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REVIEW ARTICLE

Aprepitant - where do we stand in the control of chemotherapy-induced nausea and vomiting?

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Summary

Despite progress in the area of supportive care in oncology in the last two decades, nausea and vomiting continue to be significant side effects of cancer therapy. These symptoms can escalate over time and can result in patients' refusal to continue with chemotherapy. Introduction of serotonin (5-HT_3) receptor antagonists was a major therapeutic advance in the treatment of chemotherapy-induced nausea and vomiting with enhanced efficacy when corticosteroids were added. However, these agents have limited protection in the acute phase of chemotherapy-induced nausea and vomiting with little or no effect over the delayed phase. The aim of this review was to introduce a new class of antiemetics, a selective high-affinity antagonist at human substance P neurokinin 1 (NK_1) receptors-aprepitant. Its pharmacological characteristics as well as its efficacy are reviewed. Aprepitant appears to be well tolerated but, due to its inhibitory effect on cytochrome P450 isoenzyme 3A4, it can lead to significant drug interactions, resulting in need for dose modification of concomitant therapy. The addition of aprepitant to 5-HT_3 receptor antagonists and corticosteroids was found to be superior to the combination of 5-HT_3 receptor antagonists and corticosteroids alone in patients treated with highly and moderately emetogenic chemotherapy. Clinical trials with aprepitant and other antiemetic agents are warranted to determine a regimen that will ensure complete protection from both acute and delayed chemotherapy-induced nausea and vomiting, thus contributing to improved supportive care and patients' quality of life (QoL).

Key words: aprepitant, chemotherapy, nausea, quality of life, vomiting

Chemotherapy-induced nausea and vomiting

It is well known that up to 80% of patients receiving chemotherapy develop nausea and vomiting. Approximately 55% of cancer patients experience nausea and vomiting 5-7 days after chemotherapy administration [1,2]. The data suggest that in the absence of preventive antiemetic therapy, cisplatin dose over 50 mg/m^2 causes acute vomiting in almost 100% of the patients and delayed vomiting in approximately 70-90% of them [3].

Chemotherapy causes 5 types of nausea and vomiting. The most common is acute nausea and vomiting, occurring within the first 24 h of chemotherapy administration. Despite many efforts that have resulted in improved management, acute vomiting still occurs in one third of the patients receiving high doses of cisplatin. Delayed nausea and vomiting occurs 24 h or more after chemotherapy administration, and can last 6-7 days. This type of chemotherapy-induced side effect has been reported in 20-50% of all cisplatin-treated patients. The third type is anticipatory nausea and vom-

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iting which begins prior to the administration of chemotherapy. It usually occurs in patients who had poor control of these symptoms during previous cycles of chemotherapy. Breakthrough nausea and vomiting refers to the symptoms that occur despite adequate antiemetic prophylaxis and urge the use of rescue medication. Refractory nausea and vomiting refers to the symptoms that occur during subsequent chemotherapy cycles when antiemetic control was incomplete in earlier cycles [4-8].

Nausea has been described as a feeling that vomiting may occur. Many investigators consider that recognizing and treating nausea is more difficult compared to vomiting, due to the fact that this symptom can be evaluated only subjectively by patients. One fourth of chemotherapy-treated patients experience nausea in the absence of vomiting [9].

Many mediators take part in the pathogenesis of chemotherapy-induced nausea and vomiting such as serotonin, dopamine, substance P and neurokinin. Based on this fact, the mechanisms of antiemetic drugs include blocking receptors of these mediators that result in decreased nausea and vomiting [10-15].

Standard antiemetic drugs

Many guidelines recommend standard antiemetic drugs for decrease of chemotherapy-induced nausea and vomiting. These agents are dopamine receptor antagonists (metoclopramide), corticosteroids (dexamethasone, methylprednisolone) and 5-HT_3 receptor antagonists (granisetron, ondansetron, tropisetron).

Metoclopramide is a dopamine receptor antagonist, 5-HT_3 antagonist with little affinity to this type of serotonin receptor, and partial 5-HT_4 receptor antagonist. The antiemetic effect of high dose metoclopramide is the result of 5-HT_3 receptor blockade, while side effects (extrapyramidal syndrome and diarrhea) occur due to D2 receptor blockade in the chemoreceptor zone for vomiting.

Dexamethasone is part of antiemetic therapy although the mechanism of its antiemetic effect is still unclear. Some hypotheses exist concerning this issue. These are: a) central inhibition of interleukin synthesis in the hypothalamus; b) decrease of the level of serotonin in the brain tissue; c) action on endorphin release; d) decrease of capillary permeability in the chemoreceptor trigger zone in the area postrema; e) stabilization of cell membrane; and f) decrease of inflammation in the gastrointestinal tract after chemotherapy [8,11,12].

Concerning the serotonin hypothesis, the acute emetogenic effect of cytotoxic agents is based on the release of serotonin, which, as endogenic emetic substance, indirectly activates brain structures and triggers the vomiting reflex. The most important sites of serotonin emetogenic effect are the vagal afferent neurons and other neurons in the gastrointestinal tract and vomiting center in the brain stem with nucleus tractus solitarius, area postrema, chemoreceptor trigger zone and vagal afferent terminals in the medulla.

Cytotoxic agents release serotonin from the small intestine mucosa but also from serotoninergic neurons in the central nervous system which end in the nucleus tractus solitarius [16]. The mechanism by which cytotoxic agents release serotonin is still not known. Despite that, there is evidence that these drugs do not destroy small intestine mucosa cells but on the contrary they induce the usual process of secretion.

The most used antiemetics from the group of 5-HT_3 antagonists are dolasetron, granisetron, ondansetron, palonosetron and tropisetron.

Recently it has been discovered that activation of 5-HT_3 receptor results in the release of substance P on central vagal afferent neurons from the gastrointestinal tract and that substance P acts on NK_1 receptor in the brain stem, resulting in vomiting [12]. The latest studies [2,3,5] concerning antiemetic therapy are examining the efficacy of NK_1 receptor antagonist (aprepitant) in the prevention of chemotherapy-induced vomiting.

Aprepitant

Pharmacology

Aprepitant is a substance P/neurokinin 1 (NK_1) receptor antagonist, chemically described as 5–[[(2R,3S)–2–[(1R)–1–[3,5–bis (trifluoromethyl) phenyl] ethoxy]–3–(4–fluorophenyl)–4–morpholinyl] methyl]–1,2–dihydro–3H–1,2,4–triazol–3–one. Its empirical formula is $C_{23}H_{21}F_7N_4O_3$ and its structural formula is shown on Figure 1.

Aprepitant is a selective high-affinity antagonist of human substance P/NK_1 receptors. It has little or no affinity for serotonin (5-HT_3), dopamine and corticosteroids receptors that are target sites for the existing treatment of chemotherapy-induced nausea and vomiting.

Aprepitant is given orally and has good absorption. Its bioavailability after oral administration is 60-65% with a mean peak plasma concentration at approximately 4 h. Food has no significant effect on the bioavailability of aprepitant. The agent is 95% bound to plasma proteins. The mean apparent volume of distribution at steady state is approximately 70 L. Aprepitant is metabo-

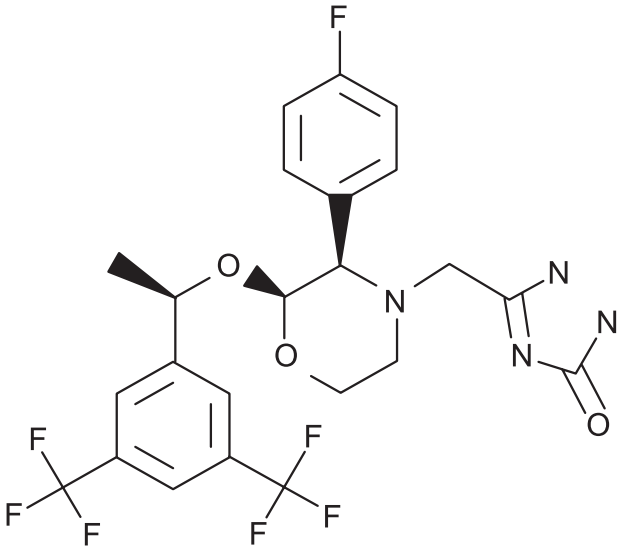

Figure 1. Structural formula of aprepitant.

lized primarily in the liver by cytochrome P450 isoenzyme 3A4 (CYP3A4) and is not excreted by the kidney. Its terminal half-life is 9-13 h. Metabolites are excreted in the urine and, via biliary excretion, in the faeces. It is proven that aprepitant crosses the blood brain barrier in humans and the placenta in animals [17,18].

Aprepitant is indicated for the prevention of acute and delayed nausea and vomiting induced by highly emetogenic chemotherapy in combination with other antiemetic drugs. It is also indicated for the prevention of postoperative nausea and vomiting.

Contraindications for aprepitant administration are concurrent use with pimozide, terfenadine, astemizole or cisapride, due to CYP3A4 inhibition. The concurrent use of aprepitant with these drugs can cause elevated plasma concentrations of these medicinal products, resulting in serious reactions, like serious cardiac arrhythmias. Aprepitant is also contraindicated in patients who are hypersensitive to any component of the drug. Caution is required when aprepitant is administered with chemotherapeutic agents that are primarily metabolized through CYP3A4 (docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, vinorelbine, vinblastine and vincristine) resulting in elevated plasma concentrations of these drugs, with warfarin that can result in clinically significant decrease of prothrombin time, with hormonal contraceptives resulting in their reduced efficacy and in patients with severe hepatic insufficiency [17,19].

Some of the side effects of aprepitant that were registered in most of the studies are presented in Table 1.

Nausea and vomiting are efficacy parameters in the first 5 days post-chemotherapy and are reported as

Table 1. Side effects of aprepitant

Most common (> 10%)	*%*	*Less common (3-10%)*	*%*
Asthenia/fatigue	17.8	Headache	8.5
Nausea	12.7	Vomiting	7.7
Hiccup	10.8	Dizziness	6.6
Constipation	10.3	Heartburn	5.3
Diarrhea	10.3	Abdominal pain	4.6
Anorexia	10.1	Gastritis	4.2
		Neutropenia	3.1
		Fever	2.9

adverse experiences only thereafter.

The recommended dose of aprepitant is 125 mg orally 1 h prior to chemotherapy (day 1) and 80 mg once daily in the morning on days 2 and 3. Aprepitant is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT_3 receptor antagonist [20]. For patients with renal insufficiency and for patients with mild to moderate hepatic insufficiency, no dose adjustment of aprepitant is necessary. It is very important to reduce the dose of aprepitant when this drug is combined with corticosteroids. In cases when dexamethasone or methylprednisolone are given orally, the corticosteroids dose must be reduced by 50% and when methylprednisolone is administered intravenously the dose must be reduced by 25%. For now, there is no evidence of clinical complications when aprepitant is administered in standard dose with high and moderate emetogenic chemotherapy [21,22].

Efficacy

Aprepitant is a novel antiemetic that antagonizes substance P, 1 of the 4 mammalian neurokinins that are present in the neurons of the nucleus tractus solitarius and the area postrema [23]. Substance P, a neuroregulatory peptide consisted of 11 aminoacids, is also present in vagal afferent neurons that innervate 2 areas in the brain [24]. Both of these regions send impulses to the vomiting centre in the brain stem [25]. Substance P is normally present in the human body and it is released as a response to numerous stimuli and also as a neurotransmitter in many emetogenic conditions [26]. In animal models, NK_1 receptor antagonists can antagonize a broad spectrum of emetogenic stimuli, such as apomorphine, morphine, copper sulphate, ipecacuanha, radiation, chemotherapy and anesthesia [19]. It is well known that aprepitant crosses the blood brain barrier and binds to NK_1 receptors in the brain. There is a theory that NK_1 receptor antagonists show their main antiemetic role by depression of the neural activity of the nucleus tractus solitarius. Centrally, blockade

of more than 95% NK_1 receptors is required to exert aprepitant maximal efficacy. Peripheral blockade of aprepitant on receptors localized on the vagal afferent neurons in the stomach is a complementary mechanism based on the decrease of emetogenic afferent stimuli. It is believed that substance P effects central events that include nausea, vomiting, behavior, anxiety, depression and pain transmission [27,28].

Even with adequate therapy, nausea and vomiting are very common chemotherapy side effects. Cancer patients describe these two symptoms as the most frightening and this fact can make some patients to experience nausea and vomiting even before chemotherapy administration [14,29].

During the last two decades there was some improvement in the treatment of chemotherapy-induced nausea and vomiting. The use of antiemetics such as dopamine receptor antagonists and 5-HT_3 receptor antagonists helped preventing nausea and vomiting but only to a certain level. Addition of corticosteroids, such as dexamethasone, improved the control of these symptoms. However, the efficacy of these drugs remained limited regarding acute vomiting, even when these agents are applied before the first dose of antitumor drugs in every chemotherapy cycle. The role of momentarily available medications for the control of delayed vomiting is little [30,31].

Aprepitant has been studied in 5 phase II [3,24-26,32,33] and in 2 phase III clinical trials [34,35]. The phase II trials did show that aprepitant is more effective when added to an ondansetron + dexamethasone regimen than when given alone. It was also shown that there is no benefit in giving aprepitant the day before cisplatin. Each of the 2 phase III randomized, double-blind, placebo-controlled trials recruited over 500 cisplatin-naïve patients who were due to receive cisplatin ≥ 70 mg/m^2 (the mean dose used was approximately 81 mg/m^2). In both trials the patients received one of the two of the following regimens: a) the first group received ondansetron 32 mg i.v. + oral dexamethasone 20 mg on day 1, followed by oral dexamethasone 8 mg twice a day on days 2-4; b) the second group received oral aprepitant 125 mg + ondansetron 32 mg i.v. + oral dexamethasone 12 mg on day 1 and then oral aprepitant 80 mg once daily on days 2-3 + oral dexamethasone 8 mg once daily on days 2-4. In patients who received aprepitant, the dose of corticosteroids was halved since aprepitant doubles dexamethasone levels. The primary endpoint in both trials was the proportion of patients with complete response i.e. no emetic episodes and no rescue medications. In both trials, the proportion of patients with complete response was significantly higher in the aprepitant group throughout the 5-day study period.

There are many studies confirming the efficacy of aprepitant in the protection of chemotherapy-induced nausea and vomiting and some of the recent studies are stated in Table 2.

In a trial conducted by Poli-Bigelli et al. during 5-day period after chemotherapy this proportion was 62.7 vs. 43.3% in favor of the aprepitant group ($p < 0.001$). On day 1, complete response was achieved in 82.8 vs. 68.4% patients, in favor of the aprepitant group ($p < 0.001$). On days 2-5, complete response was registered in 67.7 vs. 46.8% patients, in favor of the aprepitant group ($p < 0.001$). The overall incidence of side effects was similar in both groups (72.8% in the aprepitant group vs. 72.6% in the group with standard antiemetic therapy) [34].

Hesketh et al. enrolled 530 patients in their trial and they found that the proportion of patients with complete response on days 1-5 was significantly higher in the aprepitant group (72.7 vs. 52.3%, $p < 0.001$). The proportion of patients with complete response was significantly higher in the aprepitant group on day 1 (acute phase) but also on days 2-5 (delayed phase) [35].

Table 2. Recently published studies on the efficacy of aprepitant

First author	*Year*	*Number of randomized patients*	*Complete response*		*p-value*
			Aprepitant group %	*Standard antiemetic group %*	
Poli-Bigelli et al. [34]	2003	569	62.7	43.3	<0.001
Hesketh et al. [35]	2003	530	72.7	52.3	<0.001
De Wit et al. [36]	2003	202	Cycle 1: 64 Cycles 2-6: 59	Cycle 1: 49 Cycles 2-4: 34	<0.005 <0.005
Herrstedt et al. [37]	2004	866	Cycle 1: 75.7 Cycles 2-4: 62.9	Cycle 1: 58.7 Cycles 2-4: 38.8	<0.001 <0.001
Warr et al. [38]	2005	863	51	42	0.015
Schmoll et al. [39]	2006	489	72	61	0.003

QoL which was assessed by the Functional Living Index - Emesis (FLIE) questionnaire, was improved in the aprepitant group compared to the group which received standard antiemetic therapy in both trials [34,35].

The effect of aprepitant in multiple cycles of cisplatin-based chemotherapy was assessed by de Wit et al. in an extended phase III trial in 2003. Patients were divided in 3 groups. The first group received aprepitant 375 mg 1 h before cisplatin administration on day 1 and aprepitant 250 mg on days 2-5. The second group received aprepitant 125 mg before cisplatin administration and aprepitant 80 mg on days 2-5. The third group of patients received placebo before cisplatin on days 2-5. To each group ondansetron 32 mg and dexamethasone 20 mg before cisplatin and dexamethasone 8 mg on days 2-5 were administered. The primary endpoint was complete response over 5 days following cisplatin administration in up to 6 cycles. It was shown that in the first cycle significantly higher complete response rate was achieved in the aprepitant group compared with the standard therapy group (64 vs. 49%, $p < 0.05$). In cycles 2-6 the rate of complete response was also significantly higher in the aprepitant group in comparison to the standard therapy group (59 vs. 34%, $p < 0.05$). Based on these data, it was concluded that administration of aprepitant results in better and more sustained protection against cisplatin-induced nausea and vomiting over multiple cycles [36].

Superior response with aprepitant for prevention of chemotherapy-induced nausea and vomiting over multiple cycles was also documented in a clinical trial conducted by Herrstedt et al. who used moderately emetogenic chemotherapy (cyclophosphamide alone or with dexamethasone or epirubicin) [37].

A randomized multicentre trial conducted by Warr et al. evaluated aprepitant efficacy for the prevention of chemotherapy-induced nausea and vomiting in patients who received moderately emetogenic chemotherapy for breast cancer (cyclophosphamide with or without doxorubicin or epirubicin). The patients were divided in 2 groups. The group with aprepitant received on day 1 aprepitant 125 mg, ondansetron 8 mg and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later, and on days 2-3 aprepitant 80 mg daily. The group with the control regimen received on day 1 ondansetron 8 mg and dexamethasone 12 mg before chemotherapy and ondansetron 8 mg 8 h later, and on days 2-3 ondansetron 8 mg b.i.d. The primary endpoint was the complete response rate (no vomiting and no use of rescue therapy). The results showed that the complete response was higher in the aprepitant group in comparison with the control group (50.8 vs. 42.5%, p=0.015). Both treatments were generally well tolerated [38].

Schmoll et al. have randomized 489 patients who received cisplatin ≥ 70 mg/m^2 to either aprepitant (aprepitant + ondansetron + dexamethasone on day 1; aprepitant + dexamethasone on days 2-3; dexamethasone on day 4) or a control group (ondansetron + dexamethasone on days 1-4). The primary endpoint was complete response which was significantly higher overall (days 1-5) in the aprepitant group (72 vs. 61%, p=0.003). Also the complete response was higher in favor of the aprepitant group in acute (day 1; 88 vs. 79%, p=0.005) and delayed phases (days 2-5; 74 vs. 63%, p=0.004) [39].

The efficacy of aprepitant in multiple cycles of cisplatin-based chemotherapy was assessed by de Wit et al. in a phase III trial. The primary endpoint of this study was no vomiting and no significant nausea over 5 days following cisplatin administration, for up to 6 chemotherapy cycles. In every cycle, the rates of no vomiting and no significant nausea were significantly higher in the aprepitant group ($p < 0.006$). In the first cycle this rate was 61% vs. 46% in favor of the aprepitant group and thereafter the rates remained higher throughout in the group of patients receiving aprepitant (59 vs. 40%, $p < 0.05$). Comparing the aprepitant group (aprepitant + ondansetron + dexamethasone) and the standard therapy group (ondansetron + dexamethasone), the first one had better antiemetic control which was maintained over multiple cycles of highly emetogenic chemotherapy [40].

There is little information on the functional influence of effective antiemetic protection. Martin et al. conducted a trial in which they used the FLIE questionnaire to assess the influence of chemotherapy-induced nausea and vomiting after aprepitant administration. In a double-blind randomized trial included were patients treated with cisplatin and either aprepitant + dexamethasone + ondansetron on day 1 and dexamethasone on days 2-5 or standard antiemetic therapy (dexamethasone + ondansetron on day 1 and dexamethasone on days 2-5). After administration of these two regimens, nausea and need for rescue medication were registered in a 5-day diary and the FLIE was completed on day 6. The aprepitant group achieved significantly higher rate of complete response in comparison to the standard antiemetic therapy group (71 vs. 44%, $p < 0.001$). According to FLIE total score there was no impact of chemotherapy-induced nausea and vomiting on daily life activities in the group of patients receiving aprepitant (84 vs. 66%, $p < 0.001$) [41].

One German group examined the impact of aprepitant in decreasing chemotherapy-induced nausea and vomiting, as well as aprepitant cost-effectiveness. The results showed that patients treated with aprepitant (aprepitant + ondansetron + dexamethasone) in comparison to the control regimen (ondansetron + dexamethasone) over a 5-day period, had significantly higher rates

of complete response (68 vs. 48%, p-value not stated in the original article). It was estimated that because of the improved protection against chemotherapy-induced nausea and vomiting achieved with the addition of aprepitant to the standard antiemetic regimen the patients gained 15 additional hours of perfect health per cycle. In patients treated with highly emetogenic outpatient chemotherapy, the use of aprepitant is cost-effective from the perspective of statutory health insurance [42].

Conclusion

The addition of NK_1 receptor antagonist (aprepitant) to the combination of 5-HT_3 receptor antagonist and corticosteroid improves the control of nausea and vomiting caused by highly emetogenic cisplatin-based chemotherapy during both the acute and delayed phases. The regimen is generally well tolerated with occurrence of isolated clinical and laboratory side effects that are similar to the ones which are registered during the standard antiemetic treatment. The superior control of chemotherapy-induced nausea and vomiting that has been accomplished with the use of aprepitant in combination with 5-HT_3 receptor antagonist and corticosteroid represents a significant improvement that can lead to better supportive care and further amelioration of cancer patients' QoL.

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