



Bringing it all together in the treatment of CINV: application of current knowledge into routine clinical practice

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Abstract

For patients with cancer, the threat of chemotherapy-induced nausea and vomiting (CINV) can greatly influence treatment decisions and overall quality of life. Clinicians now have numerous effective antiemetic therapies to offer to patients, but selecting the optimal strategy can be complicated. Integration of current CINV guidelines, emerging data from recent clinical trials, and patient-specific risk factors can greatly improve antiemetic prophylaxis. Two challenging clinical scenarios are presented and discussed to provide insight on how to best approach these types of treatment decisions and apply recent advances in CINV prevention and management to patient care.

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

Introduction

Optimal management of chemotherapy-induced nausea and vomiting (CINV) requires clinicians to remain aware of emerging antiemetic therapies, the unique pharmacological characteristics associated with each agent, current CINV guidelines, recent clinical trial data, and the patient-related risk factors that may influence risk of CINV. By bringing all of this knowledge together, clinicians can select the best antiemetic prophylaxis for their patients with cancer. To highlight the appropriate application of recent advances to patient care, two challenging clinical scenarios focused on the prevention and management of CINV are presented and discussed below.

Case 1: a 66-year-old woman with ovarian cancer

Description A 66-year-old patient presents with ovarian cancer and will receive carboplatin and paclitaxel every 3 weeks

prior to surgery. She is thin with a weight of 48 kg and has private health insurance. She is experiencing nausea due to her intra-abdominal disease and opioid analgesia administered as needed. Your institutional preset electronic antiemetic orders specify the use of palonosetron, dexamethasone, and metoclopramide, as needed. You, however, recently attended a satellite symposium at the MASCC Annual Meeting titled “Searching for Perfection in Antiemetic Therapy.”

Which of the following would you choose?

1. Use standard orders (palonosetron, dexamethasone, PRN [as needed] metoclopramide) and use an NK-1 receptor antagonist in cycle 2 if required
2. Add an NK-1 receptor antagonist and adjust the dexamethasone dose if necessary
3. Add olanzapine 10 mg orally daily for 4 days
4. None of the above

There are a number of important considerations when selecting antiemetic prophylaxis for this patient. Option 1 (using the standard institutional orders) involves utilizing a 5-hydroxytryptamine (5-HT₃) receptor antagonist upfront and keeping the neurokinin-1 (NK-1) receptor antagonist in reserve. This is a common practice and appropriate for patients receiving moderately emetogenic chemotherapy (MEC; emetic risk of 30 to 90%). However, this approach is suboptimal based on currently available CINV guidelines that

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have revised recommendations specifically for carboplatin-based chemotherapy [1–3]. While carboplatin is classified as MEC [1–3], the emetogenic potential is at the higher end of the MEC range [4].

Several clinical trials have demonstrated significant efficacy when an NK-1 receptor antagonist was added to a 5-HT₃ antagonist and dexamethasone in patients receiving carboplatin-based chemotherapy [5–8]. A Japanese multicenter, randomized trial evaluated aprepitant vs placebo in combination with a 5-HT₃ receptor antagonist and dexamethasone in 297 patients with gynecologic cancers [7]. Compared to control, the addition of aprepitant to standard antiemetic therapy significantly increased the proportion of patients with no vomiting (78.2 vs 54.8%; $P < .0001$), no significant nausea (85.4 vs 74.7%; $P = .0143$), and complete response (CR for vomiting; 61.6 vs 47.3%; $P = .0073$) in the overall phase. Similar benefit was also observed in no significant nausea (85.4 vs 76.0%; $P = .0274$). The difference in patients with no nausea (6.1%) was not statistically significant. NEPA (netupitant/palonosetron) also demonstrated similar benefit compared to aprepitant/palonosetron in a subset analysis of patients treated with carboplatin in a phase III trial [8]. Overall rates of CR (no emesis or rescue medications) and no significant nausea were similar between the two antiemetic regimens.

Rolapitant also demonstrated similar efficacy in a post hoc analysis of a patient subgroup receiving carboplatin-based chemotherapy [5]. Adding rolapitant to granisetron and dexamethasone significantly increased the proportion of patients with a CR in the overall phase (80.2 vs 64.6%; $P < .001$) and the delayed phase (82.3 vs 65.6%; $P < .001$) (Fig. 1). Interestingly, rolapitant also significantly increased the percentage of patients who experienced no nausea in the overall phase (62.5 vs 51.2%; $P = .023$) and the delayed phase (64.1 vs 53.6%; $P = .034$). Based on the available data, the Multinational Association of Supportive Care in Cancer/

European Society for Medical Oncology (MASCC/ESMO), the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO) have now revised their recommendations to include the use of an NK-1 receptor antagonist for patients receiving carboplatin-based chemotherapy [1–3].

The second option of adding only an NK-1 receptor antagonist is reasonable for this patient based on current treatment guidelines [1–3], but may not be optimal given the efficacy of combining an NK-1 antagonist and olanzapine. Olanzapine as a PRN (as needed) medication greatly reduced the risk of both nausea and vomiting in patients receiving an NK-1 receptor antagonist, a 5-HT₃ receptor antagonist, and a corticosteroid, although this strategy is not in accordance with current antiemetic guidelines [1–3, 9].

A 4-drug combination of olanzapine, aprepitant, palonosetron, and dexamethasone was also evaluated in a phase II trial in patients receiving cisplatin-based chemotherapy for gynecologic cancers [10]. This regimen was associated with a high rate of CR for vomiting in the overall phase 92.5%. There is little doubt that olanzapine will enhance control of nausea and vomiting, but a dose of 10 mg may be problematic in a frail, older patient (hence, the caution in MASCC-ESMO and NCCN guidelines) [1, 2]. Studies that mention any grade of sedation indicate that with 10 mg, it occurs at a frequency of more than 50%, which can adversely impact the quality of life by impairing the ability to work, drive, etc. [10, 11].

The third treatment option of adding only olanzapine also fits within the current NCCN guidelines, but may not be the best option because of the potential sedation with 10 mg. This patient's insurance will cover the use of an NK-1 receptor antagonist, so there is no reason to omit this class of antiemetic therapy given the efficacy of these agents in patients receiving carboplatin [5–8].

Fig. 1 Complete response rate associated with rolapitant in patients receiving carboplatin [5]. CR complete response. Reprinted from Hesketh PJ, et al. Cancer. 2016;112:2418–2425. © 2016. Used under the Creative Commons Attribution-NonCommercial 4.0 International Public License. View the license and disclaimer here <https://creativecommons.org/licenses/by-nc/4.0/>

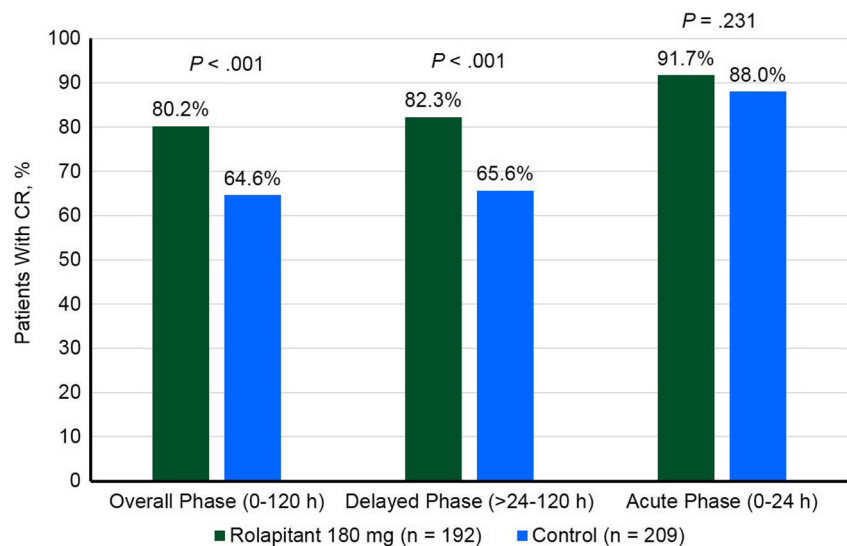
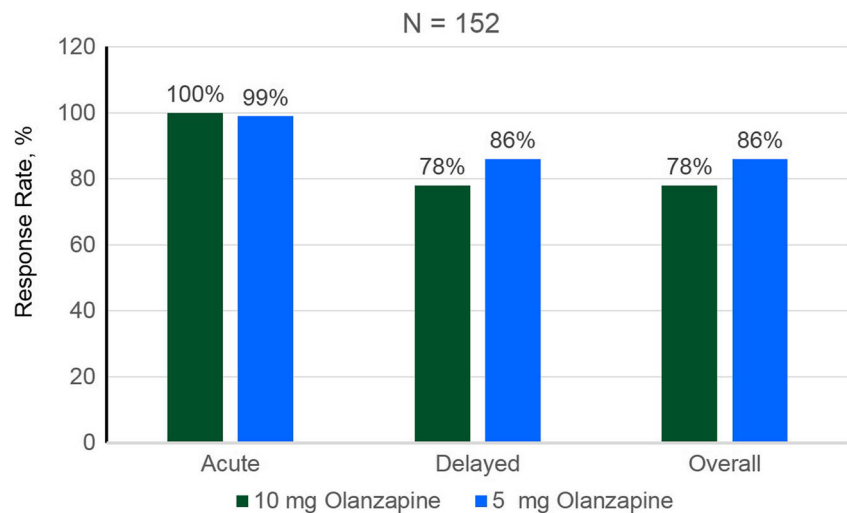


Fig. 2 Complete response rate for olanzapine 10 vs 5 mg [11]



The final option of “none of the above” is probably the best one given that this is an older, thin individual. A good approach would be to add to the “standard order” with an NK-1 receptor antagonist and replace metoclopramide with lower dose olanzapine (i.e., 5 mg for 4 days) at the time of breakthrough CINV. A large majority of the patients in the randomized carboplatin studies who received an NK-1 receptor antagonist had a complete response [5–8], indicating that a potentially sedating drug like olanzapine may not be required. In addition, olanzapine has been successful when used for breakthrough CINV [9]. Although there is a lack of large randomized trials evaluating olanzapine at a dose of 5 mg daily, several smaller randomized trials support a lower dose [11–13]. A phase II randomized trial directly compared olanzapine doses of 10 and 5 mg daily in combination with aprepitant, palonosetron, and dexamethasone for prevention of CINV in 152 patients receiving cisplatin [11]. Lowering the dose of olanzapine reduced the incidence of drowsiness (46% for 5 mg vs 53% for 10 mg) without compromising efficacy as assessed by CR rates for vomiting (86% for 5 mg vs 78% for 10 mg; $P < .001$) and total control rates for nausea and vomiting (62 vs 59%, respectively) (Figs. 2 and 3). Another randomized trial presented at the 2017 MASCC Annual Meeting compared 5 vs 10 mg of olanzapine on days 1–3 in combination with standard antiemetic therapy for patients receiving highly emetogenic chemotherapy (HEC) or MEC [13]. Chemotherapy-induced nausea and vomiting was well controlled in both dosage groups with a CR for vomiting of > 75% in both. Importantly, daytime sedation was significantly lower in patients receiving 5 mg olanzapine ($P < .02$).

In summary, the optimal approach for this thin, elderly patient receiving carboplatin-based chemotherapy for ovarian cancer would be a 3-drug combination consisting of an NK-1 receptor antagonist, palonosetron, and dexamethasone. Olanzapine could be administered, as needed, for breakthrough CINV at a lower dose of 5 mg to reduce the risk of sedation.

Case 2: 40-year-old patient receiving adjuvant anthracycline/cyclophosphamide chemotherapy

Description A 40-year-old woman was diagnosed with a 2-cm, grade 3 adenocarcinoma that is estrogen receptor-positive, progesterone receptor-negative, and HER2-positive. Two of 12 lymph nodes were positive. After recovery from breast-conserving surgery, she is planned to receive adjuvant FEC-DH (fluorouracil, epirubicin, cyclophosphamide followed by docetaxel and trastuzumab). She does not drink alcohol, has a history of morning sickness, and has private health insurance. She receives ondansetron (16 mg orally day 1, then 8 mg BID for 2 days), dexamethasone (8 mg orally day 1 only), and prochlorperazine as needed as antiemetic prophylaxis for cycle 1 of her FEC chemotherapy.

On day 3, the patient is seen in the emergency room for vomiting (5 episodes on day 1 at least 10 h after chemotherapy and 3 episodes on day 2). She is unable to keep down prochlorperazine and has had minimal fluids. She is given ondansetron (8 mg IV) and IV normal saline in the emergency

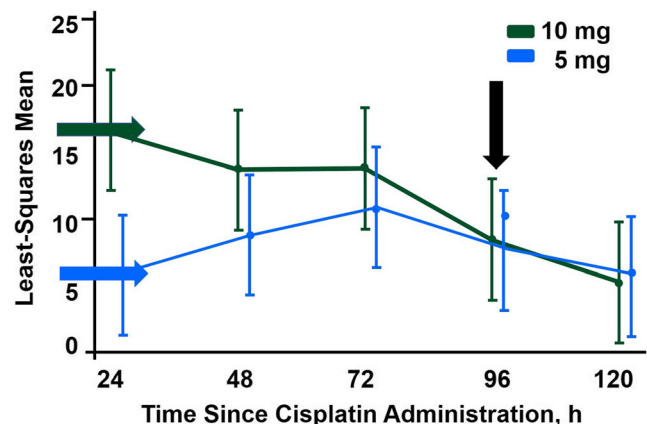


Fig. 3 Drowsiness with olanzapine 10 vs 5 mg [11]

room. She is discharged with daily IV hydration for 3 days and ondansetron (8 mg BID). On day 19, she revisits the clinic and states that, due to prolonged nausea, she was unable to leave her house to drive her children to hockey practice during the first week and had found food preparation increasingly challenging. As a result, she is reluctant to receive more chemotherapy.

What prophylactic approaches would you employ for cycle 2 of chemotherapy?

1. Add an NK-1 receptor antagonist (\pm dexamethasone dose adjusted as required if CYP3A4 inhibition)
2. Substitute metoclopramide 20 mg qid for prochlorperazine
3. Add olanzapine 5 to 10 mg daily \times 4, remove prochlorperazine
4. Send a visiting nurse to provide IV hydration \times 4 days post chemotherapy

This patient did not receive guideline-based treatment in cycle 1—she should have had an NK-1 receptor antagonist included in the antiemetic regimen. For a patient experiencing severe breakthrough CINV to the point where she is voicing concerns about continuing chemotherapy, it is paramount that the next cycle of chemotherapy be tolerated well. In addition to receiving highly emetogenic chemotherapy, this patient has several risk factors for CINV, including young age, no alcohol intake, and morning sickness during pregnancy, so it is not surprising that she had breakthrough CINV. Adding an NK-1 receptor antagonist is important but unlikely to be sufficient. In patients receiving anthracycline/cyclophosphamide (AC)-based therapy, NK-1 receptor antagonists have markedly decreased vomiting but have little effect on nausea [14]. Changing prochlorperazine to metoclopramide is an option, but would be unlikely to significantly improve the efficacy of the antiemetic regimen.

The optimal approach for this patient would likely be the addition of an NK-1 receptor antagonist and olanzapine. Addition of an NK-1 receptor antagonist to standard antiemetic therapy contributes to control of emesis in both the early and delayed phases, as demonstrated by a post hoc analysis of 4 randomized trials of aprepitant in patients receiving HEC or MEC [15]. As mentioned previously, a 4-drug regimen including olanzapine further improves CINV prophylaxis, particularly with regard to nausea control. In a randomized phase III trial investigating olanzapine vs placebo in combination with an NK-1 receptor antagonist (aprepitant or fosaprepitant), a 5-HT₃ receptor antagonist, and dexamethasone in 380 patients receiving HEC, olanzapine provided significant protection against nausea and vomiting in the acute, delayed, and overall phases [9]. A routinely administered, low dose of olanzapine (5 mg administered as 2.5 mg bid) would be a good option for this patient with young children to prevent unwanted sedation but with the proviso that, if she experiences nausea with minimal sedation,

higher doses can be used. If an NK-1 receptor antagonist and olanzapine are utilized in this patient, IV hydration should be unnecessary but can be added later if needed.

Conclusions

Antiemetic guidelines provide important direction for clinicians in the fight against CINV. This is supported by observational studies conducted in Europe and the USA that clearly showed significant reductions in the incidence of CINV when patients received guideline-consistent antiemetic therapy [16, 17]. However, as illustrated in case 1, institutional guidelines may be outdated and treatment decisions must sometimes be adjusted to reflect the individual needs of the patient. Optimal patient care requires clinicians to consider not only current guidelines and emerging clinical trial data, but also their own clinical experiences with antiemetic therapy and the factors that contribute to risk and response. These clinical scenarios illustrate the importance of bringing all of those factors together to make the most educated decision regarding antiemetic prophylaxis. Only then will patients receive truly individualized CINV care.

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Compliance with ethical standards

Conflict of interest Dr. Warr has disclosed that he has received consulting fees or honoraria from Helsinn and Merck. He also discloses that he has received payment for lectures and participation in advisory or review activities from Merck.

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