Managing Chemotherapy-Induced Nausea and Vomiting: An Adaptable, Collaborative Approach for a Patient With Colon Cancer

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Authors' disclosures of potential conflicts of interest are found on page 3 and at the end of this article.

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Although most patients at risk for chemotherapy-induced nausea and vomiting (CINV) receive appropriate prophylactic antiemetics before chemotherapy—particularly for highly emetogenic (HEC) or moderately emetogenic chemotherapy (MEC)—CINV is not typically restricted to the first 24 hours after treatment (acute CINV). In fact, health-care providers, including advanced practitioners (APs) in oncology, may underestimate the proportion of patients who will suffer inadequately controlled delayed CINV (that which occurs 24 hours to several days after chemotherapy).

Delayed CINV is more common than acute CINV: By patient report, 40% to 60% experience delayed vomiting (CIV) and 45% to 64% experience delayed nausea (CIN) after HEC, and 22% to 54% have delayed vomiting (CIV), and 33% to 74% have delayed nausea after MEC (Grunberg et al., 2004; Liau et al., 2005; Majem et al., 2011). The risk of CINV on subsequent days and in subsequent cycles of chemotherapy may be increased when CINV is not controlled on the first day of chemotherapy, but delayed CINV can occur even when it is prevented in the acute setting (Decker, DeMeyer, & Kisko, 2006; Mertens et al., 2003).

Chemotherapeutic agents associated with a high risk of delayed CINV include high-dose cisplatin-based regimens and an anthracycline (doxorubicin or epirubicin) combined with cyclophosphamide: the so-called AC regimens (Hesketh, 2014). It is important for APs in oncology to be aware that delayed CINV occurs after many MEC regimens. Regimens that include oxaliplatin, such as IV FOLFOX for colorectal cancer (CRC), have been associated with delated CINV. The FOLFOX regimen consists of oxaliplatin 85 mg/m^2 over 2 hours on day 1, leucovorin 400 mg/m^2 over 2 hours on day 1, then fluorouracil (5-FU) 400 mg/m^2 bolus on day 1 followed by 2,400 mg/m^2 continuous infusion over 48 hours (1,200 mg/m^2 per day × 2 days), repeated every 2 weeks (National Comprehensive Cancer Network [NCCN], 2014).

This article features a case report that highlights a patient with CRC who was about to start FOLFOX. It

demonstrates how APs must be knowledgeable in prescribing evidence-based, standard-of-care prophylactic antiemetics to prevent acute and delayed CINV; to use flexible approaches in the event that the patient develops delayed CINV; and to be creative in exploring other adjunctive strategies to manage delayed CINV (e.g., confirming that the patient is taking prescribed antiemetics, adding other agents, and exploring nondrug measures).

CASE STUDY

Mike, a 64-year-old man who considered himself to be "healthy," underwent a routine colonoscopy during which a large (3.4 cm) pedunculated polyp was removed. The pathology findings confirmed adenocarcinoma in the polyp with invasion into the colon submucosa. His liver function tests were normal, but his carcinoembryonic antigen (CEA) level was 12.4 ng/mL (normal level is < 2.5 ng/mL in nonsmokers). There was no other evidence of metastases in his liver or lungs. He underwent laparotomy for colectomy and en bloc regional lymph node dissection in which 6 inches of bowel and 14 lymph nodes were removed. His primary tumor did not extend through the bowel wall, but two lymph nodes were positive. His ultimate diagnosis was stage IIIB (T3N2M0) adenocarcinoma of the colon.

Mike was referred to a medical oncologist. He, the physician, and the oncology AP discussed the risk for recurrence without further treatment and the potential benefits of adjuvant chemotherapy. The oncologist recommended 6 months of FOLFOX. The AP reiterated that the major adverse effects of FOLFOX were peripheral sensory neuropathy, neutropenia and increased risk for infection, fatigue, thinning scalp hair, diarrhea, and oral mucositis, as well as nausea and vomiting. The AP stated that if Mike underwent this chemotherapy course, prophylactic medical and self-care measures would be a priority.

Mike decided to start treatment with FOLFOX. The AP caring for him was responsible for his supportive/palliative care and made decisions regarding his antiemetic medication plan. Prechemotherapy considerations included the emetogenic potential of the chemotherapy regimen and personal risk factors according to any of the current clinical guidelines from the NCCN, the American Society of Clinical Oncology (ASCO), or the Multinational Association for Supportive Care in Cancer (MASCC; Basch et al., 2011; NCCN, 2014; Roila et al., 2010). FOLFOX is rated as a MEC regimen, and Mike's history suggested no risk factors for increased likelihood of CINV (i.e., female gender, age younger than 55, chronic alcohol use, or other factors such as a history of motion sickness) See the article by Teresa Scardino on page 7 of this supplement for further discussion.

ANTIEMETIC GUIDELINES

According to current antiemetic guidelines, patients receiving HEC or MEC regimens should be given prophylactic antiemetics for acute and delayed CINV (NCCN, 2014; Basch et al., 2011; Roila et al., 2010). For a MEC regimen such as FOLFOX, a serotonin (5-HT_3) antagonist and 12 mg oral or IV dexamethasone administered before chemotherapy are recommended to prevent acute and delayed CINV. All guidelines preferentially recommend palonosetron 0.25 mg IV because of its long half-life and its US Food and Drug Administration (FDA) approval for prevention of acute and delayed CINV from MEC. If another 5-HT_3 antagonist (dolasetron, granisetron, or ondansetron) is administered on the day of chemotherapy, it should be given for delayed CINV. Dexamethasone is a preferred antiemetic for acute and delayed CINV regardless of which 5-HT_3 antagonist is used.

Unlike the ASCO and MASCC guidelines, the NCCN guidelines (2014) include "optional" drugs to be administered with antiemetic regimens. For patients receiving MEC, this may include an oral or IV neurokinin-1 (NK-1) antagonist (oral aprepitant or IV fosaprepitant) for "selected patients," with or without lorazepam, with or without a histamine (H2) blocker or proton pump inhibitor (PPI). The strategy for reserving the expensive NK-1 antagonist reflects ASCO's "Choosing Wisely" campaign that advises against common practices not supported by evidence and recommends not using antiemetics intended for HEC (i.e., aprepitant or fosaprepitant) in patients starting a MEC or lower regimen (Schnipper et al., 2013). This caution seems to contradict guideline recommendations to *prevent* CINV rather than intervene to manage it after it occurs. However, we must be mindful that all patients receiving MEC may not

require an antiemetic that costs about $389 per cycle (according to www.Epocrates.com). It is interesting to note that the tri-pack of oral aprepitant (Emend, 125 mg ×1 and 80 mg ×2) is much less expensive in other countries; online prices range from $101 to $158 in US dollars.

Lorazepam, H2 blockers, and PPIs are not antiemetics per se. However, clinicians know that lorazepam may decrease the anxiety that can worsen nausea, help a patient sleep, and add some sense of control. The evidence for the useful of H2 blockers and PPIs is more indirect. For instance, cisplatin (and probably other chemotherapy agents) causes gastric dysmotility and dysrhythmia in animals (Malik, Liu, Cole, Sanger, & Andrews, 2007), and patients who are pregnant or have diabetes can also have gastroparesis (Camilleri, Bharucha, & Farrigjia, 2011; Law, Maltepe, Bozzo, & Einarson, 2010). Gastroparesis may be accompanied by other nonspecific manifestations including delayed gastric emptying, bloating, early satiety, heartburn, reflux, and nausea. These symptoms are often alleviated with H2 blockers (e.g., cimetidine, famotidine, nizatidine, and ranitidine) and PPIs (e.g., esomeprazole, lansoprazole, omeprazole, and pantoprazole), which also reduce gastric acid.

CASE STUDY: CONTINUED

Before beginning his first cycle of FOLFOX, Mike was given palonosetron (0.25 mg IV) and dexamethasone (12 mg IV) on day 1 to prevent acute and delayed CINV. He was sent home with a prescription for dexamethasone (8 mg once a day for 3 days). Although dexamethasone is typically given in a split dose twice a day, it has a long half-life (about 36 to 54 hours) and duration of action so a single daily dose may be more practical (Cross, Paul, & Goldman, 2011).

Mike seemed to come through the first cycle of FOLFOX well, reporting "just a little nausea." However, on day 3 after starting his second cycle, Mike called his AP. He reported that his nausea was much worse this time and that he threw up the night before. He felt continuous nausea, and not knowing if or when he might throw up was interfering with his ability to perform his daily tasks and enjoy his leisure activities. He was seriously considering whether or not to continue FOLFOX.

Mike's daughter had come over to visit, and together they looked for online information about nausea with FOLFOX. They found some patient-driven information-sharing forums such as www.ehealthme.com and www.treato.com. He wants to know about other "strong" antinausea medicines. Because it is not likely that Mike has any nonchemotherapy causes of the nausea, his AP agrees it is time to take another therapeutic tack in an attempt to relieve his delayed CINV. As one patient in an online discussion noted, "Sometimes it takes some experimenting to find out what works best" (ColonClub.com, 2014).

CRAFTING A NEW TREATMENT STRATEGY

Advanced practitioners frequently care for patients like Mike who experience delayed CINV after effective antiemetic prophylaxis for acute CINV that does not continue after the second or third day. In particular, delayed nausea is often poorly managed, despite the fact that it is among the most concerning side effects to patients receiving chemotherapy (Fernández-Ortega et al., 2012; Hilarius et al., 2012). However, in antiemetic studies, definitions still focus on vomiting and "no emetic episodes" as a primary outcome variable. On the other hand, minimal or no nausea is inferred (perhaps incorrectly) in the current definition of complete response: "no vomiting and no use of rescue medication" (Andrews & Sanger, 2014). Furthermore, because of cost, implementation, analysis, and interpretation issues, patients' self-report of qualitative experiences is rarely incorporated into quantitative antiemetic studies. These facts go hand-in-hand with how little we know about the physiology of nausea. As a consequence, we know less about its prevention and management than we do about vomiting.

CASE STUDY: CONCLUDED

After he started on FOLFOX, Mike's AP telephoned on day 3 to ask about how well his CIN and CIV were being controlled, to check that he had his antiemetics and that cost was not a barrier to their acquisition, and to ensure that he was taking his antiemetics as instructed. Mike mentioned that it would be easier for him if they could communicate by texting on his mobile phone, which allows for real-time management of CINV as well as other symptoms (Weaver et al., 2007). His AP agreed to

send future reminders and/or follow-ups to his mobile phone via text message.

COMMUNICATION AND ADHERENCE

The AP must collaborate with others (the oncology pharmacist and the oncologist) to ensure that the patient has been taking the antiemetics as instructed and to develop new management and assessment strategies. In the AP's view, clear and consistent communication with the patient (in this case, Mike) regarding his opinion of the efficacy of his antiemetics is a cornerstone of patient-centered management of CINV. This includes getting the patient's assessment of how well vomiting and nausea are being prevented by the current antiemetics or, conversely, learning about any unpleasant side effects that the antiemetics are causing.

Other possible communication strategies are smartphone or tablet medication reminder apps and automatic voice mail reminder messages. And of course, regular telephone calls are still a viable option for many patients. This might seem like a big investment in time that the AP does not have, but it may prevent untimely and expensive extra visits to the clinic or emergency department. A communication strategy that does not work with the patient's lifestyle and preferences has a poor chance of bringing about any benefits. Patient-tailored follow-up not only can aid the AP in evaluating symptoms in a timely manner, but it can increase the likelihood of adherence to oral antiemetics as well as other agents (Fenerty, West, Davis, Kaplan, & Feldman, 2012).

PHARMACOLOGIC OPTIONS

Mike was taking dexamethasone as prescribed for delayed CINV. But APs should remember that the responsibility for the five "rights" of medication use—the right patient, the right drug, the right time, the right dose, and the right route—shifts to the patient and family members when oral medications are taken at home (Eaby-Sandy & Sherry, 2011). This may also be related to drugs a patient may be taking to prevent other problems, such as constipation, that could exacerbate CINV. Mike and his AP should explore other potential barriers to adherence such as lack of social support, limited health literacy, comorbid problems, polypharmacy, or other issues (Sommers, Miller, & Berry, 2012).

As mentioned previously, the NCCN guidelines (2014) suggest using adjunct medications that have some basis in other patient populations but seem to be generalizable to cancer patients receiving chemotherapy, for example, over-the-counter agents such as H2 blockers famotidine and ranitidine and PPIs lansoprazole and omeprazole are over-the-counter (OTC) products. These medications should be used before patients develop refractory symptoms. Mike's AP should be sure to share the generic and brand names of the suggested medications with Mike, as the generic formulation will be less expensive. Audience members at the *JADPRO* Live CINV symposium shared their success stories in using these stomach acid–reducing agents, particularly in patients with breast cancer.

Most APs would reserve H2 blockers or PPIs for additional adverse effects. The AP would likely recommend the lowest recommended OTC dose and increase to twice a day if the nausea does not improve with that dose. Some APs opt to start with H2 blockers, which are generally safe and cause few side effects, but they can potentially cause drug interactions as they are metabolized by cytochrome P450 enzymes (Maton, 2003). Furthermore, short-term use of PPIs causes few adverse effects, but long-term use may be associated with osteoporosis and increased risk of fractures, iron deficiency in patients with low baseline iron stores, increased risk of *Clostridium difficile* and other enteric infections, major cardiac events in patients with a cardiac history, gastric acid rebound after discontinuation of a PPI, and hypomagnesemia (Ament, Dicola, & James, 2012; Luk, Parsons, Lee, & Hughes, 2013).

Advanced practitioners should also consider adding guideline-recommended antiemetics for breakthrough CINV, such as an antiemetic from a different class (Basch et al., 2011; NCCN Antiemesis, 2014; Roila et al., 2010). Possible drugs are olanzapine, an atypical antipsychotic that is a powerful 5-HT_3 antagonist and acts at other neuroreceptors involved in vomiting; a cannabinoid (dronabinol or nabilone, or medical marijuana if legal in your state); a dopamine 2 (D2) antagonist (prochlorperazine or haloperidol); a 5-HT_4 agonist, which enhances gastric emptying (metoclopramide); or a different 5-HT_3 antagonist or a different mode of administration (e.g., olanzapine or transdermal granisetron). Although H1 blockers

are also included in the recommendations, clinical experience says that drugs like promethazine cause more sedation and other side effects (e.g., akathisia) than they add clinical benefit and are contraindicated in elderly individuals (Braude & Crandallvan, 2008; van der Hooft et al., 2002).

NONPHARMACOLOGIC ADJUNCTIVE MEASURES

Most research into nonpharmacologic measures for nausea and vomiting focuses on pregnancy and postanesthesia settings. However, clinical and research literature regarding the use of nondrug measures is increasing, particularly related to the use of ginger, acupressure, and acupuncture to alleviate nausea in cancer patients. There is some evidence for their benefit in enhancing control of CINV, but these modalities would not replace standard of care antiemetics. Some studies have shown conflicting results, while others show small effects on nausea and vomiting. Our patient Mike might be interested in exploring any or all of these approaches.

Ginger

Ginger, which has been used to prevent and treat nausea in many cultures for 2,500 years, has had contradictory results when studied in the CINV setting (Haniadka, Rajeev, Palatty, Arora, & Baliga, 2012; Marx et al., 2013). Although the antiemetic mechanisms of action are unknown, several of its component phytochemicals may act by antagonism of 5-HT_3, NK-1, and H1 receptors and may have prokinetic effects (Haniadka et al., 2012).

One trial that seems to have overcome the methodologic concerns of other studies was a relatively large prospective, randomized, double-blind study of 575 evaluable patients that compared three doses of ginger (500, 1,000, or 1,500 mg per day) to placebo (Ryan et al., 2011). Patients took half of the total dose twice a day starting 3 days before chemotherapy and continuing for 3 more days (6 days total). All patients had to have experienced CIN with previous chemotherapy, had to be receiving a 5-HT_3 antagonist, and had to be scheduled to receive at least 4 cycles of chemotherapy (the study period).

All ginger doses were significantly superior to placebo, but 500 and 1,000 mg/day most effectively reduced acute CIN. These differences were not only sustained in subsequent cycles but may have slightly improved (differences were not statistically significant). During the delayed period, all patients took other antiemetics but patients taking placebo tended to take more doses.

In another randomized, open-label study, 100 women receiving docetaxel, epirubicin, and cyclophosphamide were assigned to a control group who received standard antiemetics (granisetron plus dexamethasone) or the treatment group who received ginger (1.5 g/d in 3 divided doses every 8 hours for 4 days) plus standard antiemetics (Panahi et al., 2012). As with the previous study, a significant benefit in decreasing acute CIN was seen in the patients who received ginger plus the 5-HT_3 antagonist plus dexamethasone.

While other studies have not confirmed these results, the AP might suggest that Mike visit his local health food store and buy ginger capsules. He could try 500 to 1,000 mg once or twice a day starting a few days before chemotherapy. How long he should continue ginger is not clear, but given that it is generally safe, Mike might take it for the number of days his delayed CINV persisted after FOLFOX.

Acupuncture and Acupressure

In an extensive systematic review of acupuncture for various symptoms experienced by cancer patients, Garcia and colleagues (2013) concluded that it is a safe and inexpensive adjunctive option for patients who are experiencing nausea and vomiting but do not have adequate control with drugs. It should be pointed out, however, that most of the studies they reviewed were limited by small sample sizes and other concerns regarding methodology. Acupuncture is rarely used because of the need for a specially trained acupuncturist and the associated costs, but it is easy and convenient for patients to try acupressure.

Acupressure is a low-tech, free or almost free technique that a patient can use by him- or herself. Molassiotis and colleagues (2013) evaluated the use of acupressure in 361 evaluable chemotherapy-naive patients for CINV. Patients were randomized to standard treatment (guideline-recommended antiemetic therapy based on chemotherapy emetogenicity), standard antiemetics plus sham acupressure, or standard antiemetics plus actual acupressure with wristbands applied to the P6 point. Patients in the sham and actual

acupressure point groups had bands applied continuously for 6 days. Although patients with either actual or sham acupressure reported lower levels of CIN, there were no statistically significant differences among the treatment groups.

Another review pointed out the methodologic issues found in other acupressure studies, yet concluded that it appears to be helpful for acute CINV (Chao et al., 2009). One variable that is typically not addressed in acupressure studies is how long to apply pressure to P6; it may be that continuous pressure is counterproductive. It would be ideal for studies to refine how long each acupressure session should last and to determine whether there is an ideal schedule and duration (in days) when using it in the CINV setting. Anecdotal instructions on how to apply acupressure can easily be found on the Internet by patients wishing to experiment with how this technique may help them.

LOOKING TO THE FUTURE

The AP caring for Mike needs to assess every medication he is taking—not just what was prescribed—to learn whether medication reconciliation may be at the heart of his continued nausea. For instance, if Mike were taking high doses of natural substances such as vitamins, they may be significantly contributing to his nausea and vomiting. Older patients may be taking a long list of medications, some of which may interact with their antiemetic therapy (Eaby-Sandy & Sherry, 2011). Devoting time to discuss all medications and supplements that Mike may be taking might yield a missing piece that can help solve the puzzle of his delayed CINV.

Advanced practitioners should be attuned to the availability of new agents, formulations, or combination antiemetic products that may receive FDA approval for CINV. Such promising agents may be useful for patients like Mike who develop substantial and distressing delayed CINV, which further increases the risk for anticipatory nausea and intractable CINV. Agents in premarketing at this time include NEPA, a tablet that combines netupitant, a new NK-1 antagonist, and the 5-HT_3 antagonist palonosetron, as well as APF530, a novel formulation of a subcutaneous depot injection of granisetron in a polymer-based drug delivery system. These novel agents increase our armamentarium to help our patients at risk for or experiencing CINV.

CONCLUSION

This case presentation illustrates a stepwise approach to assessing and subsequently managing acute and delayed CINV. It may not be a direct path with one clear-cut choice, but rather an adaptable strategy that requires straightforward communication with patients and a creative mindset to address a host of potentially interrelated considerations. In this manner, symptoms of CINV may be relieved, and patients may be able to remain on necessary and often lifesaving chemotherapy regimens.

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Dr. Wickham has served on speakers bureaus for Genentech.

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