Review Article
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Chemotherapy-Induced Nausea and Vomiting: The Role of Aprepitant

Muath Mohammed Abu Hilal

School of Nursing, Hashemite University, Az Zarqa, Jordan

Abstract

Antiemetics are given to cancer patients prior to their chemotherapy sessions to protect them from nausea and vomiting induced by chemotherapy. The responsible health care team member will choose the type of antiemetic required to prevent the patient from developing nausea and vomiting according to the chemotherapy ematogenicity level. Current guidelines recommend using a single antiemetic agent or a combination of antiemetic agents such as a 5-hydroxytrypt-amine3 receptor antagonist, dexamethasone, or the neurokinin-1 receptor antagonist aprepitant. This review discusses the role of aprepitant in preventing and managing nausea and vomiting induced by chemotherapy.

Keywords: Aprepitant, Neurokinin-1 receptor antagonist, Chemotherapy induced nausea and vomiting.

Introduction

Chemotherapy is one of the therapeutic regimens for treating cancer. However, it has many adverse effects that affect the patient's quality of life and overall response to treatment. Nausea and vomiting are among the most common and distressing adverse effects associated with chemotherapy.[1] They can occur within the first 24 hours of starting chemotherapy (acute), a day after starting therapy (delayed), or before starting therapy (anticipatory).[2, 3] The severity and intensity of nausea and vomiting differ from patient to patient according to many factors such as the treatment regimen, patient-related and cancer-related factors. Recently, 5-hydroxytrypt-amine3 receptor antagonists (5-HT3RA), dexamethasone, corticosteroids, dopamine D2 antagonists and a neurokinin-1 receptor antagonists (NK1RA, e.g. aprepitant) have been used to prevent and treat chemotherapy-induced nausea and vomiting (CINV).

Inadequate control of CINV can lead to undesirable effects for patients, such as malnutrition, electrolyte imbalances and dehydration, all of which produce many other complications affecting the patient's quality of life. Therefore, the objective of this review was to

Corresponding Author:
Muath Mohammed Abu Hilal, RN, MSN
School of Nursing, Hashemite University, Az Zarqa, Jordan
Tel:+962788106210
Email:
Rn.Muathabuhilal@yahoo.com

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determine the effectiveness and tolerability of aprepitant in the prevention of CINV. I considered the effectiveness and tolerability of this drug, and offer recommendations for the use of aprepitant in treating and preventing CINV.

Material and Methods

I reviewed articles published within the preceding 10 years, available from different online databases, about the use of aprepitant to prevent CINV. To identify articles that pertained to the topic, a computer-based literature review of the EBSCO, CINAHL, MEDLINE, SpringerLink and Science Direct online electronic databases was used. The keywords used in the search process were "chemotherapy induced nausea and vomiting, aprepitant, prevention" and "neurokinin-1 receptor antagonist". The inclusion criteria were English-language, randomized clinical trial design, large sample size, treatment with highly or moderately ematogenic chemotherapy, and publication between 2004 and April 2010. Seven articles met the inclusion criteria. [4-20]

Risk factors for chemotherapy-induced nausea and vomiting

The severity of CINV depends on many factors, some of which are related to patient characteristics. The experience of CINV depends on patient age (<45 years), sex (female), alcohol consumption, and a history of nausea and vomiting with pregnancy or with the previous chemotherapy session.[4] Other factors relate to the type and dose of chemotherapy, which is classified into four groups in terms of ematogenicity level according to the percentage of patients who experience nausea and vomiting when receiving chemotherapy without antiemetic agents: high (>90%), moderate (30% to 90%), low (10% to 30%) and minimal (<10%).[5] In addition, cancer itself is a risk factor, with the level of risk related to the cancer stage and location. Other factors which may increase the risk of CINV are related to the setting, such as an unpleasant odor, physician or nurse behavior, and the unavailability of proper medication.

Pathophysiology of nausea and vomiting

Chemotherapy can activate the afferent nerve, which is located in the gastrointestinal tract (GIT). This activation can trigger impulses that affect the vomiting center in the medulla. Impulses are sent by the efferent nerve to the abdominal muscles, respiratory center and salivary glands, and lead to the onset of vomiting.[6] Many studies have addressed the role of neurotransmitters in the mechanism of nausea and vomiting. Dopamine, 5-HT3 and substance P are well known neurotransmitters which play an important role in the emesis process. Receptor antagonists are the main targets of recent efforts to control and prevent emesis.[7]

Antiemetic therapy

Factors that lead to nausea and vomiting work through different pathways, thus a combination of corticosteroids, NK1RA and 5-HT3RA should be used according to recent guidelines to treat and prevent CINV. Selective serotonin receptor antagonists are the most commonly used antiemetics to treat acute CINV. Ondansetron, dolasetron, granisetron and tropisetron, as 5-HT3RA, act on the GIT and central nervous system. Many articles reported the effectiveness of these medications in treating acute CINV, with side effects such as mild headache and in some cases, diarrhea.[6] Palonosetron is a second generation 5-HT3RA which has a longer half-life and greater binding affinity to the 5-HT3 receptor.[8]

Neurokinin-1 receptor agonists are used to treat delayed CINV in patients who rceive highly or moderately ematogenic chemotherapy. These drugs block GIT and brainstem emetic receptors, and are considered safe, although they moderately inhibit the cytochrome P450 3A4 enzyme. Therefore the dose should be adjusted for other combinations of medications such as dexamethasone.[9]

Corticosteroids such as dexamethasone are known as effective drugs to treat acute and delayed CINV in combination with 5-HT3RA and NK1RA, according to recent guidelines. However, the mechanism of action for these drugs is not well-known.[10]

Antiemetic guidelines

Recent guidelines from the Multinational Association of Supportive Care in Cancer (MASCC) consider different levels of ematogenicity of chemotherapy. For highly and moderately (anthracycline and cyclophosphamide only) ematogenic chemotherapy, 5-HT3RA is recommended in combination with dexamethasone and NK1RA. With other moderately ematogenic chemotherapies, 5-HT3RA in combination with dexamethasone is recommended.[5]

Delayed chemotherapy-induced nausea and vomiting

Delayed CINV occurs a day after chemotherapy. Cyclophosphamide and carboplatin are associated with intense delayed emesis and less acute emesis.[11] The mechanism of delayed nausea and vomiting is unclear. Possible causes of emesis by cisplatin may be related to underlying mechanisms such as disruption of the blood–brain barrier, which can lead to mild reversible cerebral edema that may produce emesis, and disruption of GIT function leading to hypomotility and gastroparesis, which may also induce emesis. Cisplatin can also stimulate the release of a hormone which may induce emesis. The accumulation of cisplatin emetogenic substance has been detected in body fluids 24 hours after its administration.[12]

Because the mechanism of action for delayed nausea and vomiting differs from acute nausea and vomiting, the two must be assessed and treated separately according to patient risk factors and type of chemotherapy. According to MASCC guidelines, delayed CINV is treated by dexamethasone with or without NK1RA.

Aprepitant

Aprepitant is a new selective NK1RA that binds to substance P receptor. Substance P is a neuropeptide found mainly in the central nervous system and GIT vomiting receptors, and is responsible for receiving and sending impulses from the brain. The activation of this substance leads to vomiting. Aprepitant has little or no affinity for serotonin 5-HT3, corticosteroid or dopamine receptors. The recommended oral dose for aprepitant is 125 mg on the first day and 80 mg on the second and third days. Aprepitant can cross the blood–brain barrier and has a half-life of 9 to 13 hours.[13]

Safety and tolerability of apripetant

Many randomized clinical trials (RCT) have been conducted with aprepitant at the recommended dose in combination with 5-HT3RA and dexamethasone to prevent emesis from highly and moderately ematogenic chemotherapy. These studies have documented the tolerability and safety of aprepitant.[14]

Aprepitant for the prevention of delayed chemotherapy-induced nausea and vomiting

A number of clinical trials have demonstrated the effectiveness of aprepitant in preventing delayed CINV after moderately[14-16] and highly ematogenic chemotherapy.[17-20] In all seven articles included in this review, a RCT research design was used to compare the effectiveness and tolerability of aprepitant therapy (aprepitant, ondansetron, and dexamethasone) versus a control therapy (odansetron and dexamethasone) in the prevention and management of CINV.

Moderately ematogenic chemotherapy

Three RCT studied 857 evaluable patients with breast cancer,[14] 848 evaluable patients with various malignancies[15] and 127 patients with breast cancer.[16] In each study the patients received a single cycle of moderately ematogenic chemotherapy. It was shown that the use of aprepitant decreased CINV. The adverse effects of aprepitant were the same as those of the control therapy. In the first study, 21.5% of the patients on aprepitant therapy had adverse effects versus 19.6% for control therapy.[14] In the second study, there were fewer adverse effects in patients on aprepitant therapy (7.2%) compared to control therapy (9.3%),[15] and in the third study, 11% of patients on aprepitant therapy had adverse effects versus 20% for control therapy.[16] The incidence

Table 1. Summary of the articles that are included in this review.

First author and year	Purpose	Design and method	Sample and setting	Findings
Rapoport et al., 2010	Assessed aprepitant in patients receiving a broad range of MEC regimens with a variety of tumor types.	Randomized Clinical Trial	848 patients, multi-center	The aprepitant regimen provided superior efficacy in the treatment of CINV in a broad range of patients receiving MEC.
Heskethet al., 2009	Assessed the impact of NK1 receptor antagonist aprepitant according to risk factors.	Randomized Clinical Trial	1043 patients	Aprepitant improved complete response regardless of risk factor in HEC.
Hesketh et al., 2006	Assessed the impact of aprepitant on CINV prevention among female patients.	Randomized Clinical Trial	1044 patients	The addition of aprepitant may negate the adverse prognostic effect of female gender on the prevention of CINV in patients receiving HEC.
Yeo et al., 2009	Compared the effectiveness of aprepitant- based regimen and standard regimen in preventing CINV.	Randomized Clinical Trial	127 patients, China	The aprepitant regimen appeared to reduce rescue medication requirements compared to the standard regimen in preventing CINV in MEC.
Warr et al., 2005	Evaluated the NK1 antagonist aprepitant for preventing cisplatin-induced nausea and vomiting.	Randomized Clinical Trial	1043 patients	The aprepitant group had significantly less nausea with HEC.
Warr et al., 2004	Evaluated aprepitant in preventing CINV with MEC.	Randomized Clinical Trial	857 patients, multi-center	The aprepitant regimen was more effective than the standard regimen in preventing CINV after MEC.
Wit et al., 2004	Evaluated the addition of aprepitant in a standard regimen to prevent CINV.	Randomized Clinical Trial	1038 patients, multi-center	The addition of aprepitant improved the prevention of CINV with HEC.

Abbreviations: CINV, Chemotherapy-Induced Nausea and Vomiting; HEC, Highly Ematogenic Chemotherapy; MEC, Moderately Ematogenic Chemotherapy; RCT, Randomized Clinical Trial

of discontinuing therapy because of adverse events in two studies from aprepitant and control therapy groups were 1.6% and 1.2%, and 0.2% and 0.5%.[14,15]

Highly ematogenic chemotherapy

One RCT that involved 1044 patients with different solid tumors evaluated the efficacy of aprepitant therapy. The results showed that aprepitant therapy was better than the control treatment. In the control group, 41% of women and 53% of men had an overall complete response. In the apripetant therapy group, 66% of women and 69% of men had a complete response.[17] Another study evaluated 1038 patients with solid tumors who received cisplatin. The effectiveness and tolerability of aprepitant therapy was studied for 6 cycles. According to the results, in the first cycle 61% of the aprepitant group and 46% of the control group were free from CINV. In the sixth cycle, 59% of patients who received aprepitant showed no CINV versus 40% of those in the control group.[18]

A third study of 1043 patients with solid tumors

treated with cisplatin assessed the effectiveness of aprepitant in treating delayed CINV. Of the patients who had acute emesis, 16% showed improvement, and among those without acute emesis, improvement was seen in 17%.[19] Another study evaluated 1043 patients with solid tumors treated with cisplatin, and assessed them for the impact of aprepitant according to patient risk factors. The impact of age on antiemetic outcome was also assessed. This study confirmed the importance of several previously reported adverse risk factors for CINV in patients who received chemotherapy. Aprepitant therapy improved complete response regardless of the risk factors and eliminated the increased risk of CINV associated with female sex.[20]

Conclusion

Preventing CINV can improve the patient's quality of life and activities of daily living, and prevent further complications. The prevention of delayed CINV is important because of its severe impact on quality of life. Current guidelines recommend the use of 5-HT3RA alone or in combination with NK1RA according to the ematogenicity level of chemotherapy. Aprepitant is considered a safe and tolerable drug for the prevention of delayed CINV. However, to ensure the effectiveness of apripetant, the health caregiver must first assess individual patient risk factors.

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