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AN EXTENSIVE REVIEW ON CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

Chemotherapy induced nausea and vomiting is the among most feared and debilitating adverse events experienced by the cancer patients. Left unaddressed, CINV symptoms not only decrease quality of life, but may also affect patients' willingness to continue chemotherapy treatment. However, adherence to guideline recommendations continues to be suboptimal therapy, and many patients still suffer unnecessarily from CINV. In addition, breakthrough/refractory CINV continues to present particular challenges. The development of effective CINV treatments with diverse mechanisms of action has expanded the options available for preventing symptoms. The US Food and Drug Administration have recently approved several new therapies for the management of CINV. NEPA is a fixed-dose combination of Netupitant (300 mg) plus Palonosetron (0.5 mg). In combination with Dexamethasone, NEPA has demonstrated superior efficacy to Palonosetron alone in patients receiving highly or moderately emetogenic chemotherapy. Rolapitant is a nextgeneration neurokinin-1receptor antagonist. Both palonosetron and rolapitant have proven particularly effective in controlling delayed CINV. Regimens that combine a serotonin 5-hydroxytryptamine–3 receptor antagonist, an NK1 receptor antagonist, and a corticosteroid now represent the standard of care for managing both acute and delayed CINV in patients receiving highly emetogenic chemotherapy.

Keywords: CINV, Seratonin, Dopamine, Neurokinin, Antiemetics.

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1.0 INTRODUCTION

Nausea and vomiting are 2 serious and related side effects of cancer chemotherapy. These adverse effects can cause significant negative impacts on patients' quality of life and on their ability to comply with therapy. Also, nausea and vomiting can result in anorexia, decreased performance status, metabolic imbalance, wound dehiscence, oesophageal tears, and nutritional deficiency despite advances in the prevention and management of chemotherapy-induced nausea and vomiting (CINV), these side effects remain among the most distressing for patients. The use of emerging antiemetic medications has reduced the incidence of vomiting substantially, but evaluations show that approximately 30% to 60% of patients still experience either acute or delayed nausea after chemotherapy. Serial evaluations throughout the 1980s and into the 2000s show that, although vomiting has fallen further down on the list of side effects that patients perceive as being their most severe, nausea remains either the first or second most severe side effect of chemotherapy. Risk factors for CINV can be divided into patient specific and treatment-specific risk factors. Female sex and history of motion or morning sickness are clear risk factors for nausea and vomiting. Younger age has also been correlated with increased risk, although this may be explained by the more aggressive chemotherapy regimens that tend to be administered to younger patients who have more aggressive diseases. Finally, alcohol intake tends to be inversely correlated with the risk of developing CINV. Many factors contribute to the treatment- specific risk, including the emetogenicity of

the agents being used the dose and schedule of each agent, and in the case of radiation-induced or postoperative nausea, the site of radiation or surgery. Emetogenicity" refers to an agent's tendency to cause nausea and/or vomiting. Initially described in 1997, the

Emetogenicity scale, also known as the Hesketh scale, divided chemotherapy agents and doses into 5 levels, based on their likelihood to cause CINV[1]. Since then, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have modified this scale to be divided into the following 4 categories.

- Highly emetogenic: medications or doses that cause CINV in >90% of patients.
- Moderately emetogenic: medications that induce CINV in 30% to 90% of patients.
- Low emetogenic: medications those are associated with CINV rates of 10% to 30%.
- Minimally emetogenic: medications that cause CINV in <10% of patients.

"CINV" is a broad term used to describe the many types of nausea and vomiting that can occur in patients with cancer. The major subtypes of nausea and vomiting associated with chemotherapy are

- Acute: onset of nausea and vomiting within minutes to hours after administration of chemotherapy and resolving within 24 hours
- Delayed: occurs 24 hours or later after administration of chemotherapy
- Anticipatory: occurs before chemotherapy administration thought to be an indicator of previous poor control of nausea and vomiting
- Breakthrough/refractory: nausea and vomiting that occur despite appropriate prophylaxis; requires the use of rescue medications. Because there are so many independent and variable risk factors that can influence the risk for CINV in any particular patient, it becomes paramount for providers to individualize the approach to the prevention and treatment of CINV in every patient case.

2.0 Pathophysiology of Nausea and Vomiting

The vomiting response is controlled centrally by the emetic centre present in the CNS, which lies in the reticular formation of the brain stem. The emetic centre is receives impulses input from the following sources.

1. The periphery,
2. The cortex,
3. Chemoreceptor trigger zone.

Peripheral pathways are mediated mainly by Serotonin (5-HT3) and Neurokinin, the cortical pathway, which is responsible for anticipatory emesis, is mediated by the dopamine and histamine[2].The chemoreceptor trigger zone, which is a collection of neurons at the base of the brain and is exposed to the body's general circulation, mediates signals through all of the above chemokines. Once the emetic centre has been triggered, signals are then sent to the salutatory, vasomotor, respiratory, and cranial centres to activate the organs involved with the vomiting reflex, namely the abdominal muscles, diaphragm, stomach, and oesophagus [3].

3.0 Pharmacotherapy

3.1 Available Agents for management

Before the 1980s, CINV was primarily managed with dopamine receptor antagonists. Today, we have a multitude of options available, targeting the various pathways of the process, to use in the prevention and management of CINV[4].

5-HT3 receptor antagonists

Ondansetron was the first US Food and Drug Administration (FDA)-approved 5- HT3 antagonist in 1991. Early trials showed that ondansetron was an effective antiemetic for patients receiving cisplatin-based regimens, and they subsequently showed it to be superior to metoclopramide in patients receiving cisplatin and noncisplatin regimens [5]. Currently, four 5-HT3 receptor antagonists are available in the United States—ondansetron, granisetron, dolasetron, and palonosetron. Palonosetron, the new est agent, was approved in 2003. These agents are believed to prevent CINV by antagonizing 5-HT3 receptors either peripherally on vagal nerve terminals and/or centrally in the chemoreceptor trigger zone[6], since their introduction, 5-HT3 receptor antagonists have become part of the cornerstone for CINV prevention, thanks to their effectiveness and tolerable side-effect profile. The most common adverse effects reported (in their respective package insert) with these agents are headache and constipation. Transient elevations of liver function enzymes and QTC prolongation have also been noted.

NK1 receptor antagonists

NK1 receptor antagonists inhibit substance P in peripheral and central emetic pathways. Aprepitant was the first drug in this class to be approved by the FDA in 2003[6]. Aprepitant was approved at doses of 125 mg orally on day 1 and 80 mg orally on days 2 and 3 for the prevention of nausea and vomiting in patients receiving highly emetogenic.

Corticosteroids

Corticosteroids were first shown to be efficacious for CINV in the 1980s, and they are now considered a mainstay of antiemetic regimens for the prevention of acute and delayed emesis[7].Although not approved by the FDA for CINV, corticosteroids have been found to be beneficial when used alone for the prevention of nausea and vomiting in patients receiving low emetogenic chemotherapy and to improve efficacy when combined with 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapies.36-39 Dexamethasone is the recommended corticosteroid according to current guidelines, although no studies have been performed comparing available corticosteroids[8,9].

Current Practice Guidelines

Practice guidelines from the NCCN and ASCO are available to help providers determine optimal prophylaxis and the treatment of CINV [10, 11]. The NCCN Antiemetic Guideline TM, a consensus-based guideline that incorporates evidence and expert opinion to make recommendations, is revised annually [12.]ASCO guidelines are purely evidence-based guidelines and are updated periodically; the last update was in 2011.10. For CINV, both guidelines outline primary prophylaxis based on the emetogenicity of the patient's chemotherapy: high, moderate, low, and minimal. For patients receiving highly emetogenic chemotherapy, both guidelines recommend a 3-drug combination that includes a 5-HT3 receptor antagonist, an NK1 receptor antagonist, and dexamethasone to prevent CINV. The NCCN specifies that the preferred 5-HT3 receptor antagonist for highly emetogenic chemotherapy is palonosetron,[11] whereas ASCO does not list a preferred 5-HT3 receptor antagonist. For patients receiving moderately emetogenic chemotherapy, the NCCN and ASCO recommend a 2-drug combination of a 5-HT3 receptor antagonist, preferably palonosetron, with dexamethasone. Dexamethasone is recommended by both organizations for the prevention of CINV in patients with low or minimal emetogenic potential. The NCCN also lists metoclopramide or prochlorperazine as possible alternatives. For patients receiving minimal-risk chemotherapy, no medications are recommended primarily as prophylaxis.

CONCLUSIONS

We are concluding that the treatment for Antiemetic regimens for particular patients should be evaluated and then revaluated at every treatment cycle. At every step of a patient's care, clinicians must incorporate clinical decision-making with value-based considerations to determine each patient's individual, most optimal approach to treatment but current scenario most of the oncologists may prefer Inj. Ondansetron is the primary option for the CINV Metaclopromide is used in the second line option for CINV.

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