

## MINI-REVIEW

# Aprepitant in the Prevention of Vomiting Induced by Moderately and Highly Emetogenic Chemotherapy

Shi-Yong Wang<sup>1\*</sup>, Zhen-Jun Yang<sup>2</sup>, Zhe Zhang<sup>1</sup>, Hui Zhang<sup>1</sup>

### Abstract

Chemotherapy is a major therapeutic approach for malignant neoplasms; however, due to the most common adverse events of nausea and vomiting, scheduled chemotherapeutic programs may be impeded or even interrupted, which severely impairs the efficacy. Aprepitants, 5-HT<sub>3</sub> antagonists and dexamethasone are primary drugs used to prevent chemotherapy-induced nausea and vomiting (CINV). These drugs have excellent efficacy for control of acute vomiting but are relatively ineffective for delayed vomiting. Aprepitant may remedy this deficiency. Substance P was discovered in the 1930s and its association with vomiting was confirmed in the 1950s. This was followed by a period of non-peptide neurokinin-1 (NK-1) receptor antagonist synthesis and investigation in preclinical studies and clinical trials (phases I, II and III). The FDA granted permission for the clinical chemotherapeutic use of aprepitant in 2003. At present, the combined use of aprepitant, 5-HT<sub>3</sub> antagonists and dexamethasone satisfactorily controls vomiting but not nausea. Therefore, new therapeutic approaches and drugs are still needed.

**Keywords:** Neurokinin-1 receptor antagonist - aprepitant - substance P - chemotherapy-induced nausea and vomiting

*Asian Pac J Cancer Prev*, 15 (23), 10045-10051

### Status of Cancer Chemotherapy, and the Prevention and Mechanism of Chemotherapy-Induced Nausea and Vomiting

Malignant neoplasms remain a leading cause of death worldwide (Siegel et al., 2014). At the beginning of this century, comprehensive treatment for malignant neoplasm had progressed considerably with advances in molecular-targeted therapy, immunotherapy and gene therapy. However, chemotherapy is still the primary treatment. Chemotherapy-induced nausea and vomiting (CINV) is the most common and intolerable adverse event, which impedes or even interrupts the scheduled therapeutic program and severely impairs the efficacy (Hassan and Yusoff, 2010; Janelsins et al., 2013; Keat et al., 2013; nccn, 2014). Therefore, this situation requires more attention from oncological physicians. In China, knowledge of the prevention in CINV has not attracted extensive attention. Since antiemetic drugs are unavailable or expensive, 5-HT<sub>3</sub> antagonists serve as the primary pharmacotherapy and strategy. By the end of 2013, prevention of CINV in China had entered a new era with the marketing of aprepitant. This article reviews the studies on the use of aprepitant for the treatment of CINV.

CINV can be broadly classified into acute, delayed, anticipatory, refractory and breakthrough type. By mechanism, it can also be classified into acute and delayed

type (Janelsins et al., 2013; nccn, 2014). However, the mechanisms of CINV are still unclear. Based on the current studies, it is generally believed that 5-HT<sub>3</sub> plays a dominant role in acute vomiting, while substance P seems to play a more important role in delayed vomiting (Bergstrom et al., 2011). In cisplatin-induced CINV, serum 5-HT<sub>3</sub> levels peak at 6-8 h after the administration of cisplatin. At this time-point, the clinical symptoms are obvious and the efficacy of 5-HT<sub>3</sub> antagonists is excellent. Neurokinin-1 (NK1) receptor antagonists are effective for both acute and delayed vomiting, especially the latter, on which the studies are also focused. The advent and application of palonosetron, a second-generation 5-HT<sub>3</sub> antagonist, furthers our understanding of the mechanisms of CINV. In contrast to the first-generation 5-HT<sub>3</sub> antagonist, it is efficacious in both acute and delayed CINV. If this efficacy is based solely on enhanced binding to the receptors and lengthened half-life, then increased administration frequency or dosage of the first-generation drugs should ensure binding saturation of receptors; however, this is not the case. More extensive studies have indicated that the 5-HT<sub>3</sub> receptor that binds palonosetron has allosteric sites, and that internalization occurs following binding, thus inhibiting receptor recycling for up to 2.5h (Rojas et al., 2010; Rojas et al., 2014). Additionally, palonosetron treats both acute and delayed vomiting via the crosstalk that exists between the 5-HT<sub>3</sub> and substance P receptor

<sup>1</sup>Department of Biotherapy and Laboratory of Biotherapy, the Fourth Affiliated Hospital of China Medical University, <sup>2</sup>Department of Medical Information, Shengjing Hospital of China Medical University, Shenyang, China \*For correspondence: [cmu4h\\_swzlk@126.com](mailto:cmu4h_swzlk@126.com), [sywang66@yahoo.com](mailto:sywang66@yahoo.com)

## Substance P and Vomiting

Substance P was discovered in the 1930s. With a broad spectrum of function, it is associated with regulation of neural activity, as well as endocrine and immune functions (Bergstrom et al., 2011). In the 1950s, it was found to be distributed at the vomiting center in the brain and proved to be associated with vomiting. In 1971, the structure of substance P was confirmed as a peptide consisting of 11 amino acids. In 1989 the synthesis of a peptidic analog and cloning of the NK1 receptor were completed successfully and in 1991, non-peptidic NK1 antagonists were synthesized. Aprepitant and fosaprepitant were successfully synthesized in 1993 and preclinical studies were conducted in 1994 followed by clinical trials in 1998. The distribution of substance P was verified by positron emission tomography (PET) in 2001. In 2004, the aprepitant dosage and administration regimen was further defined as a 3-day combination program of 125mg, 80mg and 80mg, after which the binding rate of the NK1 receptor in the brain reached in excess of 90%. However, the 6-day program of 40mg for the first day and continuous use of 25mg for the successive 5 days resulted in a 75-80% binding rate to the NK1 receptor in the brain. Thus based on these studies, administration dose and time of aprepitant were defined as the 3-day program of 125mg for the first day and 80mg per day for the following two days (Bergstrom et al., 2011; Hargreaves et al., 2004). In 2003, the marketing of aprepitant was approved by the FDA, and in 2008 fosaprepitant (the injectable preparation) was also approved for marketing (Bergstrom et al., 2011).

## Interactions among Aprepitant, Dexamethasone, 5-HT3 Antagonists and other Drugs

In CINV treated with aprepitant, combination with dexamethasone and a 5-HT3 antagonist is usually required. Aprepitant is a moderate inhibitor of CYP3A4, while dexamethasone is the substrate of this enzyme; thus, the impact of aprepitant on dexamethasone should be clarified. In 2003, Merck Research Laboratory reported the results (McCrea et al., 2003) of their study involving three groups: Group A: on day 1, 32mg ondansetron was injected intravenously (i.v.) and 20mg dexamethasone was given orally; on day 2 to day 5, 8mg dexamethasone was given orally. Group B: oral administration of aprepitant was added on the basis of group A, i.e. 125mg on day 1, 80mg per day from day 2 to day 5. Group C: dosage of orally administered dexamethasone in group B was adjusted to 12mg on day 1 and 4mg per day from day 2 to day 5. On day 1, the mean serum concentration of dexamethasone in group B was 2.2-fold greater than that in group A, while the concentration in group C was similar to that in group A. These phenomena demonstrated that the clearance rate of dexamethasone was reduced by 54% due to the use of aprepitant. In 2008 and 2011, Japanese researchers reported two similar studies (Nakade et al., 2008; Takahashi et al., 2011),

in which the only difference was the administration of dexamethasone as an intravenous injection. They found that the dexamethasone clearance rate was associated with aprepitant administration. Compared without aprepitant, when the dose of aprepitant was 125mg/80mg, patient's clearance rate of dexamethasone was reduced by 47.5%; when the aprepitant dose was readjusted to 40mg/25mg the clearance rate of dexamethasone was reduced by 24.7%. These results indicated that aprepitant has a similar impact on the dexamethasone clearance rate when administered either orally or intravenously.

Similarly, Blum et al (2003) reported the results of their study on the impact of aprepitant on serum concentrations of ondansetron and granisetron in healthy volunteers. This study comprised two experimental groups: Standard-control group 1: 32mg ondansetron (i.v.) and 20mg dexamethasone (oral) on day 1, with 8mg dexamethasone (oral) per day on day 2 to day 5. Experimental group 1: aprepitant (oral) was added on the basis of the standard-control group 1, i.e., 375mg on day 1 and 250mg per day from day 2 to day 5. Standard-control group 2: 2mg granisetron i.v. plus 20mg dexamethasone (oral) on day 1, with 8mg dexamethasone (oral) per day on day 2 to day 3. Experimental group 2: aprepitant (oral) was added on the basis of the standard-control group 2, i.e., 125mg on day 1 and 80mg per day 2 to day 3. The results indicated a slight but statistically significant increase in serum concentrations of ondansetron in group 1, with similar concentrations of granisetron found in group 2, indicating that regular dosage of aprepitant did not significantly affect the concentrations of the 5-HT3 antagonists.

Aprepitant increases the AUC of ifosfamide by approximately 11-fold but does not affect this parameter for vinblastine and exerts only a slight influence on paclitaxel. These data indicate that the dose of aprepitant added to a standard antiemetic regimen combined with vinblastine or paclitaxel does not require further adjustment (Loos et al., 2007).

## Aprepitant-Phase II Clinical Study Results

Table 1 summarizes the six phase II clinical studies of aprepitant (Navari et al., 1999; Campos et al., 2001; Cocquyt et al., 2001; Van Belle et al., 2002; Chawla et al., 2003; Takahashi et al., 2010), all of which adopted chemotherapeutic programs involving either single or combined use of cisplatin (the articles are not listed in the order of the publication date). The first study was published by Cocquyt (2001). This study consisted of two groups comparing the NK1 receptor antagonist and ondansetron, both of which were administered as a single dose 30-60 min prior to chemotherapy. The results showed that the complete response (CR) rates, defined as no vomiting or no rescue therapy, for acute vomiting in the NK1 receptor antagonist and ondansetron groups the CR rates were 37% and 48%, respectively; while for delayed vomiting, the CR rates were 48% and 17%, respectively. The second study reported by Van Belle (2002) added dexamethasone on day 1 on the basis of the first study (Cocquyt et al., 2001) and added a new group in which a NK1 receptor antagonist was added to the

chemotherapy day 2 to day 5. In this study, the CR rate for acute vomiting in the NK1 receptor antagonist plus dexamethasone group was 36-44%, which was similar to that observed for the sole use of the NK1 receptor antagonist in the study of Cocquyt (2001). However, when dexamethasone was added, the antiemetic rate in the ondansetron group was raised to 83% (increased by 35%) and the control of vomiting during the delayed phase was also improved, with a CR rate increased from 17% to 38%. However, in the NK1 receptor antagonist group, the addition of dexamethasone had no effect on the control of delayed vomiting, with a non-improved CR rate of 46%. In contrast, the continuous use of the NK1 receptor antagonist from day 2 to day 5 of chemotherapy in this group raised the CR rate to 59% (increased by 13%). The design of the third study reported by Chawla (2003) was more sophisticated with the administration of three different drugs prior to the use of cisplatin, simultaneous administration of dexamethasone and various doses of the NK1 receptor antagonist, MK-869, a NK1 receptor antagonist. The results confirmed that the combined use of ondansetron and dexamethasone has an extremely significant antiemetic role in acute vomiting, with an antiemetic rate of 71.4%. If 40mg or 125mg MK-869 was added, the antiemetic rate increased to 75.6% and 83.2% respectively, indicating a significant dose-dependent synergy. In the delayed phase, single administration of 8mg dexamethasone yielded an antiemetic rate of 45.2% and a single administration of MK-869 result increased the antiemetic rate to 63.9% (25mg) and 72.7% (80mg), thus indicating a more significant dose-dependent synergy. Before 2003, there were no reports of studies of the combined use of NK1 receptor antagonists and dexamethasone for the delayed phase. In 2010, a Japanese study was reported (Takahashi et al., 2010), the results of which basically verified that the combined administration of the NK1 receptor antagonist and dexamethasone is more efficacious than the use of dexamethasone alone in the

delayed phase. Similarly positive results were obtained in the last two comparative studies with granisetron reported by Navari (1999) and by Campos (2001).

The six phase II studies described here indicate that single use of a NK1 receptor antagonist does not provide an antiemetic advantage for acute vomiting, while the combined use of the 5-HT<sub>3</sub> antagonist and dexamethasone somehow enhances the antiemetic effects. In contrast, single use of a NK1 receptor antagonist is more advantageous in the delayed phase and the addition of dexamethasone may have certain synergetic effects. In addition, in combination treatment with two or three drugs, the maximum time for NK1 receptor antagonist administration was 7 days. This regimen was well-tolerated and dose-dependent; thus, the combined therapy is recommended.

### Aprepitant Treatment of Severe CINV-phase III Clinical Study Results

Table 2 summarizes the three phase III clinical studies of aprepitant treatment of severe CINV (Hesketh et al., 2003; Poli-Bigelli et al., 2003; Hu et al., 2014), all of which were marketing studies. The design of the first two studies (Hesketh et al., 2003; Poli-Bigelli et al., 2003) reported by aprepitant 052 group and aprepitant 054 group were identical although the study populations were different. The specific design was as follows: the aprepitant group: 125mg aprepitant+12mg dexamethasone (oral), and 32mg ondansetron (i.v.) on day 1; 80mg aprepitant + 8mg dexamethasone (oral) on day 2 and day 3; 8mg dexamethasone on day 4. The standard-control group: 20mg dexamethasone (oral), and 32mg ondansetron (i.v.) on day 1; 8mg dexamethasone (oral) per day from day 2 to day 4. This design shows that the aprepitant and dexamethasone administration regimen had been adjusted from the 5-day continuous regimen used in the phase II studies (Table 1) to the 3-day administration regimen

**Table 1. Comparison of Antiemetic Regimen and the CR Rate for Vomiting in the Six Phase II Clinical Studies of Aprepitant in Treating CINV**

Reference	Study Groups (n)	Antiemetic Regimen and the CR Rate for Vomiting	
		Acute Phase (d1)	Delayed Phase (d2-5)
Cocquyt 2001	Apr (30)	L-758298, 60-100mg(37%)	(48%)
	Control (23)	Ond 32mg(48%)	(17%)
Van Belle 2002	I (61)	L-758298,100mg+Dex20mg(44%)	MK-869,300mg(59%)
	II (58)	L-758298,100mg+Dex20mg(36%)	(46%)
	III (58)	Ond 32mg+Dex20mg(83%)	(38%)
Chawla 2003	I (131)	Ond 32mg+Dex20mg+MK-869,125mg(83.2%)	MK-869,80mg(72.7%)
	II (119)	Ond 32mg+Dex20mg+MK-869,40mg(75.6%)	MK-869,25mg(63.9%)
	III (126)	Ond 32mg+Dex20mg(71.4%)	Dex 8mg(45.2%)
Takahashi 2010	I (146)	Apr 125mg+Dex6mg+Gra 40µg/kg(87.0%)	Dex 4mg(d2-3) +Apr 80mg(72.6%)
	II (143)	Apr 40mg+Dex8mg+Gra 40µg/kg(90.0%)	Dex 6mg(d2-3)+Apr 25mg(69.9%)
	III (150)	Dex12mg+Gra 40µg/kg(83.3%)	Dex 8mg(d2-3) (51.7%)
Navari 1999	I (54)	Gra 10µg/kg+Dex20mg+L-754030 400mg(93%)	L-754030,300mg(82%)
	II (54)	Gra 10µg/kg+Dex20mg+L-754030 400mg(94%)	(78%)
	III (51)	Gra 10µg/kg+Dex20mg(67%)	(33%)
Campos 2001	I (90)	Gra 10µg/kg+Dex20mg(57%)	(29%)
	II (86)	Gra 10µg/kg+Dex20mg+MK-869 400mg(80%)	MK-869,300mg(63%)
	III (89)	Dex20mg+MK-869 400mg(46%)	MK-869,300mg(51%)
	IV (86)	Dex20mg+MK-869 400mg(43%)	MK-869,300mg(57%)

\*L-758298, MK-869, L-754030: a prodrug of NK1 receptor antagonist; Ond, ondansetron; Dex, dexamethasone; Apr, aprepitant; Gra, granisetron; CR, complete response; CINV, chemotherapy-induced nausea and vomiting

**Table 2. Comparison of the CR Rate for Vomiting in the Three Phase III Clinical Studies of Aprepitant in Treating Severe CINV**

Reference	Study Groups (n)	CR Rate for Vomiting (%)		
		Acute Phase	Delayed Phase	Overall Phase
Hesketh (2003)	APR (259)	89.2	75.4	72.7
	Control (260)	78.1	55.8	52.3
Poli-Bigelli (2003)	APR (204)	79.4	74	69.6
	Control (208)	79.3	59.4	57
Hu (2014)	APR (283)	82.8	67.7	62.7
	Control (286)	68.4	46.8	43.3

\*APR, aprepitant; CR, complete response; CINV, chemotherapy-induced nausea and vomiting

(Table 2). Furthermore, the dosage of dexamethasone on day 1 was reduced by 50%, i.e., 12mg, which ensured consistent concentrations of dexamethasone in the two groups and avoided confusion in interpreting the results. In the 052 group (Hesketh et al., 2003), the CR rate for vomiting in the aprepitant group was significantly increased (the CR rates in the acute, delayed and overall phases were increased by 11.1%, 19.6% and 20.4%, respectively),  $p < 0.001$ . Similarly, in the 054 group (Poli-Bigelli et al., 2003), the CR rates in the acute, delayed and overall phases were significantly increased by 14.4%, 20.9% and 19.4%, respectively,  $p < 0.001$ . For distribution of the enrolled population, more than 90% of the 052 group were Caucasian patients aged 58-59 with respiratory and urinary system cancers. The majority of the 054 group comprised ethnicities other than Caucasian and black patients, accounting for 64-66% of whole population, were aged 48-49 and also suffered mainly from respiratory and urinary system cancers. The third study, more recent research was published in 2014 by Hu et al. (2014). All the participants were Chinese aged 49.1-55 and suffering mainly from lung cancers, which accounted 69.9-73.9% of neoplasms of the whole population. The study design was basically the same as the previous two (Hesketh et al., 2003; Poli-Bigelli et al., 2003) with the exception that ondansetron was replaced by granisetron and a small dose of dexamethasone. The CR rate for acute vomiting was not changed ( $p = 0.9$ ); however, the CR rates for the delayed and overall vomiting phases were significantly increased by 14.6% and 11.6%, respectively ( $p < 0.001$ ).

These studies demonstrate the preventive efficacy of aprepitant in severe CINV for various races, particularly in delayed CINV.

### Aprepitant Treatment of Moderate CINV-Phase III Clinical Study Results

Here we describe three phase III clinical studies of moderate CINV treated with aprepitant in order of publishing date (Warr et al., 2005; Yeo et al., 2009; Rapoport et al., 2010).

The first one (Warr et al., 2005) was an international, prospective, double-blind and placebo-controlled study conducted in 95 international research centers. The included patients were all chemotherapy-naïve patients with breast cancer, who were administered cyclophosphamide monotherapy or combined therapy

with doxorubicin (AC) or epidoxorubicin (EC). The study design was as follows: the standard-control group ( $n = 424$ ), ondansetron 8mg (bid, oral) and dexamethasone 20mg (oral) on day 1; ondansetron 8mg (bid, oral) on day 2 and day 3. The aprepitant group ( $n = 433$ ), aprepitant 125mg (oral), ondansetron 8mg (bid, oral) and dexamethasone 12mg (oral) on day 1; aprepitant 80mg (oral) on day 2 and day 3. The primary endpoint of the experiment was CR rate for vomiting; the secondary endpoint of the experiment was the impact on quality of life. The results showed that the overall CR rate for vomiting in the aprepitant group (51%) was significantly higher ( $p = 0.015$ ) than that of the standard-control group (42%). The CR rate for acute vomiting in the aprepitant group (76%) was significantly higher ( $p = 0.034$ ) than that of the standard-control group (69%). There was no statistical difference in the CR rates for delayed vomiting in the aprepitant and the standard-control groups (55% vs 49%, respectively;  $p = 0.064$ ). However, if the response rates for vomiting control was compared separately, the differences were significant ( $p < 0.01$ ), while no differences were found when rescue therapy was added. Moreover, aprepitant was advantageous in overall improvements of quality of life and vomiting, while no differences were found in nausea control between the two groups.

The second study was conducted in Hong Kong (Yeo et al., 2009), among breast cancer patients from China receiving the AC chemotherapeutic program. Although the design and methodology of the study were the same as the first study described (Warr et al., 2005), the results were negative, i.e. the overall CR rates were 46.8% vs. 41.9% (aprepitant vs. standard-control, respectively) and no significant differences were observed ( $p = 0.58$ ). The actual CR rate difference (which was only 4.9%) did not reach the predicted rate of 25% and aprepitant-associated improvements were observed only in the secondary endpoint.

The third study (Rapoport et al., 2010) was a multi-center, prospective, double-blind and placebo-controlled study. Almost half of the subjects were breast cancer patients, while the other cancers were colon cancers (20%), lung cancers (10%) and ovarian cancers (5%). The study design was the same as that of the first two studies described (Warr et al., 2005; Yeo et al., 2009). The results indicated that the CR rates for acute and delayed vomiting were 89.2% vs 80.3% and 70.8% vs 60.9%, respectively, and the overall CR rate for vomiting was 68.7% vs 56.3% (aprepitant vs standard-control); the differences were all statistically significant ( $p < 0.01$ ). Subgroup analysis indicated that, in the AC treated group, the CR rates for acute and delayed vomiting were 84.3% vs 72.5% and 64.8% vs 52.9%, respectively, and the overall CR rate for vomiting was 62.8% vs 47.1% (aprepitant vs. standard-control); the differences were all statistically significant ( $p < 0.01$ ). However, in the non-AC treated group, the CR rates for acute and delayed vomiting were 93.4% vs 88.1% and 76.1% vs 69.0%, respectively, and the overall CR rate for vomiting was 73.9% vs 65.5% (aprepitant vs standard-control); none of the differences were statistically significant ( $p > 0.05$ ).

These studies indicate that aprepitant is a more suitable

for antiemetic for moderate CINV treated with the AC or EC programs. Furthermore, it should be noticed that no dexamethasone was used in these chemotherapeutic plans after day 2.

## **Treatment of Aprepitant in Nausea and Vomiting over Multiple Cycles of Chemotherapy**

Systematic studies on antiemetic drugs such as aprepitant for the control of nausea and vomiting over multiple cycles of chemotherapy are rare. The first, reported by de Wit et al (2004), examined combined data from the multi-cycle extensions of two phase III clinical trials of oral aprepitant plus standard therapy for the prevention of CINV. The standard-control group was treated with ondansetron and dexamethasone, and aprepitant was added to experimental group. Patient CR (without vomiting or obvious nausea, VAS <25mm) rates were recorded for up to six cycles of chemotherapy. CR rates in the aprepitant group from cycle 1 to cycle 6 were 61%, 66%, 65%, 59%, 57% and 59% respectively, while in the standard-control group the corresponding rates were 46%, 54%, 47%, 46%, 46% and 40% respectively. Variations in the CR rates were not great, and rates in the aprepitant group were increased by 12%-19% compared with the standard group. The incidence of adverse events associated with the clinical or laboratory assessments was low, indicating good tolerability. Of the 413 patients in the aprepitant group, 6 cases were adverse events in the clinical assessments and 1 case was in the laboratory assessments respectively, while of the 438 patients in the standard-control group the corresponding numbers were 4 and 1 respectively.

Choi et al (2014) published a prospective, single-center and non-randomized study of CINV in patients with ovarian cancer treated with multiple cycles of paclitaxel and carboplatin. Of the 89 patients enrolled, 85 patients were evaluable for efficacy and toxicity, and 68 (80%) completed all six cycles and the combination treatment. The chemotherapeutic plan was paclitaxel (175mg/m<sup>2</sup> i.v.) and carboplatin, while the antiemetic plan was 125mg aprepitant plus 0.6mg ramosetron and 20mg dexamethasone on day 1; thereafter, only 80mg aprepitant was administered daily on day 2 and day 3. The results showed that CR rates from cycle 1 to cycle 6 were 89.0%, 85.9%, 84.4%, 82.6%, 84.6% and 82.8% respectively; and the probabilities of no nausea from cycle 1 to cycle 6 were 60.0%, 64.1%, 59.7%, 53.6%, 55.4% and 54.7% respectively. There was a slight (approximately 5%) decrease in decreased CR rates for nausea and vomiting. The incidence rate of overall adverse events was low, with the most common being constipation (12.4%) and headache (11.1%). Differences among different cycles were not compared.

These studies indicate that the efficacy of aprepitant for multiple-cycle chemotherapy is stable, with no reduction in the antiemetic effect in later cycles compared with that of the first cycle of chemotherapy. Thus, the tolerability is good with few adverse effects.

## **Antiemetic Effect of Aprepitant in Multi-day and Multi-cycle Chemotherapy**

The studies described so far are all antiemetic investigations in single-day chemotherapy. The conditions for multi-day chemotherapy are more complicated because the overlap of acute and delayed nausea and vomiting may occur on any day of chemotherapy and, unfortunately, there are still no international antiemetic guidelines. Four reports described studies of the 3-drug antiemetic regimen involving aprepitant, three of which were phase II clinical studies (Jordan et al., 2009; Gao et al., 2013; Olver et al., 2013). The antiemetic plan of all three studies comprised aprepitant, 5-HT<sub>3</sub> antagonist and dexamethasone, with the use of a triple combination during the chemotherapeutic period. After chemotherapy, aprepitant and dexamethasone were continued for two days. The results indicated that CR (without vomiting and use of rescue therapy) rates for severe and moderate CINV were 41-58.5% and 72.5%, respectively and the probability of no nausea was 24.4-36.6%, with no improvements found as the chemotherapeutic cycles increased. No unpredictable and intolerable adverse events were observed. Therefore, triple therapy involving aprepitant is safe and efficacious in multi-day and multiple-cycle chemotherapy. The another study (Albany et al., 2012) was a small sample, randomized, crossover, placebo-controlled phase III study on the prevention of nausea and vomiting in germ cell tumor chemotherapy. The standard chemotherapeutic plan was a 5-day cisplatin treatment consisting of a daily dose of 20mg/m<sup>2</sup>. The antiemetic plan was as follows: on day 1 and 2, 5-HT<sub>3</sub> antagonistic and dexamethasone were used in both the placebo group and the aprepitant group; on day 3 to day 7, treatments remained the same with the exception of the addition of aprepitant into the experimental group; on day 8, the two groups received dexamethasone only. In this study, the acute phase was defined as day 1 to day 5 during the chemotherapeutic period and the delayed phase was defined as day 6 to day 8. The CR rate for vomiting in the aprepitant group (42%) was significantly higher than that of the placebo group (13%) ( $p < 0.001$ ). The probability of no nausea was improved in the aprepitant group but without statistical significance. No unpredictable and intolerable adverse events were observed in either group. These results further verified those of the phase II clinical studies and also provided evidence for the application of triple therapy involving aprepitant in multi-day and multi-cycle chemotherapy.

## **Factor Analysis of Aprepitant Tolerability and its Impact on Therapeutic Efficacy**

The studies described here clearly illustrate the good tolerability of aprepitant. To further investigate the adverse events to aprepitant, an analysis of data pooled from strictly designed and controlled phase III clinical studies such as the three clinical studies (Warr et al., 2005; Yeo et al., 2009; Rapoport et al., 2010) on severe and moderate CINV described here should be conducted. In

studies on severe vomiting induced by a chemotherapeutic plan consisting of cisplatin, the common adverse events include exhaustion/fatigue, constipation, belching, nausea, diarrhea, anorexia, agitation and headache. In the three studies described here, the incidence rates of exhaustion/fatigue in the aprepitant group were 17.2%, 18.4% and 5.9% respectively, and the corresponding data in the control group were 9.5%, 14.0% and 1.9%, respectively. The rates were higher in the aprepitant group, particularly the last study, which showed a statistically significant difference in the Chinese patients. If 4.0% was set as the threshold for statistical significance of the difference between the aprepitant and control groups, only the difference in the incidence rate of belching (which was 7.0%) was significant, while differences in the incidence rates of constipation (which were -4.0%, 0.1% and 2.3% in these three studies), nausea, diarrhea, anorexia, agitation and headache (all of which were below 2.0%) were otherwise insignificant. These adverse events were irregular and sometimes higher in the standard-control group. These results indicate that the application of aprepitant is not significantly relevant to these adverse events. Less severe but similar adverse events are presented in the treatment in moderate CINV.

There are two reports specifically discussing the factors that affect the efficacy of aprepitant (Hesketh et al., 2006; Hesketh et al., 2010). One, published by Hesketh (2010), described two phase III clinical studies on the application of aprepitant for CINV during cisplatin chemotherapy. This report claimed that "male, dose of cisplatin <80mg/m<sup>2</sup> and more than five alcoholic drinks per week" are factors that increase the CR rate for vomiting, while "female" seemed to be the factor neutralizing all the beneficial effects produced by the factors above. The other study published by Hesketh (2006), which focused on the impact of sex, drew the same conclusion.

## Outlook

Our discussion has so far concentrated mainly on the efficacy of aprepitant in treating chemotherapy-induced vomiting. However, in fact, as a more common symptom than vomiting, nausea is also more difficult to prevent and treat. From the studies discussed here, we can see that antiemetic therapy has proved to be far more efficacious in the treatment of vomiting than of nausea; therefore, new drugs and therapeutic approaches are required. The current recommendation of olanzapine for treating moderate and severe vomiting by the 2014 NCCN guideline version 1.0 has already shown promise. The head-to-head study of olanzapine versus aprepitant (with combined use of 5-HT<sub>3</sub> antagonist and dexamethasone) for the prevention of CINV in phase III clinical studies (Navari et al., 2011) showed that olanzapine is more advantageous than aprepitant in treating chemotherapy-induced vomiting. More importantly, olanzapine also shows better control of nausea and is more tolerable; therefore, this readily available and low cost treatment should be popularized. In addition, the understanding and research of CINV is deficiency in the Asian countries, especially in China. Therefore, the doctors and nurses should increase the

knowledge of CINV first by starting some small sample studies. For example, a retrospective study by Japanese scholars (Uchino et al., 2012) revealed that effective antiemetic regimen showed significantly higher in food intake rate, completion rate of planned chemotherapy and complete suppression rate of nausea in advanced or recurrent lung cancer patients receiving moderately emetogenic chemotherapy.

## Acknowledgments

This work is supported by Natural Science Foundation of Liaoning Province (No. 201102296) provided by Ministry of Education.

## References

- Albany C, Brames MJ, Fausel C, et al (2012). Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5-HT<sub>3</sub> receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. *J Clin Oncol*, **30**, 3998-4003.
- Blum RA, Majumdar A, McCrea J, et al (2003). Effects of aprepitant on the pharmacokinetics of ondansetron and granisetron in healthy subjects. *Clin Ther*, **25**, 1407-19.
- Bergstrom M, Hargreaves RJ, Burns HD, et al (2011). Development of aprepitant, the first neurokinin-1 receptor antagonist for the prevention of chemotherapy-induced nausea and vomiting. *Ann N Y Acad Sci*, **1222**, 40-8.
- Campos D, Pereira JR, Reinhardt RR, et al (2001). Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone. *J Clin Oncol*, **19**, 1759-67.
- Cocquyt V, Van Belle S, Reinhardt RR, et al (2001). Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. *Eur J Cancer*, **37**, 835-42.
- Chawla SP, Grunberg SM, Gralla RJ, et al (2003). Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer*, **97**, 2290-300.
- Choi CH, Kim MK, Park JY, et al (2014). Safety and efficacy of aprepitant, ramosetron, and dexamethasone for chemotherapy-induced nausea and vomiting in patients with ovarian cancer treated with paclitaxel/carboplatin. *Support Care Cancer*, **22**, 1181-7.
- de Wit R, Herrstedt J, Rapoport B, et al (2004). The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. *Eur J Cancer*, **40**, 403-10.
- Gao HF, Liang Y, Zhou NN, Zhang DS, Wu HY (2013). Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. *Intern Med J*, **43**, 73-6.
- Hesketh PJ, Grunberg SM, Gralla RJ, et al (2003). Aprepitant Protocol 052 Study Group. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin-the Aprepitant Protocol 052 Study Group. *J Clin*

- Oncol*, **21**, 4112-9.
- Hargreaves R, Ferreira JC, Hughes D, et al (2004). Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant. *Biol Psychiatry*, **55**, 1007-12.
- Hesketh PJ, Grunberg SM, Herrstedt J, et al (2006). Combined data from two phase III trials of the NK1 antagonist aprepitant plus a 5HT 3 antagonist and a corticosteroid for prevention of chemotherapy-induced nausea and vomiting: effect of gender on treatment response. *Support Care Cancer*, **14**, 354-60.
- Hassan BA, Yusoff ZB (2010). Negative impact of chemotherapy on breast cancer patients QOL-utility of antiemetic treatment guidelines and the role of race. *Asian Pac J Cancer Prev*, **11**, 1523-7.
- Hesketh PJ, Aapro M, Street JC, Carides AD (2010). Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of two phase III trials of aprepitant in patients receiving cisplatin-based chemotherapy. *Support Care Cancer*, **18**, 1171-7.
- Hu Z, Cheng Y, Zhang H, et al (2014). Aprepitant triple therapy for the prevention of chemotherapy-induced nausea and vomiting following high-dose cisplatin in Chinese patients: a randomized, double-blind, placebo-controlled phase III trial. *Support Care Cancer*, **22**, 979-87.
- Jordan K, Kinitz I, Voigt W, et al (2009). Safety and efficacy of a triple antiemetic combination with the NK-1 antagonist aprepitant in highly and moderately emetogenic multiple-day chemotherapy. *Eur J Cancer*, **45**, 1184-7.
- Janelins MC, Tejani MA, Kamen C, et al (2013). Current pharmacotherapy for chemotherapy-induced nausea and vomiting in cancer patients. *Expert Opin Pharmacother*, **14**, 757-66.
- Keat CH, Ghani NA (2013). Cost-effectiveness analysis of granisetron-based versus standard antiemetic regimens in low-emetogenic chemotherapy: a hospital-based perspective from Malaysia. *Asian Pac J Cancer Prev*, **14**, 7701-6.
- Loos WJ, de Wit R, Freedman SJ, et al (2007). Aprepitant when added to a standard antiemetic regimen consisting of ondansetron and dexamethasone does not affect vinorelbine pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol*, **59**, 407-12.
- McCrea JB, Majumdar AK, Goldberg MR, et al (2003). Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther*, **74**, 17-24.
- Navari RM, Reinhardt RR, Gralla RJ, et al (1999). Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754,030 Antiemetic Trials Group. *N Engl J Med*, **340**, 190-5.
- Nakade S, Ohno T, Kitagawa J, et al (2008). Population pharmacokinetics of aprepitant and dexamethasone in the prevention of chemotherapy-induced nausea and vomiting. *Cancer Chemother Pharmacol*, **63**, 75-83.
- Navari RM, Gray SE, Kerr AC (2011). Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol*, **9**, 188-95.
- NCCN clinical Practice guidelines in oncology-antiemesis version I. 2014 (2014). [http://www.nccn.org/professionals/physician\\_gls/f\\_guidelines.asp#supportive](http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#supportive).
- Olver IN, Grimison P, Chatfield M, et al (2013). Results of a 7-day aprepitant schedule for the prevention of nausea and vomiting in 5-day cisplatin-based germ cell tumor chemotherapy. *Support Care Cancer*, **21**, 1561-8.
- Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, et al (2003). Aprepitant protocol 054 study group.cancer. addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. results from a randomized, double-blind, placebo-controlled trial in Latin America. *Cancer*, **97**, 3090-8.
- Rapoport BL, Jordan K, Boice JA, et al (2010). Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. *Support Care Cancer*, **18**, 423-31.
- Rojas C, Thomas AG, Alt J, et al (2012). Palonosetron triggers 5-HT(3) receptor internalization and causes prolonged inhibition of receptor function. *Eur J Pharmacol*, **626**, 193-9.
- Rojas C, Raje M, Tsukamoto T, Slusher BS (2014). Molecular mechanisms of 5-HT(3) and NK(1) receptor antagonists in prevention of emesis. *Eur J Pharmacol*, **722**, 26-37.
- Siegel R, Ma J, Zou Z, et al (2014). Cancer statistics, 2014. *CA Cancer J Clin*, **64**, 9-29.
- Takahashi T, Hoshi E, Takagi M, et al (2010). Multicenter, phase II, placebo-controlled, double-blind, randomized study of aprepitant in Japanese patients receiving high-dose cisplatin. *Cancer Sci*, **101**, 2455-61.
- Takahashi T, Nakamura Y, Tsuya A, et al (2011). Pharmacokinetics of aprepitant and dexamethasone after administration of chemotherapeutic agents and effects of plasma substance P concentration on chemotherapy-induced nausea and vomiting in Japanese cancer patients. *Cancer Chemother Pharmacol*, **68**, 653-9.
- Uchino J, Hirano R, Tashiro N, et al (2012). Efficacy of aprepitant in patients with advanced or recurrent lung cancer receiving moderately emetogenic chemotherapy. *Asian Pac J Cancer Prev*, **13**, 4187-90.
- Van Belle S, Lichinitser MR, Navari RM, et al (2002). Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. *Cancer*, **94**, 3032-41.
- Warr DG, Hesketh PJ, Gralla RJ, et al (2005). Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *J Clin Oncol*, **23**, 2822-30.
- Yeo W, Mo FK, Suen JJ, et al (2009). A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy. *Breast Cancer Res Treat*, **113**, 529-35.