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Review Article

APREPITANT, A NEWER ANTIEMETIC IN CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

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ABSTRACT

Aprepitant is a recently introduced NK1 receptor antagonist. It effectively blocks Substance- P, which is supposed to have emetic action. Hence, this newer drug is being used in patients undergoing chemotherapy to prevent chemotherapy induced nausea and vomiting (CINV). This particular review article gives a bird's eye view on aprepitant, which is being tried as an adjuvant anti emetic in patients with far advanced cancer.

Keywords: aprepitant, chemotherapy, anti emetic

INTRODUCTION

Chemotherapy (abbreviation: chemo or CTX) is the use of chemical substances/ anti cancer drugs for the treatment of cancer. There are many potential side effects caused due to chemotherapy. The two most feared treatment related side effects are nausea and vomiting which accounts for 80 % of the patients receiving chemotherapy. Up to 20 % of the patients receiving these highly emetogenic agents even post pone or refuse to take treatment for cancer due to these side effects[1]. Hence adjuvant anti emetics can indirectly prolong the life and also improve the quality of life in patients undergoing chemotherapy for cancer[2]. Several novel classes of anti emetics have been developed and marketed. These drugs are being given to all chemotherapy receiving patients to successfully manage the symptoms. Our drug of discussion- aprepitant is one such novel class of anti emetics. This article aims to review, this particular drug-aprepitant in chemotherapy induced nausea and vomiting (CINV).

Chemotherapy induced vomiting

The risk of emesis is mostly based on intrinsic emetogenic potential of chemotherapy regimen, which is stratified as follows:

- Highly emetogenic potential (> 90 % risk of inducing vomiting after administration of chemotherapy)
- Moderate emetogenic potential (> 30 to 90 % risk)
- Low emetogenic potential (10 to 30 % risk)
- Minimal emetogenic potential (< 10 % risk)

Cisplatin is the main example of a drug with high emetogenic potential as doses of greater than even 50 mg/ m^2 lead to nausea and vomiting in more than 90 % of patients if no prophylactic therapy is used. Other drugs with high emetogenic potential are cyclophosphamide, carmustine, dacarbazine etc. It has been reported that many neuro transmitters like dopamine, endorphin, serotonin and NK1 (Neurokinin 1) receptors get elevated in area postrema (situated in floor of fourth ventricle) during chemotherapy. These elevated neurotransmitters stimulate the chemo receptor trigger zone (vomiting center) in area postrema which triggers emesis[3]. Hence, efforts to prevent and treat CINV have been directed to block these neurotransmitters and their receptors in area postrema (CTZ).

Lacunae with older anti emetics in CINV

Many neurotransmitter blockers like serotonin (5 HT3) receptor antagonists, dopamine (D2) receptor blockers and corticosteroids like dexamethasone are being used to manage CINV. But the main draw back with these drugs is that they exhibit good anti emetic effect only in acute phase with little or no effect in delayed onset chemotherapy induced vomiting[4]. In addition to this, there are also many studies showing patients on chemotherapy which showed no response to these drugs. Hence, there was a need for a novel group of anti-emetics which could be effective in delayed onset CINV and patients not responding to conventional anti emetics.

Role of Substance- P in vomiting

Substance P belongs to tachykinin group of neurotransmitters. This neurotransmitter has been identified on vagal fibres innervating NTS (nucleus tractus solitarious) and area postrema. The endogenous receptor for Substance – P is NK1 receptor (neuokinin 1). These NK1 receptors are also found in huge amounts in vomiting center. Hence, stimulation of these receptors triggers emesis. This leads to the development of NK1 receptor antagonists by scientists to evaluate the compounds as antiemetic.

Aprepitant in CINV

Aprepitant is the first commercially available drug from this new class of agents- Substance- P / NK1 receptor antagonists. Recent trials have shown that aprepitant, when used as a single sole agent, has a good antiemetic effect in prevention and treatment of acute and delayed chemotherapy induced nausea and vomiting, associated with highly emetogenic chemotherapy in adults. Apart from this there are also reports suggesting that aprepitant is also effective in anticipatory nausea and emesis and post operative vomiting[5]. It also increases the activity of 5 HT3 receptor antagonists like ondansetron and dexamethasone (corticosteroid) when used as a combination therapy[6].

Pharmacokinetics

Aprepitant is absorbed well orally. It is metabolized in the liver by CYP3A4 enzyme and to a minor extent by CYP1A2 and CYP2C19[7]. It is excreted via bile through faeces (86 %) and urine (5 %). Its $t_{1/2}$ is 9-13 h. It has a bioavailability of approximately 60 to 65 %. As dose increase, the clearance of the drug decreases.

Drug Interactions

It interacts with the inducers and inhibitors of CYP3A4 enzyme. Hence, caution must be taken while giving these drugs concurrently. The dose of drugs like dexamethasone and warfarin needs to be reduced if given along with aprepitant. Aprepitant should not be given along with drugs that prolong Q-T interval (e.g. cisapride).

Additional Effects

Aprepitant has been tried for the treatment of major depressive disorder in many clinical trials but has shown negative results[8]. Further ongoing clinical trials are required to confirm the same. Recent trials have shown aprepitant to be effective in the management of brain tumour as it inhibits the growth of brain tumour cells[9]. The mechanism of action of aprepitant is however not certain. It may be probably due to high levels of substance-P in tumour cells. Aprepitant being a substance –P antagonist may be responsible for the protective effect.

Side Effects

Except for increased risk of developing infections, so far no studies have reported any serious adverse event with the use of aprepitant. This makes it more suitable drug of choice for CINV.

Advantages over other anti-emetics

The advantages of using aprepitant over other anti-emetics in preventing and treating CINV are summarized as follows:

- Can be given orally (better patient compliance)
- Belongs to novel class of anti emetic drugs- NK1 receptor antagonists.
- Effective as a single sole agent in delayed phase of CINV, anticipatory nausea and vomiting and post operative nausea and vomiting.
- Increases the antiemetic effect of dexamethasone and ondensatron and minimizes their adverse effects when used as combination therapy.
- Minimal drug interactions.
- Very few side effects compared to other conventional anti emetic drugs.
- Additional effect- cyclical vomiting episodes, protective effect in brain tumor.

CONCLUSION

To conclude, aprepitant is a novel anti emetic drug effective as a single sole agent to prevent and treat delayed phase of chemotherapy induced nausea and vomiting. It is also effective in acute phase of CINV, anticipatory nausea and vomiting and post operative nausea and vomiting. Very few side effects have been reported with this drug. Since aprepitant has shown promising results, many drug candidates belonging to the same class – NK1 receptor antagonists, are in various phases of clinical trials and will be launches within a few years. However, the efficacy and safety of these drugs are yet to be confirmed with more randomized control trials. Many randomized controlled trials are also required to set up a standardized drug regimen using aprepitant to prevent and treat CINV.

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