–3]. These burdensome adverse effects are highly distressing and debilitating for patients, profoundly affecting their quality of life and seriously compromising their compliance with anticancer therapy, with detrimental consequences [4,5].

Not only are nausea and vomiting the strongest concerns for patients and the most feared side effects of antitumoral treatments, but their occurrence also markedly impairs their own and their family's daily activities [1,5]. Also, health-care providers tend to underestimate the incidence of these symptoms, particularly delayed symptoms that do not develop immediately following the administration of therapy [6].

Nausea and vomiting related to antitumoral therapies are so important and characteristic that they are recognized as specific and well-defined conditions known as CINV (chemotherapy-induced nausea and vomiting) and RINV (radiotherapy-induced nausea and vomiting) for which there are dedicated guidelines by the Multinational Association of Supportive Care in Cancer and the European Society for Medical Oncology (MASCC/ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) [7–12].

The main international antiemetic guidelines classify the available single chemotherapeutic agents for anticancer treatment into four groups according to their 'level of emetogenicity', that is, the expected frequency of emesis induced in the absence of effective antiemetic prophylaxis [7,13].

Based on solid scientific evidence, the antiemetic guidelines recommend a specific antiemetic approach for each emetogenic level, which limits their applicability because the most common and effective anticancer treatments are combinations of different antineoplastic agents, not the administration of single drugs. With the exception of the doxorubicin and cyclophosphamide (AC) regimen for breast cancer, none of the guidelines has established emetic-risk classes for combination regimens, generally stating that the emetogenic potential of the combination

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Article highlights

- The international antiemetic guidelines only partially consider the emetogenic risk of combination chemotherapy regimens.
- Guidelines for treatment of RINV have not yet been updated to consider the use of modern technologies, taking into account different risks and the corresponding preventive approaches.
- The prevention of nausea and vomiting in the continuous administration of oral chemotherapy or targeted agents is another unmet need.
- Antiemetic therapy should be targeted to individual patients' needs, based on the emetogenic potential of their antineoplastic regimen, as well as patient- and disease-specific risk factors.
- New approaches in prevention and treatment of CINV and RINV may derive from new drugs, new combinations or the use of different formulations.

This box summarizes key points contained in the article.

would automatically correspond to the potential of the component drug with the highest emetic risk.

However, as learned through the results of clinical trials and daily clinical practice, the emetogenic potentials of the different agents included in a chemotherapy regimen may be additive (in the case of drugs with a moderate or high emetogenic potential), so that the nausea and vomiting induced by an antitumor drug varies according to its possible combination with other anticancer agents [14].

Moreover, the incidence and severity of CINV (and radiotherapy or chemoradiation as well) is influenced by a wide range of factors, including dosage, duration, schedule, and route of administration of the agents, disease characteristics, and individual patient characteristics, such as age, sex, previous experience of chemotherapy or emesis during pregnancy, motion sickness, history of alcohol use, etc. [9,15]. These important variables are explicitly overlooked by the international antiemetic guidelines, possibly because of a paucity of robust evidence [8,9,16]. As a consequence, the emetic risk classification made by international guidelines can be considered quite arbitrary.

RINV is a common side effect of radiation therapy (RT) that negatively impacts patient quality of life [17]. Importantly, this condition requires expensive supportive care and, in severe cases, can result in treatment delays with a negative effect on tumor control [18].

Both radiotherapy-related and patient-related risk factors contribute to the incidence and severity of RINV [18]. Such factors include the anatomic site of radiation, the volume of the irradiated organs, the radiation dose, and the fractionation schedule (radiotherapy-related factors), along with age, gender, and concurrent or recent chemotherapy (patient-related factors) [18–20].

The IGARR (Italian Group for Antiemetic Research in Radiotherapy) studies identified other relevant risk factors for RINV: concomitant radiochemotherapy, previous experience of vomiting caused by chemotherapy, site of irradiation (upper abdomen), and field size (>400 cm^2) seem to be significantly correlated with a higher incidence of RINV [19,20].

However, current antiemetic guidelines use only the site of irradiation to categorize the emetogenic potential of RT into four risk categories (high, moderate, low, and minimal) [8,9,16]. The same guidelines state that other known risk factors for the occurrence of RINV, such as radiation dose, fractionation, technique, field size, and concomitant chemotherapy, have not been considered in the stratification of the emetic risk levels of RT, recognizing only previous chemotherapy as a significant patient-related risk factor [8,16,17].

An Italian Expert Panel, involving specialists from a range of fields, was convened to discuss these unresolved issues. They collected data in a non-systematic way from randomized and controlled clinical trials in order to identify the incidence of CINV and RINV, with a particular attention to patient- and disease-related risk factors. The aim also was to highlight any unmet needs in the prevention and control of CINV and RINV, including disease- and patient-specific personalization of CINV risk, the importance of considering the emetogenic risk of combination chemotherapy, possible drug interactions, and the use of different routes of antiemetic drug administration. It should be noted that, while the authors have structured this manuscript by different cancer types, research into antiemetic therapy is often based on the emetogenicity of different antineoplastic regimens, rather than on specific diseases.

Based on the experience gained in clinical practice and reported in the most recent scientific literature available, the authors provide suggestions for the management of CINV and RINV. They describe the antiemetic approaches that they commonly offer to their own patients, under conditions not covered by the guidelines and/or to address limitations of these guidelines.

2. CINV in different pathological conditions

Table 1 briefly summarizes the epidemiology and key antitumor treatment strategies for the conditions covered in this section.

2.1. CINV in head and neck cancer patients

Cisplatin is commonly employed in patients with locally advanced disease (Table 1). Since cisplatin is classified as a highly emetogenic chemotherapy, one may expect a high risk of CINV in this disease, which is increased by the concurrent administration of RT. However, the emetic risk in this patient population is influenced by two factors which should be considered when identifying the individual predisposition to this side effect. On one hand, alcohol addiction, which is one of the main risk factors for head and neck cancers (HNC), is actually associated with a diminished risk of emesis. On the other hand, the role of human papillomavirus (HPV) as a causal factor is increasing and patients with HPV infection are much less prone to heavy alcohol intake, so this cancer population could have a higher risk of CINV [61]. The pattern of emetic symptoms has been depicted by Chan and colleagues in an interesting study evaluating different cisplatin schedules (Table 2) [62]. The incidence of vomiting was shown to be similar with single-day and multiple-day regimens, while the incidence of nausea was higher in patients receiving a single-day regimen than in those receiving a multiple-day regimen.

2.1.1. Unmet needs in the control of nausea and vomiting in this patient population

In HNC, the disease and its treatment can increase the overall risk of nausea and vomiting, making CINV and RINV particularly

Table 1. Epidemiology and common antitumor treatment strategies for some of the cancers discussed.

Cancer site	Epidemiology	Antitumor treatment
Head and neck	• 6th most common cancer subsite worldwide, with a gradual change in epidemiology in the last 10 years • The incidence of HPV-related oropharyngeal cancer is expected to continue increasing in the next 20 years [61]	• Curative or postoperative strategy in locally advanced disease: RT + systemic therapy (mainly cisplatin) • Recurrent/metastatic: Platinum- and cetuximab-based treatment first line
Lung	SCLC: • 15–20% of new cases of lung cancer worldwide [21] • Median survival: 16–24 months (limited-stage disease), 6–12 months (extensive-stage) [22,23]	• Most commonly prescribed first line: cisplatin + etoposide • NSCLC with EGFR mutations: EGFR inhibitors
Breast	• Most common cancer in women worldwide • Most patients diagnosed at early stage, but 7–10% diagnosed with metastatic breast cancer at initial presentation and as many as 70% of node-positive patients relapse [24,25]	• Numerous chemotherapeutic agents commonly used • No established standard regimen in the metastatic setting
Gastric	• 4th most commonly diagnosed cancer worldwide [26] • 2nd most common cause of cancer-related deaths worldwide [26] • 5-year survival 19–31%; median OS <1 year [27–29]	• Most widely used: fluoropyrimidine-based and platinum-based combination ± a 3rd drug (usually docetaxel or epirubicin) [30] • Capecitibine (a fluoropyrimidines) was non-inferior to fluorouracil (for PFS, OS) in clinical trials [31,32]
Pancreatic	• 13th most common cancer worldwide [33] • 4th leading cause of cancer death in the Western world [33] • 5-year survival, 9.7%; median OS, 4.4 months [33]	• Advanced disease: gemcitabine became the reference treatment after demonstrating improved OS compared with 5-fluorouracil [34] • Clinical activity has also been demonstrated with regimens incorporating irinotecan and oxaliplatin + 5-fluorouracil • FOLFOXIRI demonstrated longer PFS and ORR than gemcitabine [35] • Nanoparticle albumin bound-paclitaxel in combination with gemcitabine showed an improvement of PFS and response rate vs gemcitabine [93]
Biliary tract	• Uncommon in developed countries	• No accepted standard palliative regimen, due to insufficient robustness of studies [36] • Fluoropyrimidines, platinum agents, and gemcitabine have shown activity [36]
Colorectal	• 2nd leading cause of cancer-related death worldwide [37] • Accounts for ≈10% of all diagnosed cancer cases and ≈9% of all cancer-related deaths [37]	• Backbone of first-line chemotherapy: a fluoropyrimidine + irinotecan or oxaliplatin; biologicals (targeted therapy) are often added [38]
Soft-tissue sarcoma	• Incidence 1.8–5 cases/100,000 population/year; account for 1% of neoplasms in adults [39,40]	• For both adjuvant therapy and metastatic disease, chemotherapy is based on anthracyclines, dacarbazine, ifosfamide, and etoposide • Chemotherapy treatment schedules, including paclitaxel, gemcitabine, trabectedin, pazopanib, and olaratumab + doxorubicin, have been recently introduced [41]
Melanoma	• In the US: 5th most common cancer in men and 6th in women; in Italy: 2nd and 3rd most common cancer in men <50 years and women <50 years old, respectively [42] • Incidence has risen dramatically in recent years; however, mortality rate has not changed markedly. In Italy, accounts for 1.0% of all cancer-related deaths [43]	• Adjuvant therapy is historically based on interferon [110] • New immunotherapeutic options have recently been approved (e.g. ipilimumab, pembrolizumab, nivolumab) [44,45] • Numerous targeted treatments have also been developed [46]
Myelodysplastic syndrome (MDS)	• Incidence 3–12 cases/100,000 population/year, increasing with age [47,48] • Secondary disease (for which it is possible to identify previous hemopathy or exposure to myelotoxic substances) has worse prognosis and greater treatment resistance than primary disease	• Low/intermediate-1-risk: based on high-dose erythropoietin and/or transfusion and/or iron chelation • MDS with deletion of the long arm of chromosome 5, and resistant to first-line treatment with erythropoietin: immunomodulatory therapy (e.g. lenalidomide) • Intermediate-2- or high risk: supportive care + demethylating agents • Bone marrow transplantation is reserved for young patients without comorbidities (sometimes after pre-treatment with demethylating agents)
Acute myeloid leukemia (AML)	• Most common leukemia in adults • Incidence: 2–3/100,000 young adults; 13–15/100,000 people in their 60s or 70s [49] • 5-year survival in patients aged >65 years is <5% [49]	• Conventional treatment includes two phases: induction and consolidation • Induction: standard in young, medical fit patients = anthracycline (usually daunorubicin) + cytarabine + etoposide • Consolidation (once complete remission achieved): intermediate/high dose cytarabine + daunorubicin, or demethylating agents for patients without hyperleukocytosis • In frail patients, supportive therapy and hydroxyurea are indicated for the control of leukocytosis [50–52] • Demethylating agents can control disease without necessarily achieving complete remission, and therefore provide an important therapeutic option for patients whose options would otherwise consist only of supportive therapy alone [53]

(*Continued*)

Table 1. (Continued).

Cancer site	Epidemiology	Antitumor treatment
Acute lymphoblastic leukemia (ALL)	• The most common neoplasm in children; relatively rare in adults • Incidence: bimodal age distribution; peaks at 2–5 years and over 50 years [54] • More common in males (2:1 male:female) [55]	• Treatment is divided into phases: induction, consolidation, maintenance, and prophylaxis of CNS involvement [56]. The intensive therapeutic approach consists of active drugs with different mechanisms of action and administered at their maximum dose, to achieve a rapid reduction in the tumor mass and avoid inducing resistance • Induction: Combination treatment with multiple drugs (including vincristine, prednisone, and anthracyclines), commonly administered in combination with L-asparaginase or Peg-asparaginase and methotrexate, the latter agent administered by intrathecal injection for CNS prophylaxis [56] • Consolidation: drugs such as cytarabine or high-dose methotrexate, which have the advantage of being able to pass through the blood-brain barrier for CNS prophylaxis [56] • Maintenance: based on a combination of drugs such as 6-mercaptopurine and methotrexate, with monthly re-induction using vincristine and prednisone given for 2–3 years [56] • For patients deemed at high risk, therapy is intensified through bone marrow transplantation procedures [57,58] • TKIs have improved the prognosis for patients with the Philadelphia chromosome (a short chromosome 22 resulting from reciprocal translocation between chromosomes 9 and 22) [59] • CNS involvement (5–8% of patients): prophylaxis and treatment may include intrathecal administration (via lumbar puncture) of methotrexate, alone or in combination with cytarabine and prednisone, systemic treatment with high doses of cytarabine and/or methotrexate, and cranial irradiation [60]

CNS, central nervous system; EGFR, epidermal growth factor receptor; FOLFOXIRI, irinotecan, oxaliplatin, 5-fluorouracil, and leucovorin; HPV, human papillomavirus; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor; US, United States

challenging to manage. Dysgeusia, concomitant infections of the oral cavity, mucositis, sticky saliva, dysphagia, use of a feeding tube, and concurrent use of opioids to alleviate mucositis pain are all linked to an increased risk of emesis in HNC patients.

Overall, we are far from being able to completely control CINV and RINV in HNC patients.

2.2. CINV in lung cancer patients

Table 3 summarizes reported incidence rates of CINV associated with chemotherapy regimens used for small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [63–72].

In a randomized trial conducted in elderly patients with SCLC, as would be expected, the split-dose cisplatin plus etoposide course showed a significantly higher rate of nausea/vomiting toxicity compared with an oxaliplatin plus etoposide regimen: 97.2% vs 65.7%; $P = 0.001$ (Table 3) [68].

Although carboplatin is considered to be moderately emetogenic, in one trial a carboplatin plus etoposide regimen gave a very low incidence of grade 3–4 nausea and vomiting in patients with SCLC (0.2% and 0.7% respectively; Table 3) [69].

In the Hoosier Oncology Group study in patients with SCLC, the combination of split-dose cisplatin + ifosfamide + etoposide was associated with grade 3–4 nausea/vomiting toxicity in 13.0% of patients (grade 4 = 4.0%), which was higher than 8% rate in patients receiving a regimen without ifosfamide (grade 4 = 0.0%) (Table 3) [66].

Etoposide administered intravenously for 5 days or given *per os* for 21 days to patients with SCLC gives a low incidence of nausea/vomiting [73].

The epidermal growth factor receptor (EGFR) inhibitors (e.g. afatinib, erlotinib, gefitinib), used in patients with NSCLC and EGFR mutations, are characterized by a low rate of vomiting toxicity; osimertinib, which is selective for both EGFR-tyrosine kinase inhibitor sensitizing and T790M resistant mutations, rarely causes grade 3 nausea/vomiting (1.0%) [74].

In patients with metastatic NSCLC, the next-generation anaplastic lymphoma kinase inhibitors have demonstrated incidences of grade 3–4 nausea and vomiting of 1.1% (alectinib), 10.9% (ceritinib), and 1.4% (brigatinib), but a not negligible rate of all-grade CINV [75].

2.2.1. Unmet needs in the control of nausea and vomiting in this patient population

Nausea and vomiting are frequent adverse effects of many lung cancer treatments, including chemotherapy regimens and some targeted therapies, although the emetogenic risk differs between agents. A comprehensive intervention is needed to effectively manage and relieve these symptoms which further impact the quality of life of lung cancer patients already very debilitated by their pathology and cancer treatments. In particular, attention should be given to CINV management in patients receiving certain treatments, such as multiple-day schedules with cisplatin or treatment with some oral agents (including ceritinib or crizotinib) on a daily continuous schedule, where long-term low-grade nausea or vomiting may severely impact the patient's quality of life.

2.3. CINV in breast cancer patients

Table 4 presents an overview of reported incidence rates of CINV caused by multiple-day chemotherapy regimens commonly administered for different types of breast cancer [76–81].

Table 2. Emetic symptoms associated with different cisplatin schedules in head and neck cancer [62]a.

	Single-day regimen (n = 190)[b]	Multiple-day regimen (n = 45) [b]
Nausea		
Incidence, % pts		
Overall	73.7	48.9
Acute	33.6	42.2
Delayed	51.5	44.4
Trajectory		
Study day with most pts experiencing nausea/% pts	3/65.5	5/42.2
Study day with most severe nausea experienced/% pts (severity)[c]	2/24.3 (moderate), 8.5 (severe)	7/22.2 (moderate), 4.4 (severe)
Vomiting		
Incidence, % pts		
Overall	24.7	28.9
Acute	12.3	20.0
Delayed	221.1	20.0
Trajectory		
Study day with most pts experiencing vomiting/% pts	3/14.1	7/13.3
Study day with most severe vomiting experienced/% pts (severity)[d]	5/6.8 (grade 2), 1.7 (grade 3)	7/6.7 (grade 2), 4.4 (grade 3)

[a]Prospective observational study in 235 adult patients with head and neck cancer receiving cisplatin-based chemotherapy; 75.7% of pts were male, 81.7% were Chinese, and their mean age was 49.5 years.
[b]Single-day regimen: cisplatin 40 mg/m^2/day every 7 days or 100 mg/m^2/day every 2 days; Multiple-day regimen: cisplatin 20 mg/m^2/day for 4 days + concurrent 5-FU 1 g/m^2/day for 4 days.
[c]Moderate nausea: 4–6 episodes, severe nausea: 7–10 episodes.
[d]Grade 2 vomiting: 2–5 episodes in 24 h, grade 3 vomiting: ≥6 episodes in 24 h.
5-FU, fluorouracil; pts, patients

The oral version of cyclophosphamide, methotrexate and 5-fluorouracil with a concomitant 14-day administration of cyclophosphamide has shown moderate potential for causing nausea/vomiting [82].

Numerous other regimens were associated with a low emetogenic potential: oral hormonal therapy (tamoxifen, aromatase inhibitors, and megestrol) [83,84], targeted therapy with lapatinib or everolimus [85,86], palbociclib or ribociclib plus letrozole (as first-line therapy in metastatic hormone receptor-positive patients) [87,88], and abemaciclib plus letrozole/anastrazole [89].

2.3.1. Unmet needs in the control of nausea and vomiting in this patient population

CINV is still a critical issue in breast cancer patients. As outlined herein, numerous chemotherapeutic agents are commonly used for breast cancer, including new agents, and they have emetogenic potential, particularly when administered in combination regimens. The high risk for emesis in this group may be due not only to chemotherapy but also to patient-specific risk factors (female, often aged <50 years old, and anxious about their diagnosis and disease prognosis). Although guidelines recommend a triple antiemetic combination (consisting of a neurokinin 1 receptor antagonist (NK_1 RA), 5HT3 RA and dexamethasone ± olanzapine) in patients receiving an AC-based regimen, evidence-based guidelines lack recommendations that address CINV related to other antineoplastic schemes, highlighting the need for specific antiemetic strategies to control this unpleasant symptom.

2.4. CINV in upper gastrointestinal tract cancer patients

2.4.1. Gastric cancer

In the ToGA trial, the incidences of nausea and vomiting were similar in patients receiving trastuzumab plus chemotherapy and those receiving chemotherapy alone (Table 5) [90], demonstrating the minimal emetic potential of trastuzumab.

Vascular endothelial growth factor receptor 2 (VEGFR-2) plays a role in gastric cancer pathogenesis and progression. The RAINBOW study explored the role of ramucirumab, a monoclonal antibody directed against VEGFR-2, with or without paclitaxel. Overall survival was longer in the exploratory arm than the control arm, and the regimen was associated with a low rate of gastrointestinal toxicity, especially in terms of CINV (grade 3 nausea: 2.0%; Table 5) [91].

In addition to CINV, patients with this disease may also have an increased risk of nausea and vomiting due to the risk of esophageal-gastric obstruction.

2.4.2. Pancreatic cancer

In a trial in patients with pancreatic cancer, the rates of vomiting (grade 3–4) were 14.5% with FOLFOXIRI (irinotecan, oxaliplatin, 5-fluorouracil, and leucovorin) and 8.3% with gemcitabine [92]. In another trial, there was no grade 3–4 nausea and vomiting in patients receiving nanoparticle albumin-bound (nab)-paclitaxel in combination with gemcitabine; this result is unsurprising, given the low emetogenic potential of these agents [93].

In patients with pancreatic cancer, disease-related factors such as bowel obstruction and cachexia can influence the incidence and severity of CINV.

2.4.3. Biliary tract cancer

In one trial, when patients were randomly assigned to receive cisplatin (25 mg/m^2) plus gemcitabine (1,000 mg/m^2) on day 1 and 8 every 3 weeks or gemcitabine alone, rates of nausea and vomiting were very low in both arms (about 4.0–5.0%) [94]; given that cisplatin is considered to be highly emetogenic, regardless of dose, this result is surprising.

2.4.4. Unmet needs in the control of nausea and vomiting in the upper gastrointestinal tract cancer population

Overall, the most common combination regimens used for upper gastrointestinal malignancies are characterized by a

Table 3. Incidence rates of nausea and vomiting induced by multiple-day chemotherapies commonly used for lung cancer in clinical practice, as reported in the scientific literature.

Study [reference]	Multiple-day regimen	Relevant patient characteristics	Incidence (% patients)		
			Nausea	Vomiting	Nausea and vomiting
SCLC					
Loehrer et al. (1995) [66]	Split-dose cisplatin (20 mg/m^2) + ifosfamide (1.2 g/m^2) + etoposide (75 mg/m^2), days 1 to 4, every 21 days	Patients with extensive-disease SCLC	–	–	13.0 (Grade 3–4) 4.0 (Grade 4)
	Split-dose cisplatin (20 mg/m^2) + etoposide (100 mg/m^2) days 1 to 4, every 21 days	Patients with extensive-disease SCLC	–	–	8.0 (Grade 3–4) 0.0% (Grade 4)
Gregor et al. (1997) [64]	Doxorubicin (day 1) + cyclophosphamide (day 1) + etoposide (days 1, 3, 5)	Patients with previously untreated SCLC	–	–	74.0 (All grades) 14.0 (Grade 3–4)
Treat et al. (2004) [72]	Topotecan alone at a dose of 1.5 mg/m^2/day on days 1-5	Patients with performance status 0-1	4.0 (Grade 3)	2.0 (Grade 3)	–
Lara et al. (2009) [65]	Cisplatin + etoposide	Caucasian population	11.0 (Grade 3)	9.0 (Grade 3)	–
Socinski et al. (2009) [69]	Carboplatin + etoposide	Chemotherapy-naïve patients with extensive-disease SCLC	0.2 (Grade 3–4)	0.7 (Grade 3–4)	–
Pu et al. (2013) [68]	Split-dose cisplatin (25 mg/m^2 days 1–3) + etoposide (80 mg/m^2 days 1–5), every 21 days	Elderly patients with extensive-disease SCLC	–	–	97.2 (All grades)
	Oxaliplatin (130 mg/m^2 day 1) + etoposide (80 mg/m^2 days 1–5), every 21 days	Elderly patients with extensive-disease SCLC	–	–	65.7 (All grades)
Sun et al .(2016) [70]	Cisplatin + etoposide	Chinese population	46.7 (All grades) 2.7 (Grade 3–4)	42.0 (All grades) 4.0 (Grade 3–4)	–
Tiseo et al. (2017) [71]	Split-dose cisplatin (25 mg/m^2 on days 1 to 3) + etoposide	Treatment-naïve patients with extensive-disease SCLC	4.9 (Grade 3–4)	2.9 (Grade 3–4)	–
NSCLC					
Camidge et al. (2012) [63]	Oral crizotinib 250 mg BID	Patients with ALK-positive NSCLC	56.0 (All grades) <1.0 (Grade 3–4)	39.0% (All grades) <1.0 (Grade 3–4)	–
Planchard et al. (2017) [67]	Oral dabrafenib 150 mg BID + oral trametinib 2 mg once per day	Patients with previously untreated metastatic BRAF^{V600E}-mutant NSCLC	–	–	35.0–40.0 (Grade 1–2) 0.0 (Grade 3)

ALK, anaplastic lymphoma kinase; BID, twice daily; BRAF: human gene encoding the protein B-Raf; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 4. Incidence rates of nausea and vomiting induced by multiple-day chemotherapies commonly used for breast cancer in clinical practice, as reported in the scientific literature.

Study [reference]	Multiple-day regimen	Relevant patient characteristics	Incidence (% patients)		
			Nausea	Vomiting	Nausea and vomiting
Burnell et al. (2010) [77]	Epirubicin 60 mg/m^2 IV (days 1 and 8) + fluorouracil 500 mg/m^2 IV (days 1 and 8) + cyclophosphamide 75 mg/m^2 orally (days 1–14)	Patients with axillary node-positive or high-risk node-negative breast cancer after lumpectomy or mastectomy	5.0 (Grade 3–4)	5.6 (Grade 3–4)	–
Baselga et al. (2012) [76]	Everolimus + exemestane	Postmenopausal women with ER-positive, HER2-nonamplified advanced breast cancer	27.0 (All grades) <1.0 (Grade 3–4)	14.0 (All grades) <1.0 (Grade 3–4)	–
Tawfik et al. (2013) [81]	Oral capecitabine 1,000 mg/m^2 BID on days 1–14 + oral vinorelbine 60 mg/m^2 on days 1 and 8	Patients with HER2-negative metastatic breast cancer	7.1 (Grade 3)	10.7 (Grade 3)	–
Pivot et al. (2015) [80]	Lapatinib + capecitabine	Patients with HER2-positive metastatic breast cancer	29.0 (All grades) 1.0 (Grade 3)	12.0 (All grades) 1.0 (Grade 3)	–
Cazzaniga et al. (2016) [78]	Metronomic oral capecitabine 500 mg TID a day + vinorelbine 40 mg three times a week	Hormone receptor-positive/HER2-negative patients	–	–	0.8 (Grade ≥3) in first-line 1.2 (Grade ≥3) in second-line
Harbeck et al. (2017) [79]	Oral capecitabine 1,250 mg/m^2 BID for 14 days	Patients with metastatic breast cancer	41.0 (All grades) 2.0 (Grade 3–4)	30.0 (All grades) 2.0 (Grade 3–4)	–

BID, twice daily; ER, estrogen receptor; HER2, human epidermal growth factor receptor type 2; IV, intravenously; TID, three times a day

moderate gastrointestinal toxicity profile, especially when oxaliplatin is included instead of cisplatin [95].

However, patients suffering from upper gastrointestinal cancer may be particularly susceptible to complications arising from poorly controlled CINV, such as dehydration, nutrient depletion, metabolic imbalances, and performance status deterioration, all of which may impair their quality of life. These conditions sometimes interfere with chemotherapy by causing dose reductions, delays, or discontinuations [96]. Therefore, CINV can exacerbate concurrent symptoms caused by the disease itself, and is more likely to develop when combination chemotherapy regimens are used.

2.5. CINV in colorectal cancer patients

According to the 2016 MASCC/ESMO guideline, the agents used in the treatment of metastatic colorectal cancer (CRC) are classified as moderate risk (irinotecan and oxaliplatin), low risk (5-fluorouracil), and minimal risk (bevacizumab and cetuximab) for CINV causation [16]. The FOLFOXIRI regimen may be more appropriately considered as moderate/high risk; however, being a combination chemotherapy regimen, the emetogenic potential of this combination is not specified in the antiemetic guidelines.

The proportion of patients who experienced nausea and vomiting while receiving multiple-day regimens in clinical studies are shown in Table 6 [97–105]. Other possible risk factors for CINV in colorectal cancer patients are bowel obstruction or electrolyte imbalances.

2.5.1. Unmet needs in the control of nausea and vomiting in this patient population

International guidelines recommend using 5-HT$_3$ RA (day 1) in combination with dexamethasone (days 1–3) to prevent CINV associated with chemotherapy with moderate emetic risk, with the exception of carboplatin, for which guidelines recommend using a 3-drug antiemetic regimen, including an NK$_1$ RA [8,16]. The most recent guidelines from the NCCN recommend that NK$_1$ RAs should be given selectively to patients with additional risk factors or to those who experienced CINV during previous therapy while receiving two-drug antiemetic medication [9].

There is a paucity of evidence from the literature on the management of delayed nausea and vomiting in patients treated with oxaliplatin- or irinotecan-based chemotherapy regimens.

In a prospective study, oxaliplatin-induced delayed nausea in 10% of patients. The use of a 5-HT$_3$ RA and dexamethasone prior to oxaliplatin resulted in excellent control of nausea and vomiting during the 24 h after chemotherapy (complete response in 90% of patients). However, without further antiemetic treatments, only 54% had a complete response during the delayed phase [106]. Therefore, routine antiemetic prophylaxis for delayed nausea and vomiting following oxaliplatin-based chemotherapy should be recommended. The use of dexamethasone on days 2 to 3, granisetron transdermal patch 24 h before chemotherapy or palonosetron on day 1 of therapy can be considered [16,107].

A 2011 study demonstrated that irinotecan has a modest tendency to cause delayed nausea and vomiting. Without any

Table 5. Incidence rates of nausea and vomiting induced by multiple-day chemotherapies commonly used for gastric cancer in clinical practice, as reported in the scientific literature.

Study [reference]	Multiple-day regimen	Relevant patient characteristics	Incidence (% patients)	
			Nausea	Vomiting
Bang et al. (2010) [90]	21 day cycles: Capecitabine (oral 1000 mg/m^2 BID, days 1–14) OR fluorouracil (IV infusion 800 mg/m^2/day) + cisplatin (IV infusion 80 mg/m^2 on day 1) + trastuzumab IV infusion, 8 mg/kg on day 1 of the first cycle, then 6 mg/kg on day 1 of subsequent cycles)	Patients with HER2-positive advanced gastric or gastro-esophageal junction cancer	67 (All grades) 7 (Grade 3–4)	50 (All grades) 6 (Grade 3–4)
	21 day cycles: Capecitabine (oral 1000 mg/m^2 BID, days 1–14) OR fluorouracil (IV infusion 800 mg/m^2/day) + cisplatin (IV infusion 80 mg/m^2 on day 1)	Patients with HER2-positive advanced gastric or gastro-esophageal junction cancer	63 (All grades) 7 (Grade 3–4)	46 (All grades) 8 (Grade 3–4)
Wilke et al. (2014) [91]	28-day cycles: Ramucirumab 8mg/kg (IV days 1, 15), paclitaxel 80mg/kg (IV days 1, 8, 15)	Patients with previously- treated advanced gastric or gastro-esophageal junction adenocarcinoma	33 (Grade 1–2) 2 (Grade 3–4)	24 (Grade 1–2) 3 (Grade 3–4)
	28-day cycles: Placebo (IV days 1, 15), paclitaxel 80mg/kg (IV days 1, 8, 15)		30 (Grade 1–2) 2 (Grade 3–4)	17% (Grade 1–2) 4 (Grade 3–4)

BID, twice daily; HER2, human epidermal growth factor receptor 2; IV, intravenous.

further antiemetic treatment, most patients (82%) do not experience delayed emesis or require rescue antiemetics. Routine prophylaxis for delayed emesis following irinotecan does not appear to be warranted. As observed in other studies, patients not achieving a complete response during the first 24 h after chemotherapy may have a higher risk of delayed emesis [108]. Therefore, patients not achieving a complete response during the first 24 h should receive prophylaxis for delayed nausea and vomiting similar to that used for patients treated with oxaliplatin-based regimes.

2.6. CINV in gynecological cancer patients

Many of these patients are treated with highly emetogenic (cisplatin based) and moderately emetogenic (carboplatin based) chemotherapy. Additionally, factors that can increase their risk of emesis include that these patients are female, and many of them have abdominal disease (e.g. ovarian or cervical cancer) and are at increased risk for bowel obstruction. Pain management medications such as opioid analgesics, which are often required in these patients, can also worsen nausea and vomiting.

In a post-hoc subset analysis of two trials, the fixed-combination antiemetic netupitant/palonosetron plus dexamethasone was effective at preventing CINV in patients with gynecological cancers who were receiving cisplatin- or carboplatin-based chemotherapy; the proportion of patients experiencing no significant nausea was >90% in the acute phase and >80% in the delayed phase [109].

2.7. CINV in soft-tissue sarcoma patients

In our clinical experience, the emetogenic potential of chemotherapy for soft-tissue sarcoma (STS) varies depending on whether they are used as single agents (e.g. moderate for anthracyclines, ifosfamide, and trabectedin, low for paclitaxel and pazopanib) or as combination regimens: high for ifosfamide + epirubicin, etoposide + ifosfamide, and doxorubicin + dacarbazine; moderate for ifosfamide + epirubicin and gemcitabine + docetaxel. The addition of olaratumab to doxorubicin or its use as maintenance monotherapy does not require a modification of the antiemetic prophylaxis, since olaratumab is characterized by a low emetogenic potential [9].

According to the ASCO, MASCC/ESMO and NCCN guidelines, the recommended antiemetic prophylaxis for a highly emetogenic chemotherapy includes the use of three drugs (dexamethasone, single dose of 5-HT$_3$ RA and NK$_1$ RA) in the acute phase and, in the late phase, of dexamethasone (from day 2 to day 4) + aprepitant, depending on the NK$_1$ RA used in the acute phase [8,9,16].

Alternatively, in patients receiving moderate emetic risk chemotherapy, the combination of 5-HT$_3$ RA + dexamethasone is used as CINV prophylaxis during the acute phase and dexamethasone alone is administered in the late phase (days 2 and 3) [8,9,16].

2.7.1. Unmet needs in the control of nausea and vomiting in this patient population

Sometimes, STS patients are treated with alternating combination chemotherapies, resulting in the frequent occurrence of intercycle nausea. The issue of how best to minimize intercycle nausea is still a matter of debate, as is the optimal approach to rescue therapy in order to maximize adherence to chemotherapy. Furthermore, STS patients are often young adults; their young age and possible high anxiety regarding prognosis and treatment outcomes can increase their risk of CINV.

2.8. CINV in melanoma patients

Adjuvant therapy is historically based on interferon for which, depending on the dosage, antiemetic prophylaxis can be avoided [110]. Similarly, no specific prophylaxis is required in patients receiving newer immunotherapy agents (ipilimumab, pembrolizumab, nivolumab, and their combinations) [8,9,16].

Targeted treatments, such as BRAF inhibitor monotherapy (dabrafenib, vemurafenib) are deemed to have a low or minimal emetogenic potential and therefore require the administration of a single antiemetic drug for acute phase prophylaxis (dexamethasone, 5-HT$_3$ RA, or metoclopramide) and no therapy in

Table 6. Incidence rates of nausea and vomiting induced by multiple-day chemotherapies commonly used for colorectal cancer in clinical practice, as reported in the scientific literature.

Study [reference]	Multiple-day regimen	Relevant patient characteristics	Incidence (% patients)	
			Nausea	Vomiting
5-Fluorouracil-based regimens				
Buroker et al. (1994) [98]	Mayo Clinic regimen	Patients with advanced CRC	60.0 (All grades) 1.8 (Grade 3–4)	24.0 (All grades) 1.4 (Grade 3–4)
de Gramont et al. (1997) [99]	De Gramont regimen	Patients with advanced CRC	61.0 (All grades) 9.0 (Grade 3–4)	43.0 (All grades) 8.0 (Grade 3–4)
Oxaliplatin-based regimens				
André et al. (2004) [97]	FOLFOX	Patients in the postoperative adjuvant setting for stage II or III CRC	73.7 (All grades) 4.8 (Grade 3)	47.2 (All grades) 5.3 (Grade 3)
Tournigand et al. (2004) [103]	FOLFOX followed by FOLFIRI in first-line therapy	Patients with advanced CRC	3.0 (Grade 3)	3.0 (Grade 3)
Giantonio et al. (2007) [102]	FOLFOX	Previously treated mCRC	–	2.8 (Grade 3) 0.4 (Grade 4)
Irinotecan-based chemotherapy regimens				
Fuchs et al. (2007) [101]	FOLFIRI	Previously untreated mCRC patients	8.8 (Grade ≥3)	8.8 (Grade ≥3)
	Modified bolus irinotecan, 5-fluorouracil, leucovorin	Previously untreated mCRC patients	7.3 (Grade ≥3)	7.3 (Grade ≥3)
	Irinotecan + capecitabine	Previously untreated mCRC patients	18.4 (Grade ≥3)	15.6 (Grade ≥3)
Falcone et al. (2007) [100]	Infusional FOLFIRI	Patients with unresectable mCRC	39.0 (Grade 1) 1.0 (Grade 3)	23.0 (Grade 1) 1.0 (Grade 3)
Van Cutsem et al. (2009) [104]	Cetuximab + FOLFIRI	Patients with mCRC	–	4.7 (Grade 3–4)
Van Cutsem et al. (2012) [105]	Aflibercept + FOLFIRI	Patients with mCRC previously treated with an oxaliplatin-based regimen	53.4 (All grades) 1.8 (Grade 3)	32.9 (All grades) 2.6 (Grade 3)
FOLFOXIRI regimen				
Falcone et al. (2007) [100]	FOLFOXIRI	Patients with unresectable mCRC	40.0 (Grade 1) 6.0 (Grade 3)	20.0 (Grade 1) 7.0 (Grade 3)

CRC, colorectal cancer; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; mCRC, metastatic colorectal cancer

the delayed phase [8,9,16]. The mitogen-activated protein kinase inhibitors cobimetinib and trametinib are not covered in the current guidelines; however, as they also have low-to-minimal emetogenic risk, the same anti-emetic approach may be used.

In light of recent innovations, the role of chemotherapy in melanoma is more marginal and the drugs used, such as dacarbazine (high emetic risk), fotemustine and temozolomide (moderate) and taxanes (low), should be administered with appropriate prophylaxis according to the emetogenic risk as described in the existing guidelines [8,9,16].

2.8.1. Unmet needs in the control of nausea and vomiting in this patient population

The impact of therapeutic innovation on the management of CINV has been much lower in melanoma than in other cancers, given the limited emetic effect of the new drugs used.

2.9. CINV in myelodysplastic syndrome patients

Myelodysplastic syndrome (MDS) is a heterogeneous group of hematologic diseases resulting from a clonal disorder of pluripotent hematopoietic stem cells [111,112]. MDS is classified as either primary (*de novo*) or secondary; in the latter, it is possible to identify a previous hemopathy or exposure to myelotoxic substances.

Drugs used in low-risk/intermediate-1 risk MDS and immunomodulatory agents such as lenalidomide (Table 1) are not emetogenic. Demethylating agents (Table 1) are characterized by a moderate emetic risk. Nausea induced by these drugs may be managed with a prophylactic regimen of oral antiemetic agents (ondansetron/granisetron/metoclopramide) before starting on the 7 days of subcutaneous chemotherapy administration.

2.9.1. Unmet needs in the control of nausea and vomiting in this patient population

Many patients with myelodysplasia are elderly and already have concomitant conditions that negatively impact their quality of life and require daily administration of multiple medications. For these patients, offering antiemetic prophylaxis via an alternative route to oral therapy may be convenient and advantageous.

2.10. CINV in acute myeloid leukemia patients

The number of studies on nausea and vomiting in patients with acute myeloid leukemia (AML) is limited (Table 7) [113]. It has been observed that more than 70% of patients have no nausea in the first 24 h of chemotherapy and about 50% experience emesis in the following days [114]. Mattiuzzi and colleagues compared the effect of ondansetron and palonosetron in patients treated with high doses of cytarabine, and found no significant difference in the incidence of acute nausea between the two treatment groups; however, patients treated with palonosetron had significantly less delayed nausea compared with the group receiving ondansetron [114].

According to recent guidelines, in patients receiving moderately or highly emetogenic multiday chemotherapies (fludarabine in combination with cytosine arabinoside and idarubicin at intermediate/high doses), it is advisable to use an NK_1 RA in conjunction with a 5-HT_3 RA and dexamethasone [8,9,16]. However, prolonged use of dexamethasone should be avoided because of the well-established side effects (insomnia, agitation, etc.) and increased susceptibility to infections [115].

In older patients treated with demethylating agents, nausea is managed with prophylactic antiemetic treatment using ondansetron, granisetron, or metoclopramide administered intravenously or orally before and during the course of chemotherapy.

2.10.1. Unmet needs in the control of nausea and vomiting in this patient population

Because of the advanced age of most AML patients, they frequently have concomitant diseases requiring multiple oral medications, which can negatively affect their quality of life. For these patients, the availability of an alternative route to oral therapy would therefore be useful.

Breakthrough emesis is still difficult to manage and is often irreversible. In such cases, antiemetic administration via the oral route is not feasible, so intravenous, transdermal, or rectal administration is required.

2.11. CINV in acute lymphoblastic leukemia patients

In patients with acute lymphoblastic leukemia (ALL), the intensive therapeutic approach consists of active drugs with different mechanisms of action and administered at their maximum dose, to achieve a rapid reduction in the tumor mass and avoid inducing resistance.

There is limited information on nausea/vomiting in hematologic diseases, particularly concerning CINV in ALL. Nausea is managed with prophylactic antiemetics (ondansetron, granisetron, or metoclopramide) administered intravenously or orally before and during chemotherapy [10,116,117].

The ondansetron and aprepitant combination appears to be effective at preventing nausea and vomiting in patients undergoing multiday moderately/highly emetogenic chemotherapy [10,116,117].

Table 7. Response rates to antiemetic regimens in patients with hematologic malignancies (including acute myeloid leukemia) receiving multiple-day chemotherapy, as reported in the scientific literature.

Study [reference]	Patient characteristics	Number of patients	Antiemetic regimen	Absence of nausea and vomiting
Musso et al. (2009) [113]	Hematologic malignancy - Non-Hodgkin lymphoma - Hodgkin disease - Acute myeloid leukemia - Solid tumor	46	Palonosetron and dexamethasone before chemotherapy	80%
			Ondansetron and dexamethasone before chemotherapy	60%

3. RINV in different pathological conditions

3.1. RINV in patients with brain, head and neck, thorax and upper trunk cancers

3.1.1. Overview

RINV is a common and troublesome side effect experienced by patients undergoing RT. It is commonly believed to be an exclusive or, at least, prevalent symptom of abdomen RT, but a significant percentage of patients undergoing RT in other parts of the body, like head and neck and thorax, also experience RINV. In this context, at the beginning of the 1990s, Scarantino *et al*. suggested that serotonin could play a role in mediating RINV induced by RT in the upper body: they documented an increase in urinary levels of the serotonin active metabolite 5-hyroxyindoleacetic acid following emetogenic upper and mid hemibody irradiation, and the efficacy of 5-HT_3 RAs in the prevention of RINV [118,119].

3.1.2. Radiation therapy and incidence rates of RINV

According to the MASCC Consensus Conference on Antiemetic Therapy, the emetogenic potential of radiation alone is classified as 'low' (30–60%) for RT of the brain, head and neck, and thorax, and as 'minimal' for RT of the breast (<30%) [11,12]. However, these guidelines were prepared before the implementation of intensity-modulated radiation therapy (IMRT) and have not been significantly updated since 2016 [16].

In the IGARR study, a prospective observational multicenter trial of 1020 patients treated with RT (with or without chemotherapy) at 45 Italian radiation oncology centers, nausea, and vomiting were most common in patients treated for brain cancer, followed by those treated for cancer of the thorax, head and neck, and breast (Table 8) [19].

The pathophysiological mechanism of RINV in patients with brain cancer or HNC is probably linked to a release of serotonin from the chemoreceptor trigger zone in the brainstem (the area postrema and dorsal vagal complex) when it is included in the radiation portals [120–122]. In Rosenthal's experience [120], the incidence of nausea and vomiting is associated with irradiation of the area postrema at a dose >36 Gy for patients treated using IMRT [120]. This observation was confirmed by Ciura et al. [122], who suggested that RINV developed around the second week of treatment, with a possible correlation between dose and toxicity in the range of 15 Gy to 25 Gy. In both these experiences, the incidence of RINV in patients with HNC was higher when IMRT was combined with emetogenic chemotherapy compared with the incidence typically reported for the same chemotherapy used in combination with 3D conformational RT or compared with IMRT alone (Table 8). Kocak-Uzel and colleagues [123] have also shown that, in patients with HNC receiving definitive IMRT, the development of RINV was related to the dose of radiation delivered to specific CNS non-target structures, including the area postrema and dorsal vagal complex [123]. Practical contouring guidelines of brainstem structures involved in the occurrence of RINV (according to a magnetic resonance-based atlas) have been recently published [124].

Unlike what we know about the causes of RINV in brain and head and neck RT, the cause and mechanisms of RINV are still unclear in patients undergoing chest RT when the upper abdomen is not included in the treatment volume. The irradiated volume is one determinant of risk for RINV, in addition to irradiation site, gender, previous or concurrent chemotherapy. IMRT and volumetric modulated arc therapy (VMAT), which are increasingly used for cancer treatment, can reduce acute toxicity by decreasing the radiation doses to uninvolved healthy tissue near the tumor targets; however, previously unaffected tissues, such as the celiac plexus and gastroesophageal junction (GEJCP) for breast or thorax cancers, may receive clinically significant doses that lead to side effects such as nausea and vomiting [125].

After having observed unanticipated RINV in some breast cancer patients treated with postoperative upper trunk IMRT-VMAT, an Italian study group hypothesized that these symptoms could be attributed to an unduly dispensed dose to the upper abdominal anatomical structures underlying the planning target volume [125]. In a retrospective analysis of standard weekly management visit forms, these researchers found >60% of patients with breast cancer experienced acute RINV (Table 8). Using the original planning computed tomography (CT) scans, the researchers retrospectively contoured a volume containing the anatomical structures relevant to the emesis-related vagal parasympathetic afferent pathways, such as the GEJCP. RINV was significantly related to a maximal dose >10 Gy and a mean dose <3 Gy to the GEJCP ($P < 0.001$). The development of RINV was weakly correlated with irradiation of the left breast ($P < 0.01$) and a planned treatment volume >700 cm^3 ($P < 0.03$), but no correlation was observed with age, previous systemic therapy, or nodal irradiation [125].

Palliative hypofractionated radiotherapy (8 Gy/1 fraction or 20 Gy/5 fractions) of the spine has been classified as a moderately emetogenic treatment schedule. Dexamethasone monotherapy given on the day of irradiation is not sufficient to control delayed nausea and vomiting; a prospective pilot study suggested that the combination of aprepitant and granisetron may provide more effective prophylaxis [126].

Table 8. Incidence rates of nausea and vomiting induced by radiation therapy in patients with brain, head and neck, thorax, and upper trunk cancers, as reported in the scientific literature.

Study [reference]	Regimen	Relevant patient characteristics	Incidence (% patients)	
			Nausea	Vomiting
IGARR study, Maranzano et al. (2010) [19]	Radiotherapy or radiotherapy + chemotherapy	Brain cancer	35.0	19.1
		Thorax cancer	30.0	17.7
		Head and neck cancer	28.4	11.9
		Breast cancer	22.8	6.0
Rosenthal et al. (2008) [120]	IMRT	Head and neck cancer	76	38
	IMRT + cisplatin-based chemotherapy	Head and neck cancer	98	68
Lazzari et al. (2017) [125]	Adjuvant VMAT	Breast cancer	55 (all grade 1 or 2)	7 (all grade 1)

IGARR, Italian Group for Antiemetic Research in Radiotherapy; IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arch therapy.

3.1.3. Unmet needs in the control of nausea and vomiting in this patient population

The literature on RINV related to the new radiation techniques, such as IMRT and VMAT, is still not extensive. The VMAT modality has become an increasingly implemented radiation technique for cancer, but the paths of the arc beams often cross healthy structures that would not be directly irradiated if using 3D-conformational RT techniques. This effect is responsible for a new acute morbidity profile not seen before the IMRT era [125]. Well-designed prospective randomized trials are needed to investigate (1) how modern radiotherapy modalities induce these symptoms, (2) the maximum doses' targets can receive to avoid these side effects, (3) suitable supportive therapy to prevent or minimize discomfort in patients. Such studies will help to identify treatment planning solutions that can be integrated into future IMRT VMAT treatments.

3.2. RINV in gastrointestinal cancer patients

To date, the largest observational studies on RINV have been conducted by the IGARR group and evaluated a total of 1,934 patients [19,20]. Within these studies, 29% of the patients who received RT to the upper abdomen reported vomiting and 56% experienced nausea. In a smaller observational series, 63% of patients treated with abdominal or pelvic RT experienced nausea [127]. In a prospective study including 45 patients with gastrointestinal cancers undergoing abdominal and/or pelvic RT with curative or palliative intent, alone or with concomitant chemoradiotherapy, nausea was reported in 83% of patients and emesis in 54% [128].

3.2.1. Unmet needs in the control of nausea and vomiting in this patient population

The neurotransmitter serotonin is thought to be the most important chemical mediator of RINV. The gastrointestinal tract houses approximatively 95% of the body's serotonin and is an important anatomic region related to RINV [129]. According to antiemetic practice guidelines, radiation treatments to the upper abdomen are considered moderately emetogenic, with an estimated risk of 60–90% [12,16]. In patients receiving radiotherapy with moderate emetogenic risk, antiemetic prophylaxis using a 5-HT_3 RA is recommended, with the option of combining this with a short course (day 1–5) of dexamethasone [12,16].

As stated in the guidelines [12,16], although all chemotherapy drugs associated with RT for the treatment of cancer of this body region belong to the intermediate-low risk class, the antiemetic prophylaxis strategy should take into account the intermediate risk of RT itself [12,16].

Over the last two decades, the most extensively used antiemetics for RINV in clinical practice have been the 5-HT_3 RAs. Many trials have reported that, in patients receiving upper abdominal irradiation, 5-HT_3 RAs provided significantly greater protection against RINV than metoclopramide, phenothiazines, or placebo [130,131].

The side effects of 5-HT_3 RAs are generally mild and mainly consist of headache, constipation, diarrhea, and weakness. Furthermore, it has been suggested that these agents may reduce the frequency of diarrhea, a debilitating adverse effect of RT for acute gastrointestinal cancers [132].

The efficacy of antiemetic drugs in the treatment of RINV has been studied in a few randomized clinical trials, and it seems clear that the prevention of RINV must be preferred to a rescue intervention [132].

However, the appropriate duration of antiemetic prophylaxis for patients receiving fractionated RT has not been determined, since there are no randomized trials comparing a five-day course of 5-HT_3 RA treatment with a more prolonged period [132]. Nonetheless, according to a systematic review including 25 randomized and non-randomized trials, 5-HT_3 RAs appear to be most commonly administered for the entire phase of radiotherapy [132]. In short, the duration and the timing of therapy with this class of antiemetics have not yet been defined and are additional unmet needs in this field of research [132].

4. Suggestions for a practical approach to CINV and RINV

The therapeutic armamentarium offers several options and strategies to relieve CINV and RINV for particular cases and conditions commonly observed in clinical practice, basing on innovative drugs or on new formulations of known compounds. For what concerns the latter case, we focused our attention on transdermal granisetron as an example of possible advantages given by an 'old' drug given in a different way, applied in different diseases. Based on the authors' experience in managing CINV and RINV, several suggestions are provided below.

We recommend that antiemetic therapy should be targeted to the patient's needs, based on the emetogenic potential of their antineoplastic regimen, as defined by the antiemetic guidelines, along with the characteristics of the disease and the patient's risk factors.

4.1. HNC treated concurrently with chemotherapy and RT

Patients with HNC often experience swallowing difficulties related to tumor location and treatment consequences, which may require a feeding tube in the last weeks of treatment. In such circumstances, oral formulations of antiemetic drugs are often difficult to administer, affecting compliance. Using an alternative route of antiemetic administration could overcome this problem, and deserves further clinical trials.

The transdermal formulation of the 5-HT_3 RA granisetron avoids the oral route of administration and could improve the management of CINV in patients with HNC, by improving compliance in patients with swallowing difficulties, allowing them to receive optimal antiemetic dose intensity and protection from symptoms. This form of antiemetic therapy could also benefit patients who are experiencing symptoms related to RT (sticky saliva, mucositis, tube feeding, etc.) by providing sustained protection against nausea and vomiting without the need to swallow a tablet or capsule. Further studies are needed to better position the use of transdermal granisetron in the prevention and treatment of CINV in patients with HNC, including evaluating its effects on quality of life.

Table 9. Efficacy of quadruple versus triple antiemetic therapy in patients receiving highly emetogenic chemotherapy.

Study [reference]	Antiemetic therapy	Relevant patient characteristics	Antiemetic efficacy (% patients)	
			No nausea in first 24 hours	Complete response rate
Navari et al. (2017) [134]	5-HT3 RA + NK1 RA + dexamethasone + olanzapine	Chemotherapy-naïve patients with malignancies receiving cisplatin or cyclophosphamide + doxorubicin chemotherapy (N = 380)	74 ($P = 0.002$)*	Acute: 86 ($P < 0.001$)* Delayed: 67 ($P = 0.007$)*
	5-HT3 RA + NK1 RA + dexamethasone + placebo		45	Acute: 65 Delayed: 52
Oflazoglu et al. (2018) [135]	Palonosetron + aprepitant + dexamethasone + metoclopramide	Chemotherapy-naïve patients with breast cancer undergoing highly emetogenic chemotherapy (N = 97)	–	45.8 ($P = 0.038$)*
	Palonosetron + aprepitant + dexamethasone		–	26.5

*P-values vs triple antiemetic therapy.
5-HT3, serotonin; NK1, neurokinin 1; RA, receptor antagonist.

4.2. Upper gastrointestinal malignancies

For the most used RT regimens in these conditions, the use of 5-HT_3 RAs and dexamethasone seems to be adequate to control RINV. For schedules with extended exposure to chemotherapy, there may be potential for 5-HT_3 RAs characterized by a prolonged action, such as the granisetron transdermal patch, to be used. However, studies are needed to explore this potential.

4.3. STS

The granisetron transdermal patch may be considered appropriate in patients with sarcoma undergoing highly emetogenic polychemotherapy administered over several days, particularly in patients who have difficulty taking oral medications or have a previous experience of nausea and vomiting not adequately controlled by the prescribed antiemetic prophylaxis.

4.4. MDS

The transdermal formulation of granisetron may be an alternative route to oral therapy. It could be applied on the day before demethylating therapy commences and kept in place for up to 7 days.

This formulation does not require any special recommendations and is extremely useful for elderly patients with swallowing dysfunction, mucositis, gastropathy, and anorexia, and may help to improve the quality of life of patients who are already taking multiple oral medications.

4.5. Brain, head and neck, thorax and upper trunk cancers treated with RT

In everyday practice, patients treated exclusively with RT on the brain usually receive prophylactic dexamethasone.

RINV prophylaxis is not usually prescribed to patients irradiated for breast or chest neoplasms (lung, thymus, and upper esophagus); these patients usually receive antiemetics only at the onset of symptoms. When chemotherapy is associated with radiotherapy, RINV prophylaxis should follow the guidelines provided for the most emetogenic treatment. In these cases, the administration of transdermal granisetron is preferred in patients with swallowing difficulties.

4.6. Gastrointestinal cancer treated with RT

The AVERT study, a multicenter phase II trial, assessed the effectiveness, safety, and tolerability of protracted dual NK_1 RA and 5-HT_3 RA as RINV prophylaxis in patients receiving RT to the upper abdomen and radiosensitizing chemotherapy. The authors concluded that RINV still represents a serious morbidity in patients receiving RT to the upper abdomen and that aprepitant plus ondansetron, as dosed in this trial, were not superior to standard ondansetron monotherapy. The authors noted that other potential prophylactic options may be considered for future investigations, such as the granisetron transdermal patch, intravenous fosaprepitant, olanzapine, and alternative NK_1 RA formulations (e.g. the combination of netupitant and palonosetron and rolapitant as a single agent) [133].

4.7. Quadruple antiemetic combinations

Several studies have explored the potential benefit of combining four antiemetic agents to alleviate CINV in patients undergoing highly emetogenic chemotherapy (HEC; Table 9). In a randomized, double-blind, phase III trial in 380 chemotherapy-naïve patients with malignancies receiving HEC, the addition of olanzapine significantly improved the antiemetic efficacy of the three-drug regimen of a 5-HT_3 RA, an NK_1 RA and dexamethasone (Table 9) [134]. Based on the improvements achieved with this new quadruple regimen, the ASCO and NCCN antiemetic guidelines included this therapeutic option in their recommendations [8,9].

In a single-blind, randomized trial in 97 chemotherapy-naïve patients with breast cancer undergoing HEC, the addition of metoclopramide to antiemetic prophylaxis with palonosetron, aprepitant, and dexamethasone significantly improved the complete response rate (Table 9) [135].

The efficacy of multi-drug combinations in managing CINV probably arises from their ability to inhibit the emetic response at multiple sites [136].

5. Conclusions

Many cancer patients are affected by CINV and RINV, and these conditions are two of the major barriers to patient acceptance of antineoplastic treatments. Nonetheless, continuous efforts and

scientific advances are being made to further develop novel therapeutic options, formulations, and combination strategies of antiemetic therapies. These will certainly contribute to extend the availability of effective antiemetic treatments in the near future, with the ultimate objective of providing promising solutions tailored to suit the condition and the needs of each individual patient.

6. Expert opinion

CINV and RINV are two of the most troublesome issues that patients experience during anticancer treatment, with a high impact on quality of life. Despite the great efforts and improvements made in recent years, many areas of uncertainty and unsolved issues still exist.

First of all, research should be tailored to identify more precise treatment-, patient-, and disease-specific risk factors for the development of nausea and vomiting. Until now, only limited clinical predictive factors have been identified, but these have not yet been included in the guidelines to differentiate preventive strategies. In this regard, prospective studies aimed at personalizing antiemetic therapies could be the next step in the landscape of a tailored approach to supportive care in cancer. Moreover, the impact of genomic predisposition to CINV and RINV should be explored, by defining categories of risk and identifying possible new targets for improving treatment of these symptoms.

Secondly, the cluster of symptoms linked to nausea and vomiting should be better explored, in order to provide new information about the associated patterns of toxicity. It is plausible that a better control of CINV and RINV may positively impact other symptoms, such as taste and swallowing, fatigue, anxiety, and depression. An analysis of the patient-reported outcome (PRO) measures, listing each symptom as perceived by the patients themselves, would allow for a comprehensive assessment. Moreover, the analysis of adverse events should not be limited to intensity or frequency, but should also evaluate the duration of symptoms of toxicity. For CINV and RINV, one would assume that low-grade toxicities lasting several days or weeks would deeply affect the quality of life of patients, however this analysis is often lacking in many studies.

Thirdly, greater attention should be devoted to nausea and vomiting with targeted agents, particularly when administered orally for a long time. Some agents are associated with long-lasting nausea, which bothers patients. The impact of nausea with targeted therapy should be studied more broadly; in fact, while there are data on the greater impact of nausea on patient quality of life compared with the impact of vomiting, this information is lacking for targeted agents [137]. Greater efforts are needed to understand how to prevent and treat nausea in such cases, as these treatments are often used for periods lasting months or years.

Finally, the studies of new drug compounds or combinations should proceed in parallel with the evaluation of different schedules (intensified or de-intensified) of antiemetics and of alternative ways of drug administration. Moreover, the study of non-pharmacological therapies should be encouraged, with the aim of reducing CINV/RINV symptoms. Non-pharmacological approaches equally deserve to be studied in a rigorous manner, using well-designed trials, to precisely define the role of such strategies in controlling nausea and vomiting.

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Author contributions

P Bossi was involved with the conception, design of the study, and in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. M Airoldi was involved with the conception, design of the study and in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. MA Aloe Spiriti was involved with the conception, design of the study and in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. A Antonuzzo was involved with the conception, design of the study and in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. G Bonciarelli was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. A Campagna was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. A Cassano was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. R Murialdo was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. D Musio was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission. G Silvano was involved in the analysis and interpretation of the data, drafting, and critically revising the manuscript and final approval of the manuscript before submission.

Declaration of interest

P Bossi has disclosed that they have had a consulting or advisory role for Angelini, AstraZeneca, Bristol-Myers Squibb, Kyowa Kirin, Merck Serono, MSD Oncology, Roche and Sanofi/Regeneron. M Airoldi has disclosed that they have had a consulting or advisory role for Angelini, Bristol-Myers Squibb, Elsevier, Merck Serono and Novartis. A Antonuzzo has disclosed that they have had a consulting or advisory role for Kyowa Kirin. D Musio has disclosed that they have had a consulting or advisory role for Kyowa Kirin. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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