The clinical research study for fosaprepitant to prevent chemotherapy-induced nausea and vomiting: A review

Fei Xue[1,D], Xin Liu[2,D], Xiao Qi[3,D], Jiajing Zhou[4,D], Yongjun Liu[5,E]

[1] Traditional Chinese Medicine General Practice Department, Yantai Hospital of Traditional Chinese Medicine, China
[2] Research and Development Department, Shandong Xianglong Pharmaceutical Research Institute Co., Ltd, Yantai, China
[3] Respiratory Department, Yantai Hospital of Traditional Chinese Medicine, China
[4] Oncology Department, Yantai Hospital of Traditional Chinese Medicine, China
[5] Department of Traditional Chinese Medicine, Shandong Drug and Food Vocational College, Weihai, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online) *Adv Clin Exp Med*. 2023;32(6):701–706

Address for correspondence
Yongjun Liu
E-mail: liuyongjun189@163.com

Funding sources
None declared

Conflict of interest
None declared

Received on May 17, 2022
Reviewed on November 18, 2022
Accepted on December 1, 2022

Published online on April 7, 2023

Abstract

In recent years, chemotherapy-induced nausea and vomiting (CINV) has become the most common adverse effect of chemotherapy in oncology patients. The CINV may reduce the quality of life in mild cases, or even make the patients resist or delay further treatment. Fosaprepitant is a newly marketed neurokinin-1 receptor antagonist (NK-1RA), which can be combined with 5-hydroxytryptamine 3 receptor antagonists (5-HT3RAs) and dexamethasone to prevent chemotherapy-induced vomiting. The dimeglumine salt form of fosaprepitant can be utilized as an intravenous injectable drug, which surpasses aprepitant's oral admistration limits. Fosaprepitant is effective and safe in the control of CINV in cancer patients receiving highly emetogenic chemotherapy (HEC), and may be an alternative option for antiemetic therapy. In general, fosaprepitant is worthy of clinical promotion and has a large market potential. This article reviews the clinical studies on fosaprepitant conducted in recent years, with the aim of providing a basis for the rational clinical selection of antiemetic drugs.

Key words: neurokinin-1 receptor antagonist, fosaprepitant, efficacy and safety, clinical research, chemotherapy-induced nausea and vomiting

Cite as
Xue F, Liu X, Qi X, Zhou J, Liu Y. The clinical research study for fosaprepitant to prevent chemotherapy-induced nausea and vomiting: A review. *Adv Clin Exp Med*. 2023;32(6):701–706. doi:10.17219/acem/157061

DOI
10.17219/acem/157061

Introduction

The treatment of malignant tumors has improved rapidly in recent years. Though there have been many breakthroughs in targeted therapeutics in oncology that are less emetogenic, chemotherapeutics have not been completely replaced. Chemotherapy-induced nausea and vomiting (CINV) are one of the most prevalent side effects of treatment, and severe vomiting can have a negative impact on subsequent therapeutic efficacy.[1] Children present a more severe response compared to adults.[2] If not managed effectively, CINV can affect patients by causing dehydration, malnutrition and electrolyte imbalance. These side effects can significantly impact patient's quality of life and instill fear of chemotherapy. The prevalence of nausea and vomiting is related to several factors, including the emetogenicity of the chemotherapy regimen, the dose and rate of administration of the chemotherapy agents, various environmental triggers, and patient-related factors. The pathogenesis involves multiple organ systems, the central nervous system, the gastrointestinal tract, and neurotransmitters.[3] Highly emetogenic chemotherapy (HEC) is defined as drugs that cause vomiting in more than 90% of patients without any emetic prophylaxis, whereas moderately emetogenic chemotherapy (MEC) is defined as drugs that cause nausea and vomiting in 30–90% of patients without any emetic prophylaxis.[4]

Neurokinin-1 receptor antagonists (NK-1RAs) in combination with 5-hydroxytryptamine 3 receptor antagonists (5-HT3RAs) and dexamethasone have been suggested by domestic and international standards to prevent and minimize CINV in patients.[4] The NK-1RAs are a novel kind of anti-nausea medication with high selectivity and affinity. These medications work by competitively binding to the NK-1R, which can block the binding of substance P and prevent the emetic signal from being transmitted. The release of 5-HT[3,5,6] is the focus of acute CINV, whereas the release of substance P is the focus of delayed CINV. All NK-1RAs are effective but exhibit important differences in efficacy against acute and delayed CINV. For delayed CINV compared to acute CINV, the benefit of NK1-RA-containing 3-drug regimens is greater than that of 2-drug regimens. Fosaprepitant, a subsequently developed aprepitant precursor drug, is given intravenously (i.v.) and is rapidly converted to aprepitant through the hydrolysis of phosphatase enzymes widely present in the body, which can mediate the blockage of substance P.[7] In China, the NK-1RA medications primarily contain aprepitant (oral) and fosaprepitant (injection). The clinical trials for aprepitant are conducted more often due to its earlier availability in the market. However, because fosaprepitant is new to the Chinese market, studies have been limited to children. The dimeglumine salt form of the novel anti-nausea medicine, fosaprepitant, can be utilized as an i.v. injectable drug, which is able to surpass the oral admistration limit of aprepitant. The bioavailability is unaffected by vomiting; therefore, it can be utilized in patients with oral mucositis who are unable to take medications orally.[8]

Objectives

This review compiles the domestic and international clinical investigations on the anti-nausea effects of fosaprepitant, and serves as a guide for choosing anti-nausea medications in the clinic.

Methodology

Studies from the years 2003–2022 were included in our review. The studies were identified using the following keywords: "fosaprepitant", "aprepitant", "CINV", "HEC", "MEC", and "NK-1RA". Several representative articles were screened to analyze and summarize the clinical therapeutic effects of fosaprepitant. The data and conclusions from clinical trials were discussed. The data are presented along historical and medical drug development routes.

The clinical efficacy of fosaprepitant in preventing HEC-induced nausea and vomiting in adults

Fosaprepitant is used to prevent acute and delayed nausea and vomiting associated with HEC, and delayed nausea and vomiting associated with initial and recurrent courses of MEC in adults when used in combination with other antiemetic medicines.[9] In a study conducted in China, 626 cancer patients who were administered HEC were randomly assigned to 2 groups: aprepitant (aprepitant+granisetron+dexamethasone) or fosaprepitant (fosaprepitant+granisetron+dexamethasone).[10] The results showed that there were no differences in the complete response (CR) rate of the acute phase (AP), delayed phase (DP) and overall phase (OP) ($p > 0.05$) between the 2 treatments, and both drugs were well tolerated. In the OP, the CR rate was achieved by 293 (89.33%) patients in the fosaprepitant group and by 294 (92.74%) patients in the aprepitant group. During the AP and DP, the CR rates in the fosaprepitant group were 95.73% and 91.16%, respectively. Thus, fosaprepitant was found to be beneficial in controlling HEC-related nausea and vomiting in Chinese patients. Saito et al. studied 347 adult patients in Japan who received chemotherapy, including cisplatin (≥70 mg/m^2), and were randomly divided into fosaprepitant and control groups.[11] The results showed that the fosaprepitant regimen was more effective than the control regimen in both the AP ($p = 0.0006$) and the DP ($p = 0.0025$).

Both of the studies were similar in regard to the CR rates observed during the AP. In contrast to the findings

Table 1. The clinical efficacy of fosaprepitant in preventing HEC

Study	Day	Cisplatin dose (mean)	Group	Antiemetic doses	CR (%) (acute phase (AP))	CR (%) (delay phase (DP))	CR (%) (overall phase (OP))
Yang et al.[10] n = 645	day 1 (before chemo-therapy)	non-cisplatin HEC regimen (148 people) or cisplatin 60–80 mg/m^2 (497 people)	fosaprepitant group	fosaprepitant 150 mg i.v. plus granisetron 3 mg i.v. plus dexamethasone 6 mg orally or i.v.	fosaprepitant group: 95.73% aprepitant group: 95.90%	fosaprepitant group: 95.73% aprepitant group: 93.38%	fosaprepitant group: 89.33% aprepitant group: 92.74%
			aprepitant group	aprepitant 125 mg orally plus granisetron 3 mg i.v. plus dexamethasone 6 mg orally or i.v.			
	day 2–3		fosaprepitant group	dexamethasone 3.75 mg orally every 12 h			
			aprepitant group	aprepitant 80 mg orally plus dexamethasone 3.75 mg orally			
	day 4		fosaprepitant group	dexamethasone 3.75 mg orally every 12 h			
			aprepitant group	dexamethasone 3.75 mg orally			
Saito et al.[11] n = 347	day 1 (before chemo-therapy)	cisplatin 76.2 mg/m^2	fosaprepitant group	fosaprepitant 150 mg i.v. plus granisetron 40 µg/kg i.v. plus dexamethasone i.v.	fosaprepitant group: 94% control group: 81%	fosaprepitant group: 65% control group: 49%	fosaprepitant group: 64% control group: 47%
			control group	placebo i.v. plus granisetron 40 µg/kg i.v. plus dexamethasone i.v.			
	day 2–3		fosaprepitant group	dexamethasone i.v.			
			control group	dexamethasone i.v.			

i.v. – intravenously; CR – complete response; HEC – highly emetogenic chemotherapy.

in Chinese patients, the CR rates in Japanese patients were different in the DP. The dose of cisplatin could have been a substantial factor causing the disparity. In the Japanese research, the target population was given cisplatin at a mean dose of 76.2 mg/m^2. In contrast, the Chinese patients were given a non-cisplatin HEC regimen or cisplatin at ≥60 mg/m^2, which is defined as HEC under treatment standards (Table 1).

The clinical efficacy of fosaprepitant in preventing MEC-induced nausea and vomiting in adults

Fosaprepitant can prevent MEC-induced nausea and vomiting, especially during the DP. Weinstein et al. selected patients aged ≥18 years who received non-cyclophosphamide MEC.[12] All patients were assigned to treatment with fosaprepitant combined with ondansetron and dexamethasone (the observation group) or with ondansetron and dexamethasone alone (the control group). The study showed that fosaprepitant significantly enhanced CR in the DP (78.9% compared to 68.5%; $p < 0.001$) and OP (77.1% compared to 66.9%; $p < 0.001$), but not in the AP (93.2% compared to 91.0%; $p = 0.184$), compared to control. Thus, the anti-nausea efficacy of fosaprepitant was comparable between the observation and control groups for acute vomiting, whereas the efficacy was considerable for delayed vomiting. The adverse response was mild, and the fosaprepitant regimen was generally well tolerated. Weinstein et al. randomly allocated patients undergoing the first day of planned i.v. anthracycline-cyclophosphamide-based MEC chemotherapy with oral ondansetron and oral dexamethasone plus a single dose of i.v. fosaprepitant (150 mg) or placebo, and found that a single dose of fosaprepitant was effective and safe in preventing CINV in different types of cancer.[13]

The clinical efficacy of fosaprepitant in preventing CINV in pediatric patients

Under the current standard of care, antiemetic regimens are more effective in adults than in children. When compared to adults, children exhibit differences in bioavailability, absorption, volume of distribution, and hepatic and renal clearance. Another factor is the widespread use of multiple-day chemotherapy regimens in pediatric patients, which are used less frequently in adult patients.[14] However, some studies have shown that fosaprepitant can effectively prevent the CINV associated with MEC in pediatric patients. Radhakrishnan et al. selected patients aged 1–12 years who received MEC from the India Cancer Institute.[15] Patients were randomly divided into an observation group and a control group. In that study,

patients in the fosaprepitant arm received 3 mg/kg (maximum 150 mg) of fosaprepitant as a 30-minute i.v. infusion in 100 mL of normal saline. The study showed that the CR for acute vomiting in the observation group (86%) was considerably higher than in the control group (60%; $p < 0.001$), and the CR for delayed vomiting in the observation group (79%) was significantly higher than in the control group (5%; $p < 0.001$). Overall, the CR in the observation group (70%) was higher than in the control group (40%; $p < 0.001$), which indicates that the anti-nausea efficacy of fosaprepitant was significant. In addition, the adverse response was mild and tolerable.[15]

In a Chinese trial on the prevention of CINV with the use of fosaprepitant in children with tumors, a total of 122 children were enrolled (62 in the fosaprepitant group and 60 in the aprepitant group).[16] In this study, patients aged 2–12 years received fosaprepitant at a dose of 3 mg/kg (maximum 150 mg). The proportions of AP, DP and OP reaching CR (no vomiting rate) were 88.5%, 71.3% and 65.6%, respectively. Fosaprepitant also had a greater CR than aprepitant in preventing acute vomiting ($p < 0.05$). There were no differences between the 2 groups in terms of adverse responses, and the drugs were well tolerated.

Recently, from August 2015 to January 2017, a retrospective chart review characterized the usage of fosaprepitant in patients aged from 10 months to 18 years at a single hospital.[17] The study included 35 patients who got fosaprepitant at a dose of 4 mg/kg (maximum 150 mg) for CINV prophylaxis. A follow-up phone call was made to 10 patients aged ≥5 who received fosaprepitant after October 2016 to assess the control of delayed CINV. During the AP, 89% exhibited complete control of emesis, while 63% presented complete control during the DP, and 60% exhibited overall control of emesis. These results provide evidence that fosaprepitant is safe and effective in the prevention of CINV in pediatric patients as young as 10 months. However, because the above studies were all single-center, small sample clinical trials, more randomized controlled multicenter clinical trials are needed to determine the efficacy and safety of fosaprepitant for the treatment of CINV in pediatric patients.

In April 2018, the U.S. Food and Drug Administration (FDA) approved the use of fosaprepitant in children over the age of 6 months.[9] The FDA recommends fosaprepitant doses of 5 mg/kg (age: 6 months–2 years) and 4 mg/kg (age: 2–12 years) capped at 150 mg and infused over 1 h. On day 1, children under the age of 12 receive 3 mg/kg fosaprepitant (maximum: 115 mg) administered over 1 h, followed by an oral 2 mg/kg aprepitant suspension (maximum: 80 mg) on days 2 and 3.

According to pharmacokinetic studies, children under the age of 12 convert fosaprepitant to aprepitant in the blood more slowly than adults and have a lower mean area under the curve (AUC). Hence, children under the age of 12 required greater doses to achieve exposures comparable to adults.[14]

Efficacy comparison for fosaprepitant and aprepitant

Aprepitant is a NK-1RA and fosaprepitant is a prodrug of aprepitant that is activated in the bloodstream after i.v. delivery. In contrast to aprepitant, fosaprepitant may be beneficial for individuals who are unable to take oral antiemetics during a bout of nausea or vomiting.[18] In order to compare the efficacy and safety of fosaprepitant and aprepitant, Zhang et al. designed a randomized, double-blind, non-inferiority clinical study in which 644 patients receiving cisplatin-based chemotherapy were randomized to fosaprepitant or aprepitant groups. In this study, it was found that the antiemetic effects of fosaprepitant and aprepitant were comparable (71.96% compared to 69.35%, $p = 0.4894$).[19] Therefore, these 2 drugs have the potential to have a positive impact on daily life by easing the completion of a patient's clinically prescribed chemotherapy treatment.

According to a randomized controlled trial, the use of aprepitant and fosaprepitant for the treatment of CINV in patients with gynecological cancer showed no significant differences between the 2 groups in the AP and DP of cycle 1 chemotherapy.[20] This study also showed that both i.v. fosaprepitant and oral aprepitant were effective in preventing vomiting, and had a beneficial effect on patients' quality of life. In another study conducted in Japan, a 5-day administration of aprepitant and a single administration of fosaprepitant for the prevention of nausea and vomiting caused by cisplatin-induced HEC were compared.[21] The results showed no significant differences between groups in the rate of complete remission and the complete control rate of vomiting during the entire treatment period. Nausea scores in both groups tended to increase from day 3, but there was no statistical significance between groups.

These results demonstrate that a single dose of fosaprepitant improves the antiemetic effects of conventional 5-HT3RAs and corticosteroid therapy compared to standard therapy alone, and may have an efficacy comparable to the recommended 3-day aprepitant regimen.

Safety and drug interactions for fosaprepitant

Fatigue, diarrhea, constipation, sleeplessness, vertigo, local pain at the injection site, and other side effects of fosaprepitant can occur throughout the therapeutic process. Other adverse responses are minor and acceptable ($p > 0.05$),[12] and the incidence of diarrhea and vertigo is lower than in the control group ($p < 0.05$). Other adverse responses, including hiccups, headache and serious adverse event (SAE; anaphylactic reaction) to the medication, were reported by only a few children in one of the pediatric cancer treatment studies, and there was no mortality in the first cycle.[14]

Drug interactions associated with fosaprepitant should be considered when selecting an antiemetic therapy. A report by Patel et al. stated that concomitant administration of aprepitant and alcohol can cause impaired cognitive function, the simultaneous use of aprepitant with vincristine and isocyclophosphamide can cause neurotoxicity, and a combination with quetiapine can induce drowsiness.[22] They have also shown that there may be local reactions at the infusion site when fosaprepitant and anthracycline drugs are given via the same peripheral i.v. route.[22] In general, adverse effects of fosaprepitant are slight, the drug is significantly safe for children, women, the elderly and patients with renal insufficiency, and there is no need to change their prescripted dosage.

Discussion

More than 90% of the vomiting caused by chemotherapy medicines is delayed vomiting, with a prevalence of more than 60%. This usually relates to inadequate control of acute CINV or the use of cisplatinum, Cytoxan, Paraplatin, or doxorubicin. The severity of the vomiting reaches its peak after 2–4 days of chemotherapy. Although the frequency of delayed vomiting is not as high as acute vomiting, it is difficult to control and normally lasts long. As a result, preventing delayed vomiting remains a challenge.[23]

The ability of NK-1RAs to bind to the NK-1R with great selectivity and potency in order to inhibit the activity of substance P offers a new treatment option for CINV.[24] The NK-1RAs have a considerable anti-nausea effect. Most people can tolerate these drugs because they are safe and induce only minor adverse reactions. The i.v. injection of fosaprepitant, the phosphate prodrug of aprepitant, is more practical for patients during nausea and vomiting than the administration of oral antiemetics. The efficacy of a single dose of fosaprepitant is comparable to that of aprepitant, allowing the antiemetic regimen to be simplified. Fosaprepitant has become one of the most important medications in antiemetic therapy. At present, the brand name "fosaprepitant" is still not available in the Chinese market. Jiangsu Hansoh Pharmaceutical Group Co., Ltd. produces genericized fosaprepitant (Tannen), which is the first injectable NK-1RA licensed for sale in China. According to clinical research, fosaprepitant (Tannen) is well tolerated and has a similar safety profile to aprepitant.[20] The launch of domestic fosaprepitant will give Chinese patients more options for CINV treatment. However, there are still very few domestic clinical studies for fosaprepitant, particularly in children. More clinical trials are needed to support the appropriate usage of NK-1RAs in clinics.

Other recently developed antiemetics, such as Zyprexa, Akynzeo and Varubi, are approved for marketing. In order to prevent CINV in adults receiving cisplatin and other highly emetic single agents, as well as in adults receiving anthracycline combined with cyclophosphamide, the updated American Society of Clinical Oncology (ASCO) antiemetic guidelines advise the addition of olanzapine (Zyprexa) to a NK1-RA, a 5-HT3RA and dexamethasone.[25]

Two published phase 3 studies compared olanzapine with aprepitant (both in combination with a 5-HT3RA and dexamethasone). Both studies showed that the 2 treatment plans had equal effects on CINV during the immediate period (0–24 h after chemotherapy), but olanzapine was superior to aprepitant at controlling nausea during the later phase (0–120 h after chemotherapy).[26,27]

For the prevention of immediate and delayed nausea and vomiting brought on by moderately and highly emetogenic cancer chemotherapy, netupitant/palonosetron (NEPA/Akynzeo) is recommended in the EU for adults. In one trial, patients receiving cisplatin-based HEC were randomized to either NEPA (plus dexamethasone) or aprepitant (plus granisetron and dexamethasone) groups. The NEPA showed non-inferiority to aprepitant for the key efficacy end objective over the course of CINV (73.8% compared to 72.4%).[28]

Rolapitant (Varubi) is also a novel NK-1RA that was approved by FDA in 2015 for the prevention of delayed CINV with MEC and HEC. It has definite advantages over aprepitant and NEPA. First, it has no CYP3A4 inhibitory or inducing effects, which restricts the ability to alter the dose of dexamethasone, a requirement for the use of aprepitant and NEPA. Unlike aprepitant, rolapitant is administered as a one-time dose.[29]

Future studies should be conducted in this area because it is unclear whether employing a NK-1RA will increase the effectiveness of nausea control. In comparison to existing agents, newer ones may provide important advantages in terms of better nausea control, tolerability, formulation options, and therapeutic plasma levels during the AP of CINV. These newer agents also give clinicians more opportunities to maximize the advantages of this significant class of antiemetics.[30]

Limitations

This article only describes the efficacy of fosaprepitant in adults and children. The use of this medication in special populations (elderly, hepatic and renal insufficiency, etc.) has been less studied, thus caution should be exercised in its use. More prospective clinical studies are needed to prove its efficacy and safety, and the efficacy of fosaprepitant and aprepitant in controlling various types of vomiting remains controversial, requiring more clinical trials or meta-analyses to confirm.

Conclusions

Fosaprepitant is effective and safe in the treatment of cancer patients receiving HEC. As an antiemetic therapy, this may be a better option. In general, fosaprepitant has a large market potential and is worthy of clinical promotion.

ORCID iDs

Fei Xue https://orcid.org/0009-0003-3128-2629
Xin Liu https://orcid.org/0000-0001-8675-3692
Xiao Qi https://orcid.org/0009-0004-4506-4742
Jiajing Zhou https://orcid.org/0000-0003-4322-754X
Yongjun Liu https://orcid.org/0000-0003-2049-7416

References

1. Soefje SA. Strategies to improve CINV outcomes in managed care. *Am J Manag Care*. 2018;24(18 Suppl):S398–S404. PMID:30328691.
2. Jordan K, Roila F, Molassiotis A, Maranzano E, Clark-Snow RA, Feyer P. Antiemetics in children receiving chemotherapy: MASCC/ESMO guideline update 2009. *Support Care Cancer*. 2011;19(S1):37–42. doi:10.1007/s00520-010-0994-7
3. Di Liso E. Chemotherapy-induced nausea and vomiting. In: Cascella M, John Stones M, eds. *Suggestions for Addressing Clinical and Non-Clinical Issues in Palliative Care*. London, UK: IntechOpen; 2021. doi:10.5772/intechopen.96194
4. Berger MJ, Ettinger DS, Aston J, et al. NCCN Guidelines Insights: Antiemesis, Version 2. 2017. *J Natl Compr Canc Netw*. 2017;15(7):883–893. doi:10.6004/jnccn.2017.0117
5. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer*. 2007;15(9):1023–1033. doi:10.1007/s00520-006-0186-7
6. Hesketh PJ, Van Belle S, Aapro M, et al. Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. *Eur J Cancer*. 2003;39(8):1074–1080. doi:10.1016/S0959-8049(02)00674-3
7. Ruhlmann CH, Herrstedt J. Fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Expert Rev Anticancer Ther*. 2012;12(2):139–150. doi:10.1586/era.11.199
8. Aziz F. Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting. *Ann Palliat Med*. 2012;1(2):130–136. doi:10.3978/j.issn.2224-5820.2012.07.10
9. U.S. Food and Drug Administration (FDA). EMEND (fosaprepitant) for injection, for intravenous use. Initial U.S. Approval. 2008. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/022023s017lbl.pdf. Accessed April 16, 2022.
10. Yang LQ, Sun XC, Qin SK, et al. Efficacy and safety of fosaprepitant in the prevention of nausea and vomiting following highly emetogenic chemotherapy in Chinese people: A randomized, double-blind, phase III study. *Eur J Cancer Care*. 2017;26(6):e12668. doi:10.1111/ecc.12668
11. Saito H, Yoshizawa H, Yoshimori K, et al. Efficacy and safety of single-dose fosaprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving high-dose cisplatin: A multicentre, randomised, double-blind, placebo-controlled phase 3 trial. *Ann Oncol*. 2013;24(4):1067–1073. doi:10.1093/annonc/mds541
12. Weinstein C, Jordan K, Green SA, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: Results of a randomized, double-blind phase III trial. *Ann Oncol*. 2016;27(1):172–178. doi:10.1093/annonc/mdv482
13. Weinstein C, Jordan K, Green S, et al. Single-dose fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy regimens: A subgroup analysis from a randomized clinical trial of response in subjects by cancer type. *BMC Cancer*. 2020;20(1):918. doi:10.1186/s12885-020-07259-5
14. Mora J, Valero M, DiCristina C, Jin M, Chain A, Bickham K. Pharmacokinetics/pharmacodynamics, safety, and tolerability of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in pediatric cancer patients. *Pediatr Blood Cancer*. 2019;66(6):e27690. doi:10.1002/pbc.27690
15. Radhakrishnan V, Joshi A, Ramamoorthy J, et al. Intravenous fosaprepitant for the prevention of chemotherapy-induced vomiting in children: A double-blind, placebo-controlled, phase III randomized trial. *Pediatr Blood Cancer*. 2019;66(3):e27551. doi:10.1002/pbc.27551
16. Yuan DM, Li Q, Zhang Q, et al. Efficacy and safety of neurokinin-1 receptor antagonists for prevention of chemotherapy-induced nausea and vomiting: Systematic review and meta-analysis of randomized controlled trials. *Asia Pac J Cancer Prev*. 2016;17(4):1661–1675. doi:10.7314/APJCP.2016.17.4.1661
17. Timaeus S, Elder J, Franco K. Evaluation of the use of fosaprepitant for the prevention of chemotherapy-induced nausea and vomiting in pediatric patients. *J Pediatr Hematol Oncol*. 2018;40(7):527–531. doi:10.1097/MPH.0000000000001213
18. Langford P. Fosaprepitant and aprepitant: An update of the evidence for their place in the prevention of chemotherapy-induced nausea and vomiting. *Core Evid*. 2010;5:77–90. doi:10.2147/CE.S6012
19. Zhang Z, Yang Y, Lu P, et al. Fosaprepitant versus aprepitant in the prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based chemotherapy: A multicenter, randomized, double-blind, double-simulated, positive-controlled phase III trial. *Ann Transl Med*. 2020;8(5):234–234. doi:10.21037/atm.2019.12.158
20. Micha JP, Rettenmaier MA, Brown JV, et al. A randomized controlled pilot study comparing the impact of aprepitant and fosaprepitant on chemotherapy induced nausea and vomiting in patients treated for gynecologic cancer. *Int J Gynecol Cancer*. 2016;26(2):389–393. doi:10.1097/IGC.0000000000000593
21. Ando Y, Hayashi T, Ito K, et al. Comparison between 5-day aprepitant and single-dose fosaprepitant meglumine for preventing nausea and vomiting induced by cisplatin-based chemotherapy. *Support Care Cancer*. 2016;24(2):871–878. doi:10.1007/s00520-015-2856-9
22. Patel P, Leeder JS, Piquette-Miller M, Dupuis LL. Aprepitant and fosaprepitant drug interactions: A systematic review. *Br J Clin Pharmacol*. 2017;83(10):2148–2162. doi:10.1111/bcp.13322
23. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Results of the Perugia consensus conference. *Ann Oncol*. 2010;21(Suppl 5):v232–v243. doi:10.1093/annonc/mdq194
24. Shillingburg A, Biondo L. Aprepitant and fosaprepitant use in children and adolescents at an academic medical center. *J Pediatr Pharmacol Ther*. 2014;19(2):127–131. doi:10.5863/1551-6776-19.2.127
25. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*. 2017;35(28):3240–3261. doi:10.1200/JCO.2017.74.4789
26. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res*. 2009;28(1):131. doi:10.1186/1756-9966-28-131
27. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A randomized phase III trial. *J Support Oncol*. 2011;9(5):188–195. doi:10.1016/j.suponc.2011.05.002
28. Zhang L, Lu S, Feng J, et al. A randomized phase III study evaluating the efficacy of single-dose NEPA, a fixed antiemetic combination of netupitant and palonosetron, versus an aprepitant regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). *Ann Oncol*. 2018;29(2):452–458. doi:10.1093/annonc/mdx698
29. Heo YA, Deeks ED. Rolapitant: A review in chemotherapy-induced nausea and vomiting. *Drugs*. 2017;77(15):1687–1694. doi:10.1007/s40265-017-0816-z
30. Navari RM, Schwartzberg LS. Evolving role of neurokinin 1-receptor antagonists for chemotherapy-induced nausea and vomiting. *Onco Targets Ther*. 2018;11:6459–6478. doi:10.2147/OTT.S158570