

mini-review

Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis

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Abstract

Despite significant advances in supportive care in oncology, many patients with cancer still experience chemotherapy-induced nausea and vomiting (CINV). Historically, there were only 3 neurotransmitter receptors (dopamine D2, cannabinoid-1, and 5-hydroxytryptamine-3) that were the known targets for antiemetic therapy. Major advances in the management of chemotherapy-induced emesis were seen with the introduction of 5-hydroxytryptamine-3 receptor antagonists, which include palonosetron, ondansetron, tropisetron, dolasetron, and granisetron. However, recently, selective inhibitors of substance P have shown promising activity in the management of CINV in patients with cancer. Substance P mediates a number of biologic effects by binding to a specific neuroreceptor, neurokinin-1 (NK-1). Among the NK-1 receptor antagonists, aprepitant has been approved for the treatment of CINV. Currently, several other NK-1 receptor antagonists, including casopitant, vestipitant, netupitant, and SCH619734, are undergoing clinical evaluation for the prevention of CINV in patients with a variety of malignancies. The clinical potential of these novel NK-1 receptor antagonists and their respective ongoing clinical trials for the management of chemotherapy-induced emesis are discussed briefly herein.

Rationale

- Chemotherapy-induced nausea and vomiting remain significant problems for patients with cancer. Uncontrolled emesis can adversely affect patients' quality of life and impair compliance with treatment.^{1,2} Until recently, only 3 neurotransmitter receptors (dopamine D2, cannabinoid-1, and 5-hydroxytryptamine-3 [5-HT₃]), were identified as targets for antiemetic drugs. A major advance in efforts to control chemotherapy-induced emesis was seen with the introduction of 5-HT₃ receptor antagonists, including ondansetron, tropisetron, dolasetron, and granisetron.³⁻⁵ However, a significant number of patients receiving chemotherapy still experience CINV. Thus, there is a compelling need to identify effective novel approaches to manage and prevent CINV in patients with emesis inadequately controlled by older antiemetic therapies.
- Palonosetron is a new antiemetic agent that differs from currently available 5-HT₃ receptor antagonists because of its longer half-life and higher binding affinity for the 5-HT₃ receptor.⁶ Several studies have shown that palonosetron as a single agent achieves better control of CINV compared with first-generation 5-HT₃ receptor antagonists.⁷⁻⁹ Although palonosetron has the single-dose logistic advantage, definitive demonstration of the superiority of this drug

compared with other 5-HT₃ receptor antagonists remains to be determined in future trials.

- Another very promising new antiemetic therapy that extends beyond 5-HT₃ receptor antagonists involves substance P as a potential therapeutic target for the treatment of CINV.¹⁰⁻¹³ Selective inhibitors of substance P have shown promising activity in the management of CINV. Substance P, a regulatory peptide of the tachykinin family, mediates a number of biologic effects by binding to a specific neuroreceptor, neurokinin-1 (NK-1). Aprepitant is the first agent available in the new drug class of NK-1 receptor antagonists. Among the NK-1 receptor antagonists, aprepitant has proceeded through full phase III evaluation. Other antagonists of the NK-1 receptor, including casopitant, vestipitant, netupitant, and SCH619734, are under clinical development for the treatment of CINV in patients with cancer.
- At the 4th Annual Future of Supportive Therapy in Oncology conference in Dallas, TX, February 24-26, 2006, the recent data with novel NK-1 antagonists were reviewed, and their clinical utility was discussed regarding the management of CINV in patients with cancer.¹⁴ This mini-review summarizes the major points of this presentation.

Key words: Aprepitant, Casopitant, 5-Hydroxytryptamine-3 receptor antagonists, Nausea, Vomiting

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Neurokinin-1 Antagonists as Antiemetics for Chemotherapy-Induced Nausea and Vomiting in Patients with Cancer

Neurotransmitters such as the tachykinin substance P play a key role in emetic response processes. Substance P can induce emesis through binding with its preferred receptor, the NK-1 receptor. Therefore, novel NK-1 receptor antagonists could play a critical role in preventing CINV in patients with cancer. Currently, several NK-1 receptor antagonists, including casopitant, vestipitant, netupitant, and SCH619734, are undergoing clinical evaluation for the prevention of CINV in patients with a variety of malignancies (Table 1).¹⁴ To date, only aprepitant has proceeded through full phase III evaluation and received regulatory approval.

Aprepitant

Aprepitant, the first available NK-1 receptor antagonist, received regulatory approval in the United States on March 23, 2003, for use in combination with a 5-HT₃ antagonist and dexamethasone, defining a new standard of care for highly emetogenic chemotherapy. Clinical studies have shown that aprepitant-containing regimens significantly reduce acute (0-24 hours after chemotherapy) and delayed (1-5 days after chemotherapy) emesis resulting from cisplatin-based chemo-

therapy and moderately emetogenic chemotherapy employing cyclophosphamide and doxorubicin.

The clinical efficacy and tolerability of aprepitant for the prevention of CINV was assessed recently in a phase III trial of patients with breast cancer receiving moderately emetogenic chemotherapy.¹⁰ The study enrolled 866 patients with breast cancer who were treated with cyclophosphamide (750-1500 mg/m²) with or without doxorubicin (≤ 60 mg/m²) and were previously naive to emetogenic chemotherapy. Eligible patients were randomized to receive an aprepitant regimen consisting of aprepitant 125 mg on day 1, ondansetron 8 mg, and dexamethasone 12 mg before chemotherapy as well as ondansetron 8 mg 8 hours later and aprepitant 80 mg once a day on days 2-3; or a placebo regimen consisting of ondansetron 8 mg on day 1 and dexamethasone 20 mg also on day 1 before chemotherapy as well as ondansetron 8 mg 8 hours later on days 2-3 and ondansetron 8 mg twice a day. The primary efficacy endpoint was complete response rate (no emesis or use of rescue antiemetics) for the 120-hour period after chemotherapy.

Of 866 patients randomized, 857 (99%) were evaluable for treatment response. Efficacy data showed that patients treated with the aprepitant regimen had a significantly higher complete response rate than those treated with the

standard regimen (50.8% vs. 42.5%; $P = 0.015$). Importantly, a significantly higher number of patients receiving aprepitant therapy reported minimal or no impact of CINV on daily life compared with those treated with the placebo regimen (63.5% vs. 55.6%; $P = 0.019$).

The aprepitant regimen was generally well tolerated with an acceptable safety profile. The incidence of adverse events was similar in both arms. However, the incidences of constipation and dyspepsia were slightly higher in patients receiving the aprepitant regimen than those treated with the placebo regimen.

Casopitant (GW679769)

Casopitant (GW679769) is a NK-1 antagonist currently being developed to prevent CINV and postoperative nausea and vomiting in patients with cancer. Preclinical studies demonstrated that a single dose of casopitant significantly inhibited the number of retching and vomiting episodes in a dose-related manner in cisplatin-induced acute and delayed emesis.¹⁵ In addition, complete responses were also seen with a 2-mg/kg dose in ferrets with cisplatin-induced acute and delayed emesis.

In another preclinical study, the antiemetic activity of casopitant was compared with aprepitant in ferret models of cisplatin-induced acute and delayed emesis.¹⁶ In acute emesis, food and water consumption was increased in ferrets treated with casopitant, whereas aprepitant reduced the food and water intake during acute emesis in ferrets. Casopitant and aprepitant blocked the retching and vomiting after cisplatin administration in a dose-related manner. Of note, casopitant has greater potency in enhancing food and water intake and reducing nausea-like symptoms compared with aprepitant after administration of cisplatin.

Two recent, phase II, dose-ranging studies with a combined patient popu-

Table 1

Novel NK-1 Antagonists as Antiemetics in Clinical Development¹⁴

Antagonist	Sponsor	Form of Therapy	FDA Status
Aprepitant	Merck	Oral	Approved
Casopitant (GW679769)	GlaxoSmithKline	Oral and I.V.	Phase II; start of phase III
Netupitant	Roche-Helsinn	Oral	Phase I/II
Vestipitant	GlaxoSmithKline	NR	Phase II/PONV
SCH619734	Schering	Oral and I.V.	Phase I (soon)

Abbreviation: FDA = Food and Drug Administration; NR = not reported; PONV = postoperative nausea and vomiting

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lation of approximately 1200 revealed that the addition of casopitant to the 5-HT₃ antagonist ondansetron plus dexamethasone enhanced the benefit in patients receiving highly or moderately emetogenic chemotherapy.¹⁷ More than 85% of patients exhibited a complete response after treatment with casopitant in combination with ondansetron and dexamethasone, which is significantly higher (43% in patients receiving highly emetogenic chemotherapy and 21% in patients receiving moderately emetogenic chemotherapy) compared with treatment with ondansetron and dexamethasone.

The ongoing, randomized, phase II trials are currently evaluating the clinical activity of casopitant plus ondansetron versus ondansetron in patients with CINV from moderately and highly emetogenic chemotherapy. The results of these trials are expected at the 2006 Annual Meeting of the American Society of Clinical Oncology.

Conclusion

Ongoing development of new antiemetic drugs in recent years has provided an opportunity to further improve the control of CINV in patients with cancer. Selective NK-1 antagonists can be differentiated from the 5-HT₃ antagonists in preclinical models by virtue of their broader spectrum of clinical activity with a variety of emetic stimuli. Among the NK-1 receptor antagonists that have been evaluated, aprepitant has been the most widely studied and has demonstrated significant activity against CINV

in patients with cancer. The newer NK-1 antagonists are in various stages of clinical development. The initial data with casopitant are promising, and the regulatory filing of this drug for moderately and highly emetogenic chemotherapy is scheduled for 2007.

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