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Aprepitant, a novel neurokinin-1 receptor antagonist in management of chemotherapy induces nausea vomiting (CINV) in cancer patients

Robin George*, E. Sunil Kumar, Kondi Charitha Reddy, Shaik Habeebjan

¹Department of Pharmacy Practice, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, India.

ABSTRACT

Nausea and emesis are two major concerns for patients undergoing chemotherapy for cancer. The 5HT₃ receptors antagonist ondansetron is the major factor for preventing and treatment for CINV either alone or often is combination with dexamethasone. Even these treatment options exist, CINV remind as major adverse event for all chemotherapeutic agents. The adverse events have major impact on patients quality of life and compliance with treatment. Aprepitant, a novel neurokinin-1 (NK-1) antagonist has been introduced as a new class of drug to prevent CINV. Many trials and studies reveals that comparison of aprepitant to the standard ondansetron and dexamethasone is superior in protecting against CINV. Here this study evaluate and reveals the use and benefits of aprepitant in the management of CINV.

Keywords: Aprepitant; Chemotherapy; Neurokinin-1; Nausea; Vomiting.

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Corresponding Author

Name: Dr. Robin George

Email: dhanyadharman07@gmail.com

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CANCER THE GROWING TISSUE

Cancer describes the disease that result when cellular changes cause uncontrolled growth and division of cells, the term 'neoplastic' a synonym of cancer which means 'new growth'. The meaningful definition of a neoplasm or tumour is 'a mass of tissue formed as a result of abnormal, excessive, uncontrolled, autonomous and purposeless proliferation of cells even after the cessation of the stimulus to growth which caused it^[1]. In the most basic term, cancer refers to calls that grow out of control and invade other tissue. Cells are

capable of detect and repair DNA damage, if cells is severely damaged and cannot repair itself, it usually undergoes programmed cell death so called apoptosis, cancer occurs when damaged cells grows, divide and spread abnormally instead of self-destructing as they should^[2].

In United States, an estimate of 15.5 million people with a history as of Jan 1, 2016, according to the 2018 report from the American cancer society^[3]. There are many causes of cancer and over genetics' most of them are preventable. Cancer is the 2nd leading cause of death in United States^[4].

There are many causes of cancer and some of them are preventable smoking, heavy alcoholism, obesity, physical activity, poor nutrition etc. Genetics influence the cell production of protein, and proteins that carry many of the instruction for cellular growth and division. Cancer is more curable when detected early, although some cancers develop completely without symptoms, or the symptoms are non-specific. Cancer treatment advances every year and early detection has made many cancers treatable. Cancer symptoms and signs are also depend on the size and location of the cancer as well as the presence or absence of metastasis.

Cancer can occur anywhere in the body either on epithelial or non-epithelial tissue as well as connective tissues broadly cancer can classified as either solid (ex: breast, lung, prostate) or liquid (blood, lymph). Even the cancer can further classified according to

the tissue which they arise like, carcinoma, sarcoma, myeloma, leukaemia etc.

Chemotherapy and chemotherapy induced nausea vomiting

Chemotherapy works against cancer by killing fast-growing cancer cells. It is a type of cancer treatment that uses drug to kill cancer cell. It works by stopping or slowing of cancer cells, which grow and divide quickly. Chemotherapy is the primary strategy for malignancy with a tendency to spread throughout the body and advanced cancers that have metastasized. Nearly 70% cancer patients have undergone chemotherapy. If there were no effective interventions, the incidence of nausea and vomiting after chemotherapy would be as high as 70–80% [5], which was clinically called chemotherapy-induced nausea and vomiting (CINV). Although not life-threatening, these symptoms have been ranked as the two of the most distressing side effects affecting cancer patient's well-being and overall response to chemotherapy. Chemotherapy regimen and inter-individual differences are the most critical factors affecting the frequency and extent of CINV. CINV not only reduces the patient's tolerance to chemotherapy, prevents the treatment from completing on time or even stops therapy [6], but also causes anorexia, nutritional deficiencies, and even water and electrolyte disorders [7], which directly affect the patients' short-term efficacy and quality of life. A variety of neurotransmitters and their receptors is involved in the development of CINV. At present, a combination of peripheral, central, psychological and sensory factors is known to be associated with CINV, but the underlying mechanisms remain mostly unclear [5]

Table 1: Classification of CINV (Chemotherapy induced nausea and vomiting)

Types of CINV	Description
Acute	Nausea and/or vomiting occurring within 24 hours of chemotherapy administration.
Delayed	Nausea and/or vomiting occurring at least 24 hours post chemotherapy administration; often peaks between 48 and 72 hours.
Break-through	Nausea and/or vomiting that occur within 5 days post chemotherapy despite optimal antiemetic regimen used; requires rescue therapy with other antiemetics.
Refractory	Nausea and/or vomiting that occurs in subsequent chemotherapy cycles despite maximum antiemetic protocol.
Anticipatory	Nausea and/or vomiting that is triggered by sensory stimuli associated with chemotherapy administration.

Management of CINV

Effective antiemetic regimens for highly and moderately emetogenic chemotherapy or radiotherapy have historically been based on the combination of a serotonin antagonist and a corticosteroid, as reflected in numerous antiemetic treatment guidelines [5,8]. This combination is highly effective for the control of acute emesis but less so for delayed emesis, and the contribution of serotonin antagonists to the management of delayed emesis has been questioned. It is thus imperative that feasible and effective regimens be developed that address both acute and delayed nausea and vomiting. Although these treatments effectively enhance the control of acute-phase CINV, it still should pay more attention to the control of delayed-phase CINV.

Ondansetron was the first US food and drug administration (FDA)- approved 5HT₃ antagonist in 1991. Ondansetron is the one of the medications most commonly used for empiric treatment. It is considered first-line therapy for the treatment of chemotherapy and radiotherapy induced nausea and vomiting. Ondansetron is the 5HT₃ receptor antagonist used to treat and prevent chemotherapy-induced nausea and vomiting and radiotherapy-induced nausea and vomiting. It appears on the World Health Organization (WHO) list of essential medicines, which is a list of medications that considered being the most effective and safe with regards to meeting the most important needs in a health system. Other antiemetic that appear on this list with ondansetron include dexamethasone. In 2006, the brand name version of ondansetron was the 20th highest – selling brand-name drug in the United States, and its popularity continues today. Ondansetron has extreme utility as an antiemetic drug, and it is effective against prevention of chemotherapy induced nausea and vomiting and radiation induced nausea and vomiting[7].

The development of 5HT₃ antagonist has been a major step forward in the prevention and treatment of chemotherapy – induced nausea and vomiting (CINV). These agents had been widely regarded as the most efficacious and antiemetic available until recently and have been recommended for several years, often in combination with corticosteroids, as the agents of first choice to control nausea and vomiting in most instances. Despite these existing preventative measures, CINV remains a major adverse events can have a major impact to patients quality of life and compliance with treatment, and represent a major therapeutic challenge that potentially threatens the success of therapy.

Neurokinin 1 receptor antagonist is one of the classes of the drug used to suppress nausea and vomiting in patients associated with cancer chemotherapy. Aprepitant, a novel neurokinin-1 antagonist, has been recently introduced as a new class of drugs available to prevent CINV. It is always used in combination

with other antiemetic agents. Aprepitant is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Phase III clinical trials in patients receiving highly emetogenic cisplatin-based chemotherapy as well as in patients receiving moderately emetogenic chemotherapy have shown that aprepitant, in combination with a 5HT3 receptor antagonist and dexamethasone provides superior protection against CINV compared with standard therapy alone with preventative regimens. Aprepitant has been proven effective not only for acute CINV, but also for delayed CINV^[5].

A combination of a serotonin antagonist, a corticosteroid, and an NK-1 antagonist has proven effective against this problem. Aprepitant, a novel neurokinin-1 (NK-1) antagonist, has been recently introduced as a new class of drugs available to prevent CINV.

Table 2: Treatment guidelines for CINV

Emetic risk	Treatment regimen
High	Day 1: NK1 antagonist + 5HT3 antagonist + Dexamethasone
	Day 2-3: NK1 antagonist (if using Aprepitant) + dexamethasone
	Day 4: Dexamethasone
Moderate	Day 1: 5HT3 antagonist (palonosetron preferred) + dexamethasone + NK1 antagonist
	Day 2-4: 5HT3 antagonist (if did not use palonosetron preferred) or dexamethasone or Aprepitant + dexamethasone + 5HT3 antagonist. If Aprepitant used on day 1, days 2-3 aprepitant + dexamethasone on days 2-4 + lorazepam
Mild	Metoclopramide, dexamethasone, or prochlorperazine + lorazepam.
Minimal	No routine prophylaxis.

However, the key question in this setting is whether aprepitant should be a part of the antiemetic prophylaxis. The ASCO and MASCC guidelines recommend the triple combination (a 5HT3 RA, dexamethasone, and aprepitant) for patients receiving the cisplatin-based chemotherapy. The NCCN guidelines, however, broaden the spectrum of the use of aprepitant in this setting and advise use in selected patients receiving other chemotherapies of moderately emetogenic risk. Dexamethasone is the preferred agent to use for delayed CINV with moderately emetogenic chemotherapy. Nonetheless, When aprepitant is used for the prevention of acute CINV then it should be used for prophylaxis of delayed CINV as monotherapy, as stated by the MASCC and ASCO guidelines suggest aprepitant with or without dexamethasone in this situation. A 5HT3 RA can be

used as an alternative, although their therapeutic role in the delayed phase is rather limited.

CONCLUSION

Anti-emetic treatment guidelines have indicated that 5HT3 receptor antagonists (RAs) effectively prevent and control CINV during the acute phase in patients receiving chemotherapy however, they are less effective in preventing CINV in the delayed phase. Aprepitant is a potent and selective neurokinin 1 receptor antagonist that has been effective against CINV in both acute and delayed phase when added to a standard antiemetic regimen (a 5HT3 RA and dexamethasone) in patients receiving chemotherapy. The NK-1 receptor antagonist aprepitant has been shown to markedly improve control of delayed emesis after both highly and moderately emetogenic chemotherapy. Of interest, aprepitant also improves control of acute emesis when used in combination with a serotonin antagonist and a corticosteroid.

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