

Historical Perspective on the Progress of Chemotherapy-Induced Nausea and Vomiting Treatment in *Oncology Nursing Forum*

Chemotherapy-induced nausea and vomiting (CINV) has been a priority symptom in the management of patients with cancer since the inception of chemotherapy. In the mid-1970s, the most effective agents available were the standard antiemetics used for gastrointestinal illnesses, postoperative nausea, and morning sickness. The Oncology Nursing Forum has documented the study of this symptom—causes, pathophysiology, and manifestations—in the past four decades as well as emerging treatment therapies. To date, CINV is fairly well controlled, but work still needs to be done, particularly in delayed and refractory management.

Oncology Nursing Forum (ONF) published an article in its early newsletter format in 1977 entitled “Variables Affecting Nausea and Vomiting” (Mayer Scogna, 1977). That literature review provided an excellent analysis of the state of the art in the management of chemotherapy-induced nausea and vomiting (CINV) at that time. Healthcare providers knew that the vomiting center, chemoreceptor trigger zone (CTZ), and vagal afferents in the gastrointestinal (GI) tract were intimately involved in CINV and that multiple and varied chemoreceptors existed in the CTZ. Unfortunately, interventions lagged compared to the knowledge of the pathophysiology of the CINV process. Only 13 studies on the effectiveness of available antiemetics were published from 1964 to 1977, and no new agents had been developed since the 1950s (Mayer Scogna, 1977). That study investigated whether extrinsic factors, subjective attitude about effectiveness of chemotherapy, hours of sleep prior to treatment, activity level, or food intake affected CINV and found that they did not. Mayer Scogna (1977) recognized anticipatory nausea and vomiting, referring to this as a conditioned psychological component, and noted the lack of reliable tools to objectively measure nausea and vomiting.

The 1980s presented a particular challenge with the introduction of cisplatin, which is a very novel and effective agent, yet highly emetic. Maxwell (1982) published a special feature in *ONF* to express the frustration of the oncology field with not only the lack of well-performed antiemetic clinical trials, but the lack of effective antiemetics available. Maxwell also reviewed the current antiemetics with phenothiazines (i.e., prochlorperazine)

recommended as first-line treatment and cannabinoids and butyrophenones (i.e., haloperidol) and corticosteroids as second-line treatment. The difficulties associated with quantitatively measuring nausea and vomiting also presented a challenge. Gralla (1981) investigated the use of high-dose metoclopramide as an antiemetic for cisplatin-based chemotherapy. Although Gralla reported effective emetic control and safety, another study (Aapro, 1982) reported excessive central nervous system toxicity with high-dose metoclopramide.

Wickham (1989) published a state-of-the-art article in *ONF*, and the understanding of CINV broadened to include neurotransmitters involved with CINV, acute and delayed nausea and vomiting, and the emetic potential of various chemotherapeutic agents. Although, overall, the choice of antiemetics did not change, healthcare providers became more comfortable using high doses of metoclopramide and treating extrapyramidal side effects. Lorazepam was widely used as an amnesiac because the experience of nausea and vomiting was so unpleasant. Clinical trials with antiemetics revealed that prophylactic administration of antiemetics and combination antiemetics provided better emetic control. In addition, if acute nausea and vomiting were well controlled, delayed control was improved. Wickham (1989) also presented an assessment tool for nurses to use when caring for patients receiving chemotherapy.

Difficult for Patients

As a nurse caring for patients receiving highly emetogenic chemotherapy at this time, it was extremely stressful for the patient experiencing significant nausea and vomiting when little could be done to improve the situation. Waves of nausea and vomiting came rhythmically with little control, and the nurse had to support the patient with a basin, cool wash cloth, and a cup of water to rinse (Rhodes, Watson, Johnson, Madsen, & Beck, 1987). Behavioral interventions also began to emerge as an adjunct to traditional antiemetics (Wickham, 1989). Relaxation techniques, distraction, exercise, guided imagery, and hypnosis were studied to establish their role in decreasing nausea and vomiting. Trials with acupuncture and acupressure applied to P6 (pericardium 6) were conducted to look at their effect on emesis (Price, Williams, & Sergiou, 1992).

The 1990s saw the emergence of a new class of antiemetics that would significantly impact CINV. The serotonin receptors of the 5-HT₃ type are located in both the CTZ and vagal afferent fibers of the gastrointestinal tract. Ondansetron, a 5-HT₃ receptor antagonist, was

the premier agent used in the clinical trials. It was available via IV as well as orally, so premedication was convenient. Side effects were very tolerable compared to those with high-dose metoclopramide, lorazepam, and prochlorperazine.

The most dramatic change in caring for patients receiving chemotherapy was that everyone was awake and alert with minimal nausea and vomiting. In the past, patients did not eat during chemotherapy. Now lunch was served and patients comfortably watched TV or read while receiving highly emetogenic chemotherapy. Eagan, Taggart, and Bender (1992) published the first review of the new antiemetic ondansetron and educated oncology nurses regarding administration, adverse events, and implications for practice.

Guidelines

After the introduction of the 5HT₃ receptor antagonists and once clinicians became comfortable using them, guidelines based on clinical research were developed in the late 1990s by a number of associations—American Society of Clinical Oncology, Multinational Association of Supportive Care in Cancer, European Society for Medical Oncology and the National Comprehensive Cancer Network (NCCN) (Gralla et al., 1999; NCCN, 2012; Roila et al., 2010). Now that oncology nurses had more effective agents, standardizing the implementation of those new agents became the goal so as to ensure that all patients had access to the best supportive care for CINV.

In 1999, *ONF* published a study by Engstrom, Hernandez, Haywood, and Lilenbaum (1999) looking at the efficacy and cost effectiveness of the new emetic guidelines. They used recommendations from the leading groups of researchers at the time because the first edition of guidelines put forth by the organizations mentioned previously in this article were not yet published. The purpose of the Engstrom et al. (1999) study was to develop antiemetic regimens that would increase efficacy and patient compliance, optimize nursing and pharmacy efficiency, and accomplish these things in a cost-effective way. The results showed that antiemetic guidelines invoke improved efficacy, proper use of these new agents, and a cost savings of \$20,000 a year as well

as more efficient use of nursing and pharmacy time (Engstrom et al., 1999).

Continuing Difficulty

Although the introduction of serotonin receptor antagonists dramatically impacted the control of acute CINV, patients were still having difficulty with delayed nausea and vomiting, and others had refractory acute nausea and vomiting. In 2003, *ONF* published a continuing education monograph examining antiemetic therapy for patients receiving chemotherapy (Marek, 2003). The monograph provided an excellent review of where the science was at that time and what was going on in clinical trials. On the verge of approval was aprepitant, a neurokinin-1 (NK-1) receptor antagonist which not only improved acute nausea and vomiting control, but also impacted delayed emesis. Additional studies at the time looked at optimal dosing in the face of QT interval prolongation induced by serotonin receptor antagonists, particularly ondansetron and dolasetron (U.S. Food and Drug Administration, 2011). Routes of administration expanded beyond oral and IV to transmucosal and transdermal. That offered patients additional options for home administration, particularly patients with poor oral absorption or significant emesis.

To date, recommended guidelines for highly emetic chemotherapy include serotonin receptor antagonists, corticosteroids, and NK-1 receptor antagonists. The guidelines are updated with current evidence and healthcare providers are beginning to fine tune management. Optimum control with minimal side effects and toxicities from the antiemetics is the goal. Although the NK-1 receptor antagonists are effective, pathways for metabolism and drug interactions are important considerations.

No discussion of management of CINV would be complete without including cannabinoids. Delta-9-tetrahydrocannabinol, or THC, was studied in the 1970s as a possible antiemetic for patients receiving chemotherapy. Its use has come in and out of vogue over time and no well-designed conclusive studies have provided evidence to endorse its use. Cotter (2009) presented a systemic literature review on the efficacy of crude marijuana and THC. In the review, THC was as effective as smoked marijuana and both were more effective than pla-

cebo in CINV. Both also were found to be as effective as prochlorperazine and ondansetron. The major concerns about cannabinoids are the significant side effects—sedation, hallucinations, dysphoria, and dizziness—and how they impact patient safety, particularly in the older adult population. As more states legalize marijuana for medicinal use, it may become more prevalent in this discussion.

Complementary Medications

Refractory nausea and vomiting, despite the best interventions, continues to challenge oncology nurses. Complementary interventions in the form of guided imagery, meditation, progressive muscle relaxation, counseling, acupuncture, and acupressure have been suggested to improve emetic control beyond standard antiemetics. Little evidence exists to support these recommendations. In January 2012, *ONF* published an online study of the effects on P6 acupressure and nurse-provided counseling on CINV in patients with breast cancer (Suh, 2012). This well-designed, randomized study compared four interventions for women who had moderate nausea and vomiting after their first cycle of chemotherapy for breast cancer. One group received acupressure to S13 (control group), and three experimental groups received acupressure to P6, counseling only, or counseling and acupressure to P6. Acupressure to P6 combined with nurse-provided counseling significantly reduced CINV in those patients (Suh, 2012).

Future Research

Oncology nurses have always considered CINV a priority and a focus for research. Future research should be directed toward reliable and accurate assessment tools, additional antiemetics for acute and delayed control, and effective complementary interventions. Because CINV significantly impacts quality of life, accurate assessment and treatment are priorities. Healthcare professionals underestimated the incidence of both acute and delayed CINV when Grunberg et al. (2004) performed the ANCHOR (Anti-Nausea Chemotherapy Registration) study. Not only was incidence underreported, severity was as well, leading to undertreatment of this very distressing

symptom. New antiemetics need to be developed to further improve on emetic control, particularly in the delayed setting. Control might be improved if evidenced-based complementary interventions are routinely used with standard antiemetics. A lot of work certainly needs to be done, and ONF will continue to communicate these innovations through print and online publications.

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