Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

May 2010 www.clinicaladvances.com Volume 8, Issue 5, Supplement 9

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Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Case Study Compendium

A CME Activity
Approved for
1.0 *AMA PRA*
Category 1
Credit(s)™

Release date: May 2010
Expiration date: May 31, 2011
Estimated time to complete activity: 1.0 hour

Sponsored by the Postgraduate Institute for Medicine

Supported through an educational grant from Eisai, Inc.

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Target Audience: This activity has been designed to meet the educational needs of oncologists, hematologist/oncologists, nurses, hematologists, and other health care professionals involved in the management of patients with chemotherapy-induced nausea and vomiting.

Statement of Need/Program Overview: Advances in the treatment of cancer patients with chemotherapy-induced nausea and vomiting (CINV) have improved response rates and quality of life outcomes dramatically. In order to maintain and further these advancements, it is essential that cutting-edge medical developments be communicated as effectively and efficiently as possible in order to optimize patient care. This monograph will enable medical professionals to quickly and accurately synthesize the plethora of new information presented at recent meetings through actual case studies by reviewing and learning how to apply it appropriately to positively impact patient management strategies for CINV.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the importance of new study findings and clinical trial data in the natural history of CINV in cancer patients
- Assess the results of these new study findings including updates on guidelines for highly and moderately emetogenic chemotherapy and radiotherapy
- Integrate into clinical practice the latest knowledge and methods for treating cancer patients with CINV in an effort to improve current quality of life statistics
- Identify future research directions for all therapies in CINV in cancer patients

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Guidelines for the Treatment of Chemotherapy-induced Nausea and Vomiting

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Chemotherapy-induced nausea and vomiting (CINV) is one of the most common—and most feared—side effects reported by cancer patients.[1] CINV is classified as either acute (within the first 24 hours of chemotherapy administration) or delayed (between 24 hours after chemotherapy administration up to 5 days post-chemotherapy). Poorly controlled CINV is associated with higher direct medical costs as well as a significant loss of the patient's ability to work. A 2007 study by Shih and colleagues found that, among 2,018 patients who underwent highly or moderately emetogenic chemotherapy, 28% experienced uncontrolled CINV.[2] The average total direct medical costs per patient per month for the uncontrolled CINV group were $1,383 higher than those for the controlled CINV group ($P<.0001$). In addition, the average number of work-loss days per month was 6.23 for the uncontrolled CINV group, compared with 3.61 days for the controlled CINV group. Thus, controlling CINV is an important goal for clinicians, and made even more important by the fact that if a patient experiences CINV during one cycle of chemotherapy, he or she is much more likely to experience it during subsequent cycles.[3]

In 1997, a group of investigators who were members of the Multinational Association of Supportive Care in Cancer (MASCC) met to create the first clinical practice guidelines for anti-emetic treatment for patients undergoing chemotherapy. This was prompted by the advent of the 5-HT_3 receptor antagonists as well as by the contradictory and confusing nature of the published anti-emetic literature at the time. There were 2 major advances that came from this meeting. First, the MASCC guidelines made clear that the task at hand for clinicians was to prevent CINV, rather than treat it after the fact. The committee was able to demonstrate through a review of the available data that anti-emetic agents are much more efficacious when used prior to the administration of chemotherapy, cementing that practice as standard-of-care. The second major advance made with the MASCC guidelines was the idea that there are quantifiable emetic risk levels of chemotherapy drugs: high risk (greater than 90% risk); moderate risk (30–90% risk); low risk (10–30% risk); and minimal risk (less than 10% risk).[4] These categories are now also used in both the National Comprehensive Cancer Network (NCCN) guidelines[5] and the American Society of Clinical Oncology (ASCO) guidelines[6] (Table 1).

Beginning with highly emetogenic chemotherapy, the current guidelines recommend triple therapy with a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant given on day 1 before chemotherapy is begun. On days 2 and 3, the recommendation is to use dexamethasone and aprepitant, because 5-HT_3 receptor antagonists do not appear to have increased efficacy when used after day 1. On day 4, the recommendation is to use dexamethasone alone. For moderately emetogenic chemotherapy, the preferred treatment is to use a 5-HT_3 receptor antagonist plus dexamethasone on day 1, followed by dexamethasone alone on days 2 and 3. For patients receiving low emetic-risk chemotherapy, the recommendation is for monotherapy with a low dose of dexamethasone on day 1. Minimal emetic-risk chemotherapy requires no preventative anti-emetic treatment.

Although the best treatment for CINV is prevention, there will be instances in which treatment for breakthrough emesis is required. Multiple concurrent agents may be necessary to bring breakthrough CINV under control. The general principle of treatment for breakthrough emesis is to add an agent from a different drug class than those that the patient is already receiving. Some guideline-recommended agents include dopamine antagonists, haloperidol, and benzodiazepines. Nabilone, a cannabindoid, has also been approved in the United States for the treatment of CINV in patients who have failed to respond adequately to conventional anti-emetic treatments, although this agent requires close supervision and should not be dosed on an as-needed basis.[7] None of these are recommended for use as first-line agents. Before the next round of chemotherapy, a re-evaluation of the patient's anti-emetic regimen should be conducted. Clinicians can consider moving the patient to treatment

Table 1. Emetogenic Potential of Intravenous Antineoplastic Agents

High emetic risk (>90% frequency of emesis)	Low emetic risk (10–30% frequency of emesis)
• AC combination defined as either doxorubicin or epirubicin with cyclophosphamide • Carmustine >250 mg/m^2 • Cisplatin ≥50 mg/m^2 • Cyclophosphamide >1,500 mg/m^2 • Dacarbazine • Mechlorethamine • Streptozocin	• Aldesleukin ≤12 million IU/m^2 • Amifostine ≤300 mg • Cytarabine (low dose) 100–200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Etoposide • 5-Fluorouracil • Floxuridine • Gemcitabine • Interferon alfa >5 million IU/m^2 and <10 million IU/m^2 • Ixabepilone • Methotrexate >50 mg/m^2 and <250 mg/m^2 • Mitomycin • Mitoxantrone • Paclitaxel • Paclitaxel-albumin • Pemetrexed • Pentostatin • Romidepsin • Topotecan
Moderate emetic risk (30–90% frequency of emesis)	
• Aldesleukin >12–15 million IU/m^2 • Altretamine • Amifostine >300 mg/m^2 • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin • Carmustine ≤250 mg/m^2 • Cisplatin <50 mg/m^2 • Clofarabine • Cyclophosphamide ≤1,500 mg/m^2 • Cytarabine >200 mg/m^2 • Dactinomycin • Daunorubicin • Doxorubicin • Epirubicin • Idarubicin • Ifosfamine • Interferon alfa ≥10 million IU/m^2 • Irinotecan • Melphalan • Methotrexate 250 mg/m^2 to >1,000 mg/m^2 • Oxaliplatin • Temozolomide	**Minimal emetic risk (<10% frequency of emesis)**
	• Alemtuzumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine (2-chlorodeoxyadenosine) • Cytarabine <100 mg/m^2 • Decitabine • Denileukin difitox • Dexrazoxane • Fludarabine • Gemtuzumab ozogamicin • Interferon alpha ≤5 million IU/m^2 • Methotrexate ≤50 mg/m^2 • Nelarabine • Panitumumab • Pegaspargase • Rituximab • Temsirolimus • Valrubicin • Vinblastine • Vincristine • Vinorelbine

Data adapted from Hesketh PJ et al. *J Clin Oncol.* 1997;15:103-109 and Grunberg SM et al. *Support Care Cancer.* 2005;13:80-84.

recommended for the next higher emetic risk level of chemotherapy. The use of concomitant antacid therapy may prove useful because the sensations of dyspepsia are often confused with and contribute to those of nausea.[5]

Unfortunately, the treatment advances described in the anti-emetic guidelines have not been put into practice universally. One of the reasons for this is the subjective nature of nausea and vomiting. They occur outside the

clinic and are self-reported. Although visual analog scales for nausea are readily available and have been for many years, CINV is often not well-documented. Thus, the need for controlling CINV may not seem as pervasive as it is in actuality. One strategy for improving CINV care that is being tried at the M.D. Anderson Cancer Center is a voice response system that patients are asked to call and report their symptoms to at certain pre-designated times. If the patient fails to call, the system will call them. Other clinics have been experimenting with computer or mobile device systems for tracking CINV; time will tell if these have any effect upon a more universal application of the anti-emesis guidelines. In my opinion, more than any new drug, the future improvement of anti-emetic therapy really hinges on applying the knowledge that we already have to everyday practice for patients across the board.

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Delayed Nausea and Vomiting Following Highly Emetogenic Chemotherapy

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A 52-year-old woman with a diagnosis of stage IIB non–small cell lung cancer had recently undergone a right upper lobe resection revealing a poorly differentiated adenocarcinoma. An adjuvant chemotherapy regimen employing cisplatin and pemetrexed was initiated. In her initial cycle of chemotherapy, she received cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2. Anti-emetic prophylaxis included intravenous ondansetron 8 mg and intravenous dexamethasone 20 mg prior to the start of chemotherapy. The patient was also instructed to take dexamethasone 8 mg twice daily for 3 additional days, and she received a prescription for prochlorperazine 10 mg to be taken as needed.

The patient did very well on the day of treatment and experienced no acute adverse events (AEs). On day 2, she developed moderate nausea in the afternoon and vomited a single time. Prochlorperazine was ineffective in relieving the nausea. The nausea continued on days 3 and 4 such that the patient decided she would be unable to go to work. On day 5, the nausea resolved.

Discussion

This case illustrates the challenge of delayed CINV, which is defined as any nausea or vomiting that occurs more than 24 hours after chemotherapy. This phenomenon was first documented with cisplatin. In the absence of any delayed prophylaxis, approximately 90% of patients experience emesis in the 3 to 4 days after administration.[1] Traditionally, the pattern of CINV with cisplatin is biphasic, with an intense initial peak within approximately the first 8–12 hours after administration, followed by a second, more prolonged phase of lesser intensity occurring during days 2–4 (Figure 1).[1] Risk factors for delayed CINV with cisplatin are the presence of acute CINV, emesis with prior chemotherapy cycles, higher dose, female sex, and younger age.[2]

One of the most important developments in the treatment of CINV over the last decade has been the introduction of a newer class of anti-emetic agents, the neurokinin-1 (NK1) receptor antagonists. One of these agents, aprepitant, was approved by the US Food and Drug Administration in 2003 for use in combination with other anti-emetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and moderately emetogenic cancer chemotherapy.[3] This approval was based on data from 2 multinational phase III studies that were conducted in patients receiving high doses of cisplatin chemotherapy: protocol 052 and 054 studies. Both studies used the same protocol.[4,5] Patients receiving cisplatin at a dose of at least 70 mg/m^2 for the first time were randomized 1:1 to either standard anti-emetic therapy (ondansetron 32 mg and dexamethasone 20 mg on day 1; dexamethasone 16 mg plus placebo on days 2 and 3; dexamethasone 16 mg on day 4) or an aprepitant regimen (aprepitant 125 mg plus ondansetron 32 mg and dexamethasone

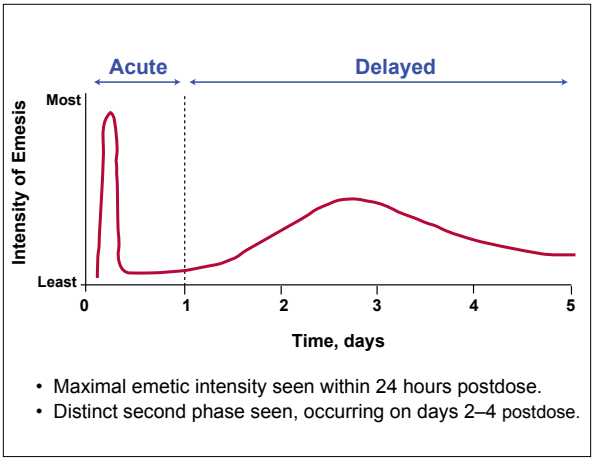

Figure 1. Cisplatin biphasic pattern of chemotherapy-induced nausea and vomiting.

Adapted from Tavorath R, Hesketh PJ. *Drugs.* 1996;52:639-648.

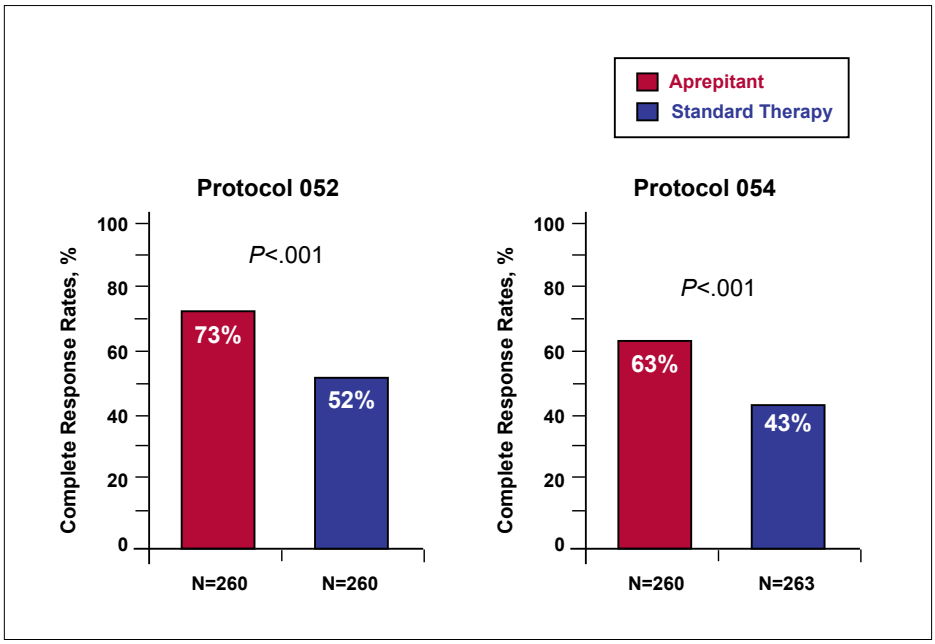

Figure 2.
Overall complete response rates on days 1 to 5 after cisplatin administration.

Data adapted from Hesketh et al. *J Clin Oncol.* 2003;15:4112-4119.

Poli-Bigelli et al. *Cancer.* 2003;97:2290-2300.

12 mg on day 1; aprepitant 80 mg and dexamethasone 8 mg on days 2 to 3; dexamethasone 8 mg on day 4). Patients were instructed to record nausea and vomiting episodes in a diary. The primary endpoint in both studies was complete response (CR), defined as no emesis and no rescue therapy on days 1 to 5 after the administration of cisplatin (Figure 2). In study 052 (n=520), the CR rate on days 1–5 was 73% in the aprepitant group and 52% in the standard therapy group (P<.001). In study 054 (n=523), the CR rate on days 1–5 was 63% in the aprepitant group and 43% in the standard therapy group (P<.001). Aprepitant was generally well tolerated in both studies.

A reasonable methodological question that can be asked of these studies is whether the advantage of aprepitant in preventing delayed emesis is simply due to differences in the level of acute emesis that may have been experienced in the 2 arms. These differences could have arisen because different regimens were used in the control arm and in the aprepitant arm on day 1. A subsequent analysis by Grunberg and colleagues argues against this explanation.[6] Among patients with acute vomiting in these studies, the percentage of patients with delayed vomiting was 85% in the control arm and 68% in the aprepitant arm. Among patients with no acute vomiting, the percentage with delayed vomiting was 33% in the control arm and 17% in the aprepitant arm. This suggests that the positive effects upon delayed vomiting seen in the aprepitant arm are real effects of the NK1 receptor antagonist.

There has been much interest in determining whether 5-HT_3 receptor antagonists have any role in the treatment and prevention of cisplatin-induced delayed emesis. The experience with first-generation 5-HT_3 receptor antagonists suggests that although they are effective for the prevention of acute emesis, they have limited efficacy in the delayed setting. Three studies with a total of 1,022 patients compared granisetron or ondansetron combined with dexamethasone alone for control of delayed emesis, and in all 3 studies the combination was no better than dexamethasone alone.[7-9] The newer 5-HT_3 receptor antagonist palonosetron, however, has shown more promise in the delayed setting. Palonosetron has a higher binding affinity for the 5-HT_3 receptor than do the first-generation agents, and it has a longer half-life, exerting its effect for several days after a single administration.[10] In a phase III trial by Aapro and colleagues, 667 patients were randomized to receive either a single intravenous dose of palonosetron 0.25 mg or 0.75 mg, or ondansetron 32 mg prior to the administration of highly emetogenic chemotherapy.[11] Dexamethasone pre-treatment (with stratification) was used at investigator discretion. The primary endpoint was the CR rate during the first 24 hours post-chemotherapy, and the CR rate during hours 24–120 was a secondary endpoint (acute phase). Overall, there was no significant difference between palonosetron and ondansetron in the control of acute or delayed emesis. However, a post hoc secondary subgroup analysis of the patients receiving dexamethasone demonstrated superior control of acute and delayed emesis in the group receiving palonosetron.

Saito and colleagues[12] recently published a phase III trial with 1,143 Japanese patients with cancer who were receiving highly emetogenic chemotherapy, with either cisplatin or an anthracycline and cyclophosphamide combination. Patients were randomized to receive either single-dose palonosetron 0.75 mg or granisetron 40 μg/kg 30 minutes before chemotherapy on day 1. All patients received dexamethasone 16 mg intravenously on day 1, followed by additional doses on days 2 and 3 (8 mg intravenously for patients receiving cisplatin or 4 mg orally for patients receiving an anthracycline/cyclophosphamide combination). The primary endpoints were a CR during the acute phase (hours 0–24) and a CR during the delayed phase (hours 24–120). The CR rate during the acute phase was 75% in the palonosetron group and 73% in the granisetron group. During the delayed phase, the CR rate was 57% in the palonosetron group compared with 45% in the granisetron group ($P<.0001$). The authors noted that both agents were well tolerated with similar safety profiles.

Referring back to our patient, she was clearly at high risk for delayed CINV: she is female, younger in age, and she received a moderately high dose of cisplatin. Her anti-emetic therapy could have been improved with the addition of aprepitant beginning with cycle 1 of treatment. Corticosteroids also have an important role for our patient and for the prevention of delayed CINV in general. The optimal dose when used with aprepitant has not yet been defined, but it should be approximately half the dose used without aprepitant, given the inhibitory effect of NK1 receptor antagonists on the metabolic pathway for dexamethasone. In my practice, I use a single 8 mg dose daily on days 2–4.

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Delayed Nausea and Vomiting Following Moderately Emetogenic Chemotherapy

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A 55-year-old white man presented with T3N1 stage III colon cancer with a tumor in the cecum and with 2 positive lymph nodes. He underwent a resection of the right side of the colon with a primary anastomosis, followed by adjuvant chemotherapy beginning 4 weeks post-surgery. The recommended regimen was FOLFOX6 (5-fluorouracil 400 mg/m^2 IV, leucovorin 400 mg/m^2 IV, and oxaliplatin 85 mg/m^2 IV on day 1 followed by 5-fluorouracil 2,400 mg/m^2 IV over 46 hours via a pump). The patient received intravenous ondansetron 16 mg and dexamethasone 20 mg before chemotherapy was initiated as prophylaxis against nausea and vomiting, and he experienced no AEs on day 1. The patient was given oral ondansetron 4 mg to take on days 2 and 3. When the patient returned 48 hours later for pump removal, he noted that he had experienced 1 episode of vomiting on day 2 and 2 episodes of nausea on day 3. He was given another dose of intravenous ondansetron 8 mg in the office when the pump was disconnected, and was instructed to continue the oral ondansetron. The patient was also given a prescription for prochlorperazine 15 mg to take for breakthrough nausea every 4 hours as needed. When he returned 2 weeks later for his second cycle of FOLFOX6, he mentioned that he had experienced nausea and 2 episodes of vomiting requiring him to take prochlorperazine on days 4–6.

Discussion

The most current guidelines from the NCCN[1], MASCC[2], and ASCO[3] recommend that patients undergoing moderately emetogenic chemotherapy receive combination treatment with a 5-HT$_3$ receptor antagonist and dexamethasone. An NK1 receptor antagonist can be added, depending upon individual patient factors. In this case, a more detailed nausea and vomiting history was taken before the second cycle of chemotherapy was begun, and the patient reported previous problems with motion sickness and tendency toward nausea and vomiting in response to other stimuli, suggesting that he is at higher risk for developing CINV. In addition, the patient had recently undergone a bowel operation and had been experiencing delayed emptying of his bowel as a result. This illustrates how important it is to carefully evaluate those individual patient factors in order to provide the most effective anti-emetic care possible. Clinicians should take a detailed nausea and vomiting history when prescribing moderately emetogenic chemotherapy, paying particular attention to the patient's natural tendencies as well as any previous abdominal surgeries that might contribute to the development of CINV.

Two changes were made to the patient's anti-emetic regimen to improve his response during the second cycle of chemotherapy. First, he was switched from the first generation 5-HT$_3$ receptor antagonist ondansetron to the second-generation agent palonosetron. As discussed by Dr. Hesketh, the data indicate that palonosetron is superior to the first-generation 5-HT$_3$ receptor antagonists for the prevention of delayed CINV, including for moderate emetogenic regimens (Figure 1).[4] Thus, the common practice of giving an oral first-generation 5-HT$_3$

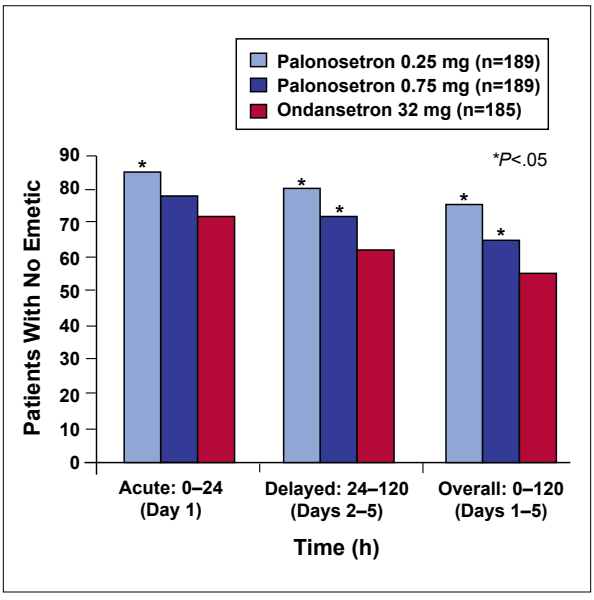

Figure 1. Comparison of palonosetron to ondansetron following moderately emetogenic chemotherapy during the acute, delayed, and overall time periods.

Data from Gralla R et al. *Ann Oncol.* 2003;14:1570-1577.

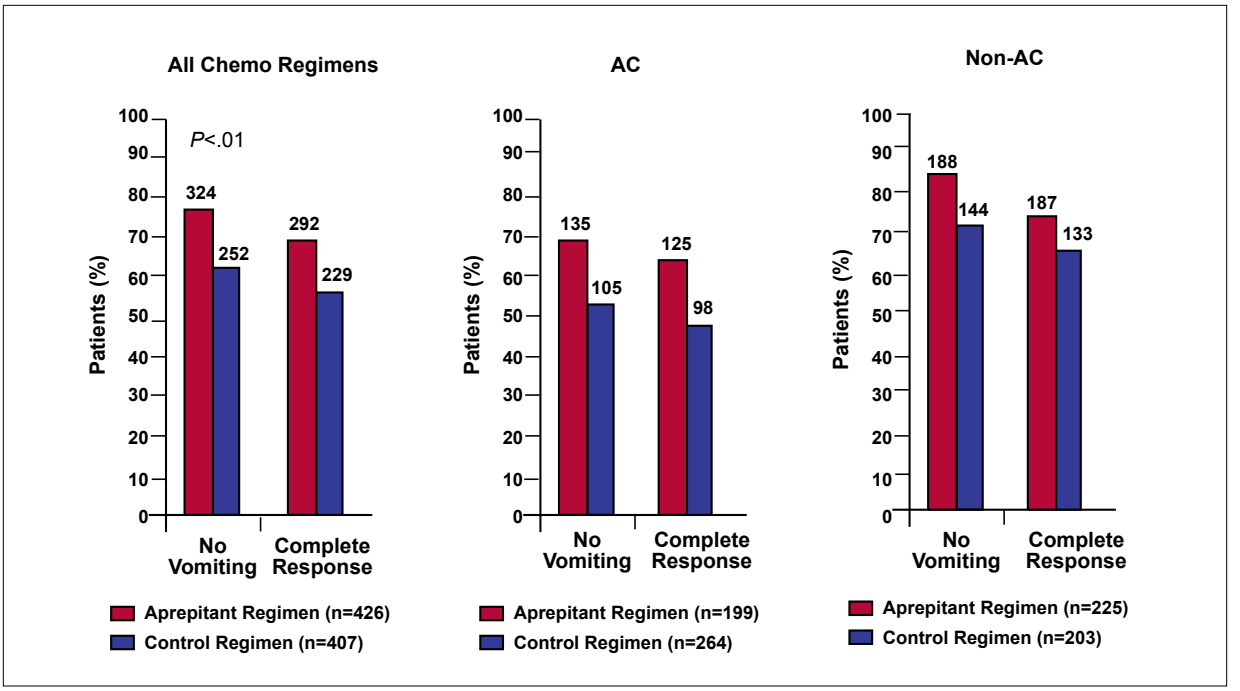

Figure 2. Benefit of addition of aprepitant for moderately emetogenic chemotherapy.

AC=anthracycline and cyclophosphamide.

Data from Rapoport BL et al. *Support Care Cancer.* 2010;18:423-431.

receptor antagonist after day 1 or even as a breakthrough anti-emetic is likely only minimally effective. Indeed, a 2005 meta-analysis by Geling and Eichler found that, on average, 74 doses of first-generation 5-HT_3 receptor antagonists must be administered to 12 patients to protect 1 patient from delayed emesis.[5]

The second change that was made to improve the management of this patient's CINV was the addition of the NK1 receptor antagonist aprepitant to his regimen. The benefit of adding aprepitant to the anti-emetic regimen used with highly emetogenic chemotherapy is well-recognized, but it has been demonstrated to be effective in the moderately emetogenic setting as well. A study by Rapoport and colleagues[6] in 848 patients receiving a broad range of moderately emetogenic chemotherapy found that triple therapy with aprepitant, ondansetron, and dexamethasone was superior to ondansetron plus dexamethasone alone for the prevention of both acute CINV (89% vs 80%, *P*<.001) and delayed CINV (71% vs 61%, *P*<.01; Figure 2). For our patient, the addition of the NK1 receptor antagonist during the second cycle was appropriate due to his history of abdominal surgery and a tendency toward nausea and vomiting. He thus received palonosetron IV, dexamethasone IV, and aprepitant on day 1 before chemotherapy was begun, and dexamethasone and aprepitant on days 2 and 3, a highly effective anti-emetic regimen.[7] When the patient returned to the office for pump disconnection at 48 hours post-chemotherapy, he noted that he had experienced 1 episode of nausea on day 2 and 1 episode on day 3, but that he had not vomited, and that he felt better, in general, on the second cycle than he had on the first.

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Nausea and Vomiting with Multi-day Chemotherapy

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A 39-year-old man with no smoking history presented with a nonproductive cough and anterior chest pain and facial swelling for 3 weeks. On physical examination, he had evidence of superior vena cava syndrome. The patient's complete blood count, liver function tests, serum electrolyte levels, kidney function tests, alpha-fetoprotein level, and beta human chorionic gonadotropin level were all normal. A chest x-ray revealed an anterior mediastinal mass. A computed tomography (CT) scan of the chest and abdomen confirmed an anterior mediastinal mass with periaortic adenopathy. A biopsy of the mass revealed an undifferentiated carcinoma. Based on the patient's age, the location of the tumor, and the rapidity of the tumor growth, he was diagnosed with extragonadal germ cell tumor syndrome.

The patient was started on intravenous etoposide 100 mg/m^2 and intravenous cisplatin 20 mg/m^2 on days 1–5, repeated every 3 weeks for 4 cycles. The patient also received bleomycin 30 units weekly throughout. This regimen is considered moderately emetogenic, with risks of CINV on days 1–8. His anti-emetic regimen, as reported by Einhorn and colleagues,[1] consisted of intravenous palonosetron 0.25 mg daily 30 minutes before chemotherapy on days 1, 3, and 5; intravenous dexamethasone 20 mg before chemotherapy on days 1 and 2; oral dexamethasone 8 mg twice daily on days 6 and 7, and oral dexamethasone 4 mg twice daily on day 8. The patient experienced mild nausea on days 6–8 only, which did not affect his ability to work.

Discussion

The standard of care for the prevention of CINV in patients who are undergoing multi-day chemotherapy is a 5-HT$_3$ receptor antagonist combined with dexamethasone.[2-4] Unfortunately, there are no randomized phase III trial data available in this setting, although there are some phase II trial data that can offer guidance. For example, Musso and colleagues examined the efficacy of palonosetron combined with dexamethasone for the prevention of acute and delayed CINV in patients receiving multi-day chemotherapy for hematologic malignancies.[5] Forty-six patients received intravenous palonosetron 0.25 mg and intravenous dexamethasone 8 mg 15 minutes before chemotherapy was given on day 1, followed by intravenous dexamethasone 4 mg twice daily throughout the entire period of chemotherapy. If breakthrough emesis occurred within 5 days after the end of chemotherapy, a second dose of palonosetron was administered, provided that at least 72 hours had elapsed since the first palonosetron dose was administered. The results from these patients were retrospectively compared to a second group of patients who had similar clinical characteristics and underwent similar multi-day chemotherapy (n=45). This comparison group received a single dose of intravenous ondansetron 8 mg plus intravenous dexamethasone 8 mg 15 minutes before chemotherapy was begun, followed by intravenous dexamethasone 4 mg twice daily throughout the entire period of chemotherapy. Intravenous metoclopramide 20 mg every 6–12 hours was given for breakthrough emesis within 5 days after the end of chemotherapy. The authors found that CINV during the chemotherapy period and in the 5 days following were absent in 80% of patients in the palonosetron group and 60% of the

Table 1. Guidelines/Recommendations For CINV with Multiple Consecutive Days of Chemotherapy

- American Society of Clinical Oncology (ASCO): Antiemetics appropriate for the risk of the chemotherapy be administered for each day of the chemotherapy and for 2 days after
- Multinational Association of Supportive Care in Cancer (MASCC): No guidelines
- National Comprehensive Cancer Network (NCCN): Recommendations included under Principles of Managing Multi-Day Emetogenic Chemotherapy Regimens (Table 2)

Table 2. Principles of Managing Multi-day Emetogenic Chemotherapy Regimens

- Patients receiving multi-day chemotherapy are at risk for both acute and delayed nausea/vomiting based upon the emetogenic potential of the individual chemotherapy agents and their sequence. It is therefore difficult to recommend a specific anti-emetic regimen for each day especially since acute and delayed emesis may overlap after the initial day of chemotherapy until the last day of chemotherapy. The period of risk for delayed emesis after chemotherapy administration has concluded also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.
- Examples illustrating the above include BEP (bleomycin 30 units IV weekly, etoposide 100 mg/m^2 IV days 1–5 and cisplatin 20 mg/m^2 IV days 1–5) versus ASHAP (doxorubicin 25 mg/m^2 IV day 1, methylprednisolone 500 mg/day IV days 1–5, cisplatin 25 mg/m^2 IV continuous infusion days 1–4 followed by cytarabine 2,000 mg/m^2 on day 5). BEP is moderately emetogenic with risk for emesis on days 1–8 whereas ASHAP is moderately emetogenic on days 1–4 but becomes highly emetogenic on day 5 due to the administration of high-dose cytarabine. Risk for acute and delayed emesis for ASHAP may last up to 10 days.

Accordingly, the panel recommends the following as general principles:

- A 5-HT$_3$ receptor antagonist should be administered prior to each day's first dose of moderately- or highly-emetogenic chemotherapy.
- Dexamethasone should be administered once daily either orally or intravenously for every day of moderately- or highly-emetogenic chemotherapy and for 2–3 days after chemotherapy for regimens that are likely to cause significant delay in emesis. Dexamethasone should not be added when the chemotherapy regimen already includes a corticosteroid (as in ASHAP illustrated above).
- Intravenous palonosetron may be used prior to the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT$_3$ receptor antagonists. Repeat dosing of palonosetron 0.25 mg IV is likely to be safe, based upon a dose-ranging phase II trial, where up to 30 times the FDA-approved dose (90 µg/kg) was administered, and 3 phase III trials that evaluated palonosetron 0.75 mg as a single fixed dose. Compared to the approved dose of palonosetron (0.25 mg), these higher doses were not associated with significantly different grades or durations of adverse events. In terms of efficacy, need for repeat dosing with palonosetron, either daily or less frequently, in the setting of multi-day chemotherapy is not yet known.
- Aprepitant may be used for multi-day chemotherapy regimens likely to be highly-emetogenic and associated with significant risk for delayed nausea and emesis. Category 1 evidence is available for single-day chemotherapy regimens only, and aprepitant 125 mg should be administered orally 1 hour prior to chemotherapy on day 1, along with a 5-HT$_3$ receptor antagonist and dexamethasone. Aprepitant 80 mg should be administered daily on days 2 and 3 after the start of chemotherapy along with dexamethasone. Based upon phase II data, aprepitant 80 mg may be safely administered on days 4 and 5 after multi-day chemotherapy. It is not yet known if dosing aprepitant after day 3 improves control of nausea or emesis in this clinical setting. Note that fosaprepitant dimeglumine (115 mg) may be substituted for apreprintant (125 mg) on day 1 only.

Data from National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Antiemesis, V.2.2010. Available at http://www.nccn.org/ professionals/ physician_gls/PDF/antiemesis.pdf.

ondansetron group (P<.05). In the palonosetron group, 67% of patients who experienced CINV were successfully rescued by a second dose of palonosetron, while in the ondansetron group, only 22% were rescued by metoclopramide treatment (P=.04). Thus, palonosetron appears to offer very good control of both acute and delayed CINV for patients undergoing multi-day chemotherapy, as can be seen with our patient.

There has been much interest in testing aprepitant in the multi-day chemotherapy setting, although no phase III data are yet available. One preliminary study by Jordan and colleagues showed promising results.[6] In their study, cancer patients undergoing multi-day chemotherapy of high (n=38) or moderate (n=40) emetic risk received granisetron, dexamethasone, and aprepitant before chemotherapy was begun and each day during chemotherapy. After the end of chemotherapy, aprepitant and dexamethasone were given for another 2 days. A complete response, defined as no CINV during chemotherapy and the 5 days following chemotherapy, was seen in 58% of patients in the highly emetogenic chemotherapy group and 73% of patients in the moderately emetogenic chemotherapy group. The investigators noted that the tolerability of the multi-day aprepitant regimen was comparable with that reported for the 3-day aprepitant regimen. Further studies of aprepitant in the multi-day setting are warranted.

Another option for patients undergoing multi-day chemotherapy is transdermal granisetron, which is supplied as a patch containing 34.3 mg of granisetron that releases 3.1 mg of granisetron per 24 hours. The patch can be applied to the upper arm between 24 and 48 hours before chemotherapy and can be worn for up to 7 days, depending on the duration of the chemotherapy regimen. Transdermal granisetron was approved in the United States in late 2008 and is specifically indicated for the prevention of nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy regimens of up to 5 consecutive day's duration.[7,8] The approval was based on data from an international, randomized phase III study that is of yet unpublished.[7] In that study, 641 patients receiving multi-day highly or moderately emetogenic chemotherapy were randomized to receive either treatment with the granisetron patch or oral granisetron 2 mg once daily. The granisetron patch was applied 24–48 hours before the first dose of chemotherapy and was kept in place for 7 days. Oral granisetron was administered daily for the duration of the chemotherapy regimen, 1 hour before each dose of chemotherapy. The trial evaluated efficacy from the first administration until 24 hours after the end of chemotherapy. Complete response, defined as no vomiting, no rescue medication, and no more than mild nausea, was seen in 61% of patients in the granisetron patch group and in 65% of the oral granisetron group (difference, -4.89%; 95% confidence interval, -12.91% to +3.13%). This trial showed that the transdermal system is just as effective as oral granisetron, with the added advantage of patients not having to take pills, which can be lost due to vomiting. One drawback to this trial was that the efficacy assessment was only carried through for 24 hours after the last chemotherapy administration, so the effects of the drug upon delayed CINV were not fully evaluated out to 5 days post-chemotherapy.

Unfortunately, because of a paucity of studies evaluating the prevention and treatment of nausea and vomiting associated with patients receiving multi-day emetogenic chemotherapy, antiemetic guidelines do not fully address this problem, although the NCCN has a section of principles of managing multi-day emetogenic chemotherapy regimens (Tables 1 and 2).

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Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Case Study Compendium

CME Post-test: *Circle the correct answer for each question below.*

1. Which of the following chemotherapy regimens carries a high emetic risk?

   a. An anthracycline and cyclophosphamide combination
   b. Cyclophosphamide at a dose of greater than 1,500 mg/m^2
   c. Carmustine at a dose of greater than 250 mg/m^2
   d. All of the above

2. In the study by Shih and colleagues, the average total direct medical costs per patient per month for the uncontrolled CINV group were $_____ higher than those for the controlled CINV group.

   a. $1,729
   b. $1,578
   c. $1,383
   d. $1,117

3. What is the MASCC guideline-recommended antiemetic regimen for patients undergoing low emetic risk chemotherapy?

   a. Monotherapy with a 5-HT$_3$ antagonist on day 1
   b. Monotherapy with lorazepam on day 1
   c. Monotherapy with dexamethasone on day 1
   d. Monotherapy with an NK1 receptor antagonist on day 1

4. Which of the following is NOT a risk factor for CINV with highly emetogenic chemotherapy?

   a. emesis with prior chemotherapy cycles
   b. higher chemotherapy dose
   c. female sex
   d. age over 50

5. In the phase III trials of aprepitant to prevent cisplatin-induced nausea and vomiting (protocols 052 and 054), the addition of aprepitant to a standard ondansetron plus dexamethasone regimen increased the complete response rate by approximately ____ percentage points.

   a. 10
   b. 20
   c. 25
   d. 30

6. Which of the following 5-HT$_3$ receptor antagonists has demonstrated superior efficacy for the prevention of delayed CINV associated with highly emetogenic chemotherapy?

   a. palonosetron
   b. granisetron
   c. ondansetron
   d. dolasetron

7. TRUE OR FALSE? Triple therapy with a 5-HT$_3$ receptor antagonist, dexamethasone, and a NK1 receptor antagonist is warranted for patients undergoing moderately emetogenic chemotherapy when a history of early nausea and vomiting exists.

   a. True
   b. False

8. What is the standard-of-care for the prevention of CINV in patients who are undergoing multi-day moderately emotogenic chemotherapy?

   a. Triple therapy with a 5-HT$_3$ receptor antagonist, dexamethasone, and a NK1 receptor antagonist, given daily during chemotherapy and for 2 days afterward
   b. A 5-HT$_3$ receptor antagonist plus dexamethasone given daily during chemotherapy, followed by dexamethasone monotherapy for 2 days afterward
   c. Dexamethasone monotherapy given daily during chemotherapy and for 2 days afterward
   d. A 5-HT$_3$ receptor antagonist given daily during chemotherapy

9. According to the study by Jordan and colleagues in patients undergoing multi-day chemotherapy of high or moderate emetic risk, daily administration of aprepitant during multi-day chemotherapy produced a safety profile _____ that reported for the 3-day aprepitant regimen.

   a. much worse than
   b. slightly worse than
   c. similar to
   d. better than

10. TRUE OR FALSE? Transdermal granisetron is more effective than oral granisetron for the prevention of acute CINV.

    a. True
    b. False

Evaluation Form Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Case Study Compendium

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
(1 = Strongly Disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly Agree)

1. Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the importance of new study findings and clinical trial data in the natural history of chemotherapy-induced nausea & vomiting (CINV) in cancer patients 1 2 3 4 5
2. Assess the results of these new study findings including updates on guidelines for highly and moderately emetogenic chemotherapy and radiotherapy 1 2 3 4 5
3. Integrate into clinical practice the latest knowledge and methods for treating cancer patients with CINV in an effort to improve current quality of life statistics 1 2 3 4 5
4. Identify future research directions for all therapies in CINV in cancer patients 1 2 3 4 5

2. Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

3. Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity: _____

_____

Please list any topics you would like to see addressed in future educational activities: _____

Additional comments about this activity: _____

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