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SPECIAL ARTICLE

Getting it right the first time: recent progress in optimizing antiemetic usage

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Abstract

Recent years have witnessed significant improvements in the prevention and management of chemotherapy-induced nausea and vomiting (CINV), allowing patients to complete their prescribed chemotherapy regimens without compromising quality of life. This reduction in the incidence of CINV can be primarily attributed to the emergence of effective, well-tolerated antiemetic therapies, including serotonin (5-hydroxytryptamine or 5-HT3) receptor antagonists, neurokinin-1 (NK-1) receptor antagonists, and the atypical antipsychotic olanzapine. While 5-HT3 receptor antagonists are highly effective in the prevention of acute CINV, NK-1 receptor antagonists and olanzapine have demonstrated considerable activity against both acute and delayed CINV. Various combinations of these three types of agents, along with dexamethasone and dopamine receptor antagonists, are now becoming the standard of care for patients receiving moderately or highly emetogenic chemotherapy. Optimal use of these therapies requires careful assessment of the unique characteristics of each agent and currently available clinical trial data.

Keywords Chemotherapy-induced nausea and vomiting · CINV · 5-HT3 receptor antagonist · NK-1 receptor antagonist · Olanzapine · Radiotherapy-induced nausea and vomiting

Introduction

The goal of selecting optimal antiemetic therapy continues to be a moving target with the emergence of newer agents and patient-related risk factors, as well as the rapid evolution of guidelines for management of chemotherapy-induced nausea and vomiting (CINV). Utilizing an appropriate degree of prophylaxis for the first cycle of chemotherapy is critical to prevent breakthrough CINV, which is difficult to manage and can lead to later anticipatory vomiting during subsequent cycles of therapy. Optimizing antiemetic usage requires awareness of available and emerging agents and the unique characteristics of these therapies that impact their role in CINV management.

5-HT3 receptor antagonists

The first-generation 5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, and tropisetron) revolutionized the management of CINV in terms of both efficacy and safety compared to historical antiemetics (e.g., metoclopramide) [1]. These agents exhibit comparable efficacy, preventing 50 to 80% of acute CINV in patients receiving moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) regimens and are considered equivalent in CINV guidelines. Importantly, despite their efficacy against acute CINV, these agents are much less effective in prevention of delayed CINV.

In an effort to improve response to antiemetic therapy, the second-generation 5-HT3 receptor antagonists palonosetron and APF530 were subsequently developed and are now approved for patients with CINV [1–3]. Palonosetron has unique, advantageous pharmacodynamic properties, including a longer half-life and higher receptor binding affinity compared to the first-generation 5-HT3 receptor antagonists [4, 5]. In addition, binding of palonosetron to the 5-HT3 receptor creates positive cooperativity that results in further palonosetron binding and eventual receptor internalization, blocking 5-HT3 signaling and preventing crosstalk with NK-1 receptor signaling. APF530 is a novel, extended-release, subcutaneous formulation of granisetron with a unique biochronomer delivery system that provides sustained release to improve

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the therapeutic concentration of granisetron over an extended period (> 5 days) [3]. Both palonosetron and APF530 demonstrate superior prevention of both acute and delayed CINV compared to the first-generation 5-HT3 receptor antagonists [2, 6–8].

Several phase III trials directly compared palonosetron to either dolasetron, ondansetron, or granisetron in patients treated with MEC or HEC and demonstrated significantly higher efficacy in the acute and delayed phases in patients receiving palonosetron [6]. A pooled analysis of palonosetron phase III trials confirmed significantly higher complete response (CR, no emesis, and no rescue antiemetics) rates in the delayed (57 vs 45%; $P < .0001$) and overall period (51 vs 40%; $P < .0001$) for palonosetron compared to the first-generation 5-HT3 receptor antagonists [6]. Palonosetron also significantly decreased nausea severity in the delayed and overall periods. Based on these trials, the US Food and Drug Administration (FDA) approved palonosetron for the prevention of acute and delayed CINV associated with initial and repeat courses of MEC and HEC.

In a phase III trial of APF530 versus palonosetron in over 1400 patients receiving MEC or HEC, APF530 was noninferior to palonosetron in preventing acute CINV after MEC or HEC and delayed CINV associated with MEC [7]. A second phase III study compared APF530 to ondansetron, both in combination with fosaprepitant and dexamethasone, in patients receiving HEC [8]. Delayed phase CR was significantly more common in patients receiving APF530 compared to the delayed phase CR found with ondansetron (65 vs 57%; $P = .014$). The most common treatment-related adverse events were constipation, fatigue, headache, and infusion-site reactions.

Overview of NK-1 receptor antagonists

Development of NK-1 receptor antagonists has greatly improved our ability to control CINV, with aprepitant, fosaprepitant, netupitant, and rolapitant demonstrating similar efficacy in the prevention of CINV. Differences in the pharmacokinetic properties of NK-1 receptor antagonists influence the dosing frequency and use of these agents (Table 1) [9–12]. Aprepitant and its prodrug fosaprepitant have a relatively short half-life of 9–13 h, with aprepitant dosed daily for 3 days and fosaprepitant dosed on day 1 only [9, 10]. In contrast, NEPA (netupitant with palonosetron) and rolapitant have half-lives of approximately 80 and 180 h, respectively, and both agents can be administered as a single dose prior to each chemotherapy cycle [11, 12]. Another key difference in the NK-1 receptor antagonists is their interaction with other drugs. Aprepitant, fosaprepitant, and netupitant induce or inhibit cytochrome P450 3A4 (CYP3A4), while rolapitant does not [9–13]. This interferes with the metabolism of CYP3A4 substrates, such as dexamethasone and some chemotherapeutic agents, requiring careful consideration and appropriate dose reductions of concomitant dexamethasone. Aprepitant and fosaprepitant also interact with warfarin and oral contraceptives [9, 10]. Rolapitant, on the other hand, inhibits CYP2D6, breast cancer resistance protein (BCRP), and P-glycoprotein [12]. Administration of agents metabolized by CYP2D6 with rolapitant is not recommended and concomitant use with thioridazine is contraindicated due to risk for QT prolongation.

Aprepitant and fosaprepitant

Oral aprepitant was the first NK-1 receptor antagonist to be approved for CINV, based on demonstrated protection against delayed CINV in patients receiving HEC or MEC [14–16]. In two phase III, randomized trials evaluating ondansetron and dexamethasone with or without aprepitant in patients receiving high-dose cisplatin, the addition of aprepitant significantly increased CR rates during the delayed phase (68 vs 47%; $P < .001$ and 75 vs 56%; $P < .001$) [14, 15]. The addition of aprepitant significantly increased the proportion of patients experiencing no vomiting, but did not have a significant protective effect against nausea. This aprepitant triplet regimen also showed superior prevention of CINV (no vomiting and CR) in patients receiving MEC in a phase III randomized trial compared to ondansetron/dexamethasone [16]. The addition of aprepitant to ondansetron (with or without dexamethasone) also significantly increased the rate of CR (51 vs 26%; $P < .0001$) in pediatric patients receiving HEC or MEC [17]. Aprepitant was well tolerated in all of these trials [14–17].

The water insolubility of aprepitant led to development of the prodrug fosaprepitant, which is readily converted to aprepitant following IV administration [18, 19]. A phase III noninferiority trial then compared a single dose of IV fosaprepitant to the standard 3-day regimen of oral aprepitant, both in combination with ondansetron/dexamethasone, in 2247 patients receiving cisplatin-based chemotherapy [18]. Both regimens demonstrated similar rates of CR and no vomiting for the overall, acute, and delayed phases. Fosaprepitant was associated with increased infusion site reactions, but no other major differences in safety were observed. A more recent phase III study examined the addition of fosaprepitant to ondansetron and dexamethasone in patients receiving non-anthracycline/cyclophosphamide (AC)-based MEC [20]. Compared to placebo, the addition of fosaprepitant significantly improved rates of delayed CR (79 vs 69%; $P < .001$) and no delayed emesis (84 vs 75%; $P < .001$) (Fig. 1). The impact on nausea was less pronounced and did not reach statistical significance.

A novel intravenous formulation of aprepitant (HTX-019) was recently developed in an effort to improve the safety of

Table 1 Characteristics of available NK-1 receptor antagonists

	Aprepitant [9]	Fosaprepitant [10]	Netupitant [11]	Rolapitant [12]
Formulation	Oral	IV	Oral	Oral
Plasma half-life	9–13 h	9–13 h	80 h	180 h
Dosing	Days 1–3	Day 1	Day 1	Day 1
Significant interaction with CYP3A4 substrates (e.g., dexamethasone)	Yes	Yes	Yes	No
Significant interaction with CYP2D6 substrates (e.g., thioridazine)	No	No	No	Yes
Significant interaction with CYP2C9 substrates (e.g., warfarin)	Yes	Yes	No	No
Available as single-dose with a 5-HT3 RA	No	No	Yes, with palonosetron as NEPA	No

CYP cytochrome P450, *IV* intravenous, *NEPA* netupitant/palonosetron, *RA* receptor antagonist

this NK-1 receptor antagonist [21]. HTX-019 was formulated without polysorbate 80, a synthetic surfactant associated with increased risk for hypersensitivity reactions and infusion-site reactions. HTX-019 was approved by the FDA in 2017 for acute or delayed emesis associated with HEC, as well as emesis associated with MEC, based on results from two pivotal randomized bioequivalence studies [22]. In these studies, HTX-019 demonstrated comparable pharmacokinetics and safety to fosaprepitant, with fewer infusion-site reactions.

Netupitant and NEPA

Preclinical studies revealed synergistic activity for netupitant and palonosetron (NEPA) that, coupled with the unique pharmacologic features of palonosetron, suggested that this combination could be highly effective against CINV [3, 23]. A pivotal phase II trial examined multiple dosing combinations of these two agents versus palonosetron alone or an exploratory arm of aprepitant and ondansetron in 694 patients receiving cisplatin-based chemotherapy [24]. All the patients receiving NEPA were significantly more likely to achieve a CR compared to those receiving palonosetron alone in the delayed and overall phases (89.6 vs 76.5%; $P = .004$). NEPA at a netupitant dose of 300 mg (NEPA300) significantly improved the rates of CR, no emesis, no significant nausea, and complete protection (CR plus no significant nausea) in the acute, delayed, and overall phases compared to palonosetron. An oral fixed-dose combination of netupitant (300 mg) and palonosetron (0.5 mg) was subsequently developed to provide a convenient antiemetic therapy that combined a 5-HT3 and NK-1 receptor antagonist as suggested by current CINV guidelines.

A subsequent randomized phase III trial directly compared a single dose of NEPA to a single dose of oral palonosetron

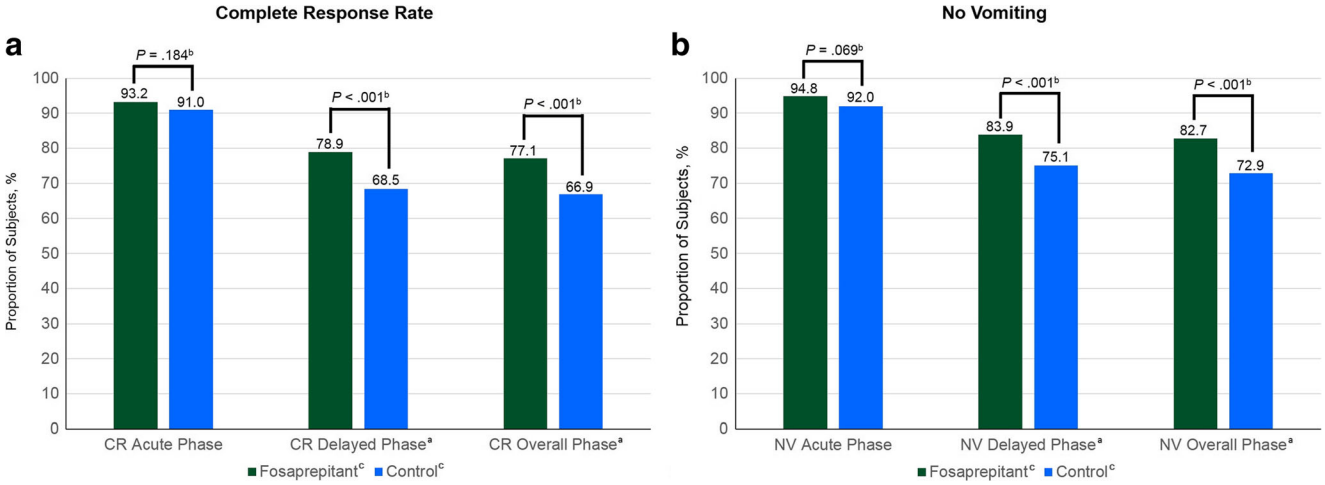

Fig. 1 Efficacy of fosaprepitant against CINV in patients receiving MEC [20]. **a** Complete response rate. [a]Primary endpoint. [b]Based on Cochran-Mantel-Haenszel method with stratification by sex. [c]All patients received ondansetron and dexamethasone and were randomized to either fosaprepitant or placebo. **b** No vomiting. [a]Exploratory endpoint. [b]Based on Cochran-Mantel-Haenszel method with stratification by sex. [c]All patients received ondansetron and dexamethasone and were randomized to either fosaprepitant or placebo. Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CR, complete response; MEC, moderately emetogenic chemotherapy; NV, no vomiting. Weinstein C et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: Results of a randomized, double-blind phase III trial, Annals of Oncology, 2015, volume 27, issue 1, 172-178, by permission of Oxford University Press on behalf of the European Society for Medical Oncology

(0.5 mg), both with dexamethasone, in 1455 patients receiving AC-based chemotherapy [25]. NEPA significantly increased the CR rate compared to palonosetron during the delayed phase (76.9 vs 69.5%; $P = .001$), acute phase (88.4 vs 85.0%; $P = .047$), and overall (74.3 vs 66.6%; $P = .001$) (Fig. 2). NEPA provided more protection than palonosetron alone from both emesis and nausea in the delayed and overall phases. NEPA was well tolerated in both of these studies and the most common adverse events were hiccups, headache, and constipation [24, 25].

Rolapitant

Oral rolapitant was approved by the FDA in 2015 in combination with other antiemetic therapies for the prophylaxis of delayed CINV associated with initial and repeat courses of MEC or HEC. Two phase III trials evaluated rolapitant in patients receiving HEC (HEC-1 and HEC-2), each of which enrolled over 500 patients [26]. Patients were randomized to receive either rolapitant (180 mg orally on day 1) or placebo and all patients received granisetron (10 μg/kg IV on day 1) and dexamethasone. In a pooled analysis of both studies, the addition of rolapitant to granisetron and dexamethasone significantly increased the percentage of patients who experienced a CR in the delayed phase (71 vs 60%; $P = .0001$) (Fig. 3). In HEC-1 and the pooled analysis, significantly more patients in the rolapitant arm achieved CR in the acute phase as well. Rolapitant also significantly increased the percentage of patients experiencing no nausea in the delayed phase (56 vs 44%; $P = .0002$) and the overall phase (52 vs 42%; $P = .0004$). Rolapitant was well tolerated; the most common adverse events included dyspepsia, headache, constipation, and hiccups and occurred in less than 2% of patients.

A third phase III study examined 1369 patients receiving MEC, randomizing them to rolapitant (180 mg orally on day 1) or placebo with granisetron (2 mg orally days 1–3) and dexamethasone [27]. Of note, at the time of the study design, AC was considered an MEC and patients receiving this combination were included. Significantly more patients receiving rolapitant achieved a CR in the delayed phase (71 vs 62%; $P = .0002$) and the overall phase (69 vs 58%; $P < .0001$) compared to the control group (Fig. 4). This benefit was maintained in a post hoc analysis of the subgroup of 401 patients treated with carboplatin in cycle 1 [28]. Patients who received carboplatin during cycle 1 and were randomized to rolapitant were significantly more likely to achieve a CR in the delayed phase (82 vs 66%; $P < .001$) and the overall phase (80 vs 65%; $P < .001$). Rolapitant also significantly increased the proportion of patients on carboplatin with no emesis, no nausea, and complete protection (no emesis, no rescue medication, and maximum visual analog scale [VAS] score < 25 mm).

Interestingly, rolapitant did not demonstrate a significant benefit in prevention of nausea in the primary analysis of the MEC trial [27]. A prespecified analysis of quality of life (QoL) in the MEC trial and a post hoc analysis of the HEC trials also showed that rolapitant improved the Functional Living Index-Emesis score, including both individual nausea and vomiting scores [29]. Rolapitant also significantly increased the proportion of patients in the MEC trial who reported that CINV had no impact on their daily lives.

In 2017, an intravenous formulation of rolapitant was approved by the FDA for use in combination with other

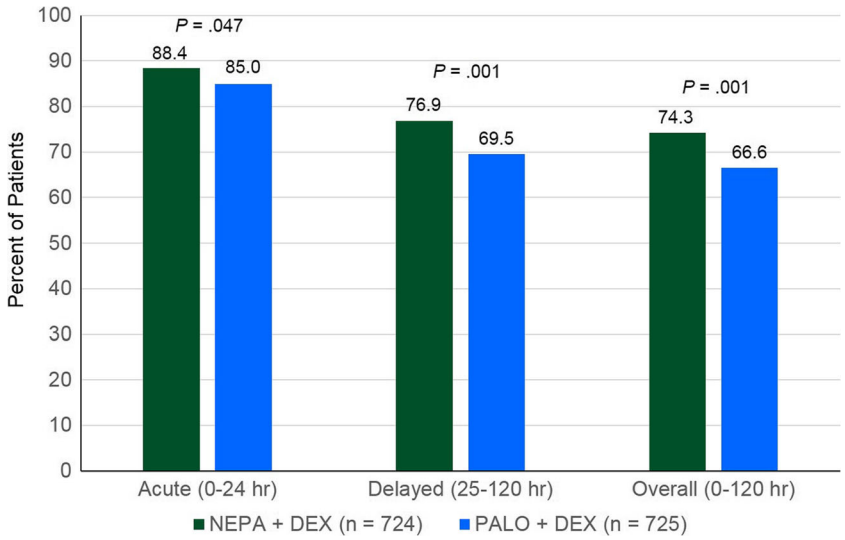

Fig. 2 Complete response rates for NEPA versus palonosetron after moderately emetogenic chemotherapy [25]. Abbreviations: DEX, dexamethasone; NEPA, netupitant/palonosetron; PALO, palonosetron. Aapro M et al. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy, Annals of Oncology, 2014, volume 25, issue 7, 1328-1333, by permission of Oxford University Press and the European Society for Medical Oncology

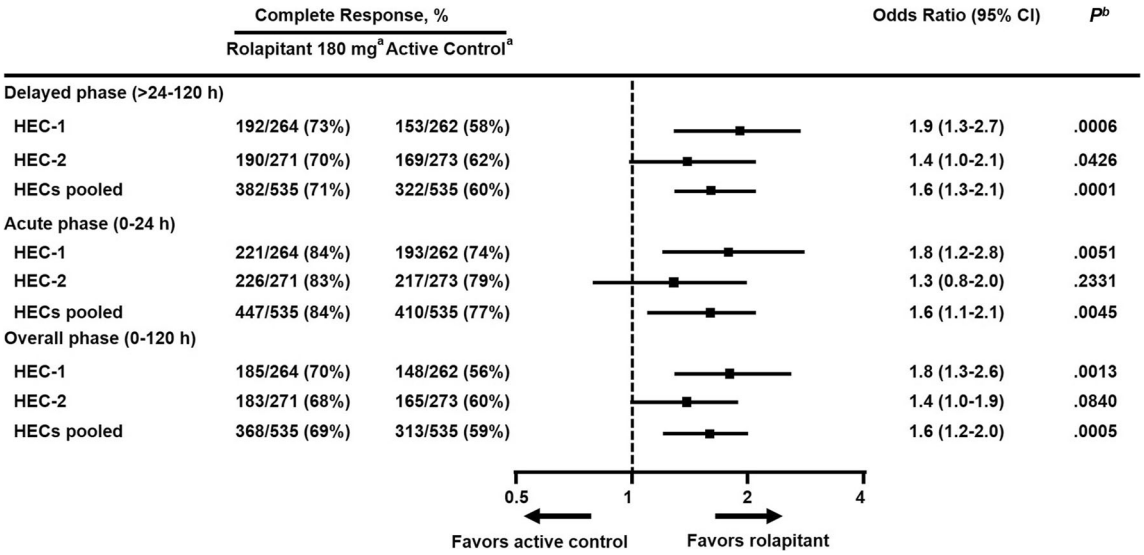

Fig. 3 Pooled analysis of the efficacy of rolapitant in patients receiving highly emetogenic chemotherapy [26]. [a]Unadjusted *P* values. [b]All patients received granisetron and dexamethasone and were randomized to either rolapitant or placebo. Abbreviations: HEC, highly emetogenic chemotherapy. Reprinted from The Lancet Oncology, Vol 16/Issue 9, Rapoport BL, Chasen MR, Gridelli C, Urban L, Modiano MR, Schnadig ID, Poma A, Arora S, Kansra V, Schwartzberg LS, Navari RM, Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: Two randomised, active-controlled, double-blind, phase 3 trials, 1079-1089, Copyright 2015, with permission from Elsevier

antiemetic agents for patients at risk for delayed CINV [30]. A bioequivalence trial demonstrated comparability between the oral and intravenous formulations, with similar pharmacokinetic and safety profiles. The prescribing information was recently updated to include a warning regarding the risk for hypersensitivity reactions such as anaphylaxis and anaphylactic shock, which have been observed in some patients in the post-marketing setting [31]. Intravenous rolapitant provides an important new option for patients and clinicians in the prevention and management of CINV, as intravenous

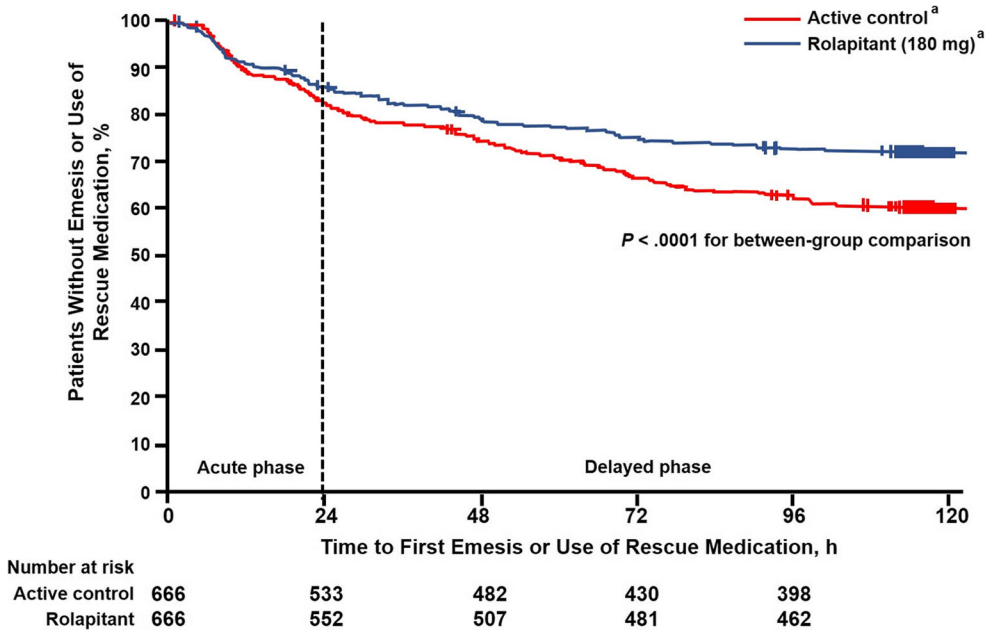

Fig. 4 Complete response rate for rolapitant versus control after moderately emetogenic chemotherapy [27]. [a]All patients received granisetron and dexamethasone and were randomized to either rolapitant or placebo. Reprinted from The Lancet Oncology, Volume 16/Issue 9, Schwartzberg LS, Modiano MR, Rapoport BL, Chasen MR, Gridelli C, Urban L, Poma A, Arora S, Navari RM, Schnadig ID, Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: A randomised, active-controlled, double-blind, phase 3 trial, 1071-1078, Copyright 2015, with permission from Elsevier

antiemetic agents are particularly helpful for patients experiencing substantial vomiting and/or unable to take oral medications.

NK-1 receptor antagonists over multiple cycles of chemotherapy

Chemotherapy-induced nausea and vomiting is an ongoing challenge that must be effectively prevented, not only in the first cycle of chemotherapy, but each subsequent cycle as well. Aprepitant demonstrated continued activity against CINV across multiple cycles of chemotherapy in several trials [32, 33]. In a multicycle extension of the phase III trial comparing NEPA to palonosetron, the benefit observed for NEPA over palonosetron in the delayed phase and overall phase was maintained for chemotherapy cycles 1 through 4 [34]. Patients who received NEPA and responded well were also significantly more likely to sustain a CR and nausea control beyond cycle 1. Another multinational randomized phase III trial compared NEPA plus dexamethasone to aprepitant, palonosetron, and dexamethasone over multiple cycles of chemotherapy in 413 chemotherapy-naïve patients receiving HEC or MEC [35]. NEPA demonstrated a small increase in the CR rate compared to aprepitant/palonosetron during cycle 1 that was maintained through 6 cycles of chemotherapy. In both of these studies, adverse events did not appear to increase over time.

In all the rolapitant trials mentioned above, patients could choose to continue the same antiemetic regimen for subsequent cycles of chemotherapy regardless of response during cycle 1 [36]. A post hoc analysis of these trials for cycles 2 through 6 of chemotherapy showed that rolapitant continued to provide superior protection from CINV compared to the control regimen over multiple cycles of MEC or HEC. The rate of treatment-emergent adverse events was low and did not increase with each subsequent cycle. Thus, a single dose of rolapitant at the beginning of each chemotherapy cycle effectively reduced emesis and nausea that can negatively impact daily life.

Olanzapine

Olanzapine is an atypical antipsychotic that blocks multiple neurotransmitters and interacts with dopaminergic, serotonergic, adrenergic, and histamine receptors [37]. A randomized phase III trial directly compared the efficacy of olanzapine (10 mg daily days 1 to 4) to standard 3-day aprepitant in 241 chemotherapy-naïve patients receiving HEC (cisplatin or cyclophosphamide/doxorubicin) [38]. All patients received palonosetron and dexamethasone. Rates of CR were similar between the two arms. Olanzapine nearly doubled the percentage of patients without delayed nausea or overall nausea (69 vs 38% for aprepitant), although there was no difference observed for acute nausea (87% for both arms).

To further explore the potential for olanzapine in CINV prophylaxis, a small randomized study compared the addition of olanzapine at 5 mg daily for 6 days versus placebo to standard triple antiemetic therapy with 5-HT3 and NK-1 receptor antagonists and dexamethasone in 44 patients receiving MEC or HEC [39]. Adding olanzapine to standard antiemetic therapy significantly increased the total control rate (no vomiting, no rescue medications, and maximum VAS score ≤ 5 mm) in the acute phase (86 vs 55%; $P = .045$) and the delayed phase (64 vs 23%; $P = .014$). Complete protection (no vomiting, no rescue medications, and maximum VAS score of ≤ 25 mm) was also significantly improved in the acute and delayed phase. Importantly, olanzapine was well tolerated and significantly improved patient quality of life ($P = .0004$).

A recent, large, randomized phase III trial evaluated the addition of olanzapine versus placebo to a standard triplet antiemetic regimen of aprepitant or fosaprepitant, a 5-HT3 receptor antagonist, and dexamethasone [37]. A total of 380 chemotherapy-naïve patients receiving HEC (cisplatin or cyclophosphamide/doxorubicin) were randomized to either olanzapine (10 mg orally) or placebo on days 1 through 4. The addition of olanzapine significantly improved the primary endpoint of no chemotherapy-induced nausea in both the acute period (74 vs 45%; $P = .002$) and delayed period (42 vs 25%; $P = .002$).

Table 2 Guideline-based therapy for radiation-induced nausea and vomiting [44, 45]

Emetic risk	Irradiated area	Antiemetic guideline (MASCC and ASCO)
High	Total body irradiation	Prophylaxis with 5-HT3 RA + DEX
Moderate	Upper abdomen and craniospinal	Prophylaxis with 5-HT3 RA + optional DEX
Low	Cranium	Prophylaxis (MASCC guidelines only) or rescue with DEX[a]
	Head and neck, thorax region, pelvis	Prophylaxis (MASCC guidelines only) or rescue with DEX, a 5-HT3 RA, or a dopamine RA[a]
Minimal	Extremities, breast	Rescue with DEX, a 5-HT3 RA, or a dopamine RA

[a] MASCC guidelines recommend prophylaxis or rescue therapy, while ASCO guidelines recommend rescue therapy only

ASCO American Society of Clinical Oncology, *DEX* dexamethasone, *MASCC* Multinational Association of Supportive Care in Cancer, *RA* receptor antagonist

Overall nausea prevention was also significantly increased (37 vs 22%; $P = .002$). The CR rate was also significantly improved when olanzapine was added in the acute phase (86 vs 65%; $P < .001$), delayed phase (67 vs 52%; $P = .007$), and overall (64 vs 41%; $P < .001$). In this phase III trial, sedation was significantly increased in those receiving olanzapine, including severe sedation in 5% of patients.

Olanzapine has also been investigated as a rescue therapy for patients with breakthrough CINV. A double-blind, randomized phase III trial directly compared olanzapine to metoclopramide in chemotherapy-naïve patients receiving HEC (cisplatin or doxorubicin/cyclophosphamide) who experienced breakthrough CINV despite prophylactic fosaprepitant, palonosetron, and dexamethasone [40]. One hundred and eight evaluable patients experiencing breakthrough CINV were randomized to receive 10 mg daily olanzapine for 3 days or 10 mg metoclopramide 3 times daily for 3 days. This reduced dose of metoclopramide had not yet demonstrated efficacy in clinical trials, but was mandated by the European Medicine Agency to reduce the risk of neurotoxicity. Olanzapine prevented vomiting in 70% compared to 31% with metoclopramide ($P < .01$). Nausea was also significantly reduced (68 vs 23%; $P < .01$).

In summary, olanzapine significantly improved nausea control and is at least as effective as aprepitant in prevention of vomiting. Drowsiness is the main adverse event to be considered and appears to be particularly evident in elderly patients [41]. Caution should be used when prescribing olanzapine with dopamine receptor antagonists such as metoclopramide or haloperidol, as there is an increased risk of extrapyramidal symptoms [42].

Radiotherapy-induced nausea and vomiting

Radiotherapy-induced nausea and vomiting (RINV) is often underestimated by clinicians, but can occur in 50 to 80% of patients undergoing radiotherapy [43]. The risk of RINV depends on the site of irradiation, dosing, fractionation, irradiated volume, radiotherapy technique, and patient-related factors such as age < 55 years, female sex, no alcohol consumption, history of nausea and vomiting, and anxiety [43, 44]. The emetogenic potential for radiotherapy and recommended prophylaxis according to the MASCC/ESMO and ASCO guidelines are based solely on the radiation field (Table 2) [44, 45]. Those at high or moderate risk for RINV should receive a 5-HT3 receptor antagonist with or without dexamethasone. For patients undergoing fractionated radiotherapy, 5-HT3 receptor antagonist therapy should be given before each fraction and continued at least 24 h after completion of radiotherapy [45]. Clinical trial data on patients receiving chemotherapy and radiotherapy concurrently is lacking. Current guidelines recommend selection of CINV prophylaxis based on the emetic risk of the chemotherapeutic regimen, unless the emetic risk of the planned radiotherapy is greater.

A recent meta-analysis confirmed the value of 5-HT3 receptor antagonists for RINV, with these agents increasing the rate of complete control of vomiting and complete control of nausea compared to control antiemetic regimens [46]. Very few studies have examined the potential role for NK-1 receptor antagonists in RINV. A recent phase III trial compared fosaprepitant versus placebo, both in combination with palonosetron and dexamethasone, in patients receiving 5 weeks of fractionated radiotherapy and weekly cisplatin for cervical cancer [47]. The triplet combination significantly increased the proportion of patients experiencing sustained lack of emesis at 5 weeks (65.7 vs 48.7%; hazard ratio 0.58; $P = .008$). The addition of fosaprepitant also increased the proportion of patients with an overall complete response (24 vs 14%; $P = .007$) and no nausea during the 5 weeks (15 vs 8%; $P = .007$). Further studies of NK-1 antagonists are warranted in the setting of RINV.

Conclusions

Numerous therapeutic options for prevention and treatment of CINV are now available, and many of the alternatives in each class of agents are very similar to each other with regard to efficacy and safety. It is important that clinicians employ optimal CINV prophylaxis right from the start based on current guidelines and clinical trial data to improve patient QoL and prevent chemotherapy delays and discontinuations. The ultimate goal is complete control of all aspects of CINV, including both nausea and vomiting. This will require further evaluation of optimal dosing, timing of administration, and effective combination strategies.

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Compliance with ethical standards

Conflict of interest Dr. Schwartzberg has disclosed that he has received consulting fees or honoraria from Eisai, Helsinn, Heron, and TESARO. He also discloses that he has received research funding from TESARO and fees for participation in advisory or review activities from Helsinn and Heron.

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