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Effectiveness and safety of combined neurokinin-1 antagonist aprepitant treatment for multiple-day anthracycline-induced nausea and vomiting

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ABSTRACT

Objective: To assess the safety and efficacy of combined neurokinin-1 antagonist aprepitant treatment for multiple-day anthracycline chemotherapy-induced nausea and vomiting.

Methods: One hundred patients with breast cancer from department of Medical Oncology of Ordos Central Hospital from June 2015 to February 2018 were selected and randomize subdivided into 2 groups. All cases received anthracycline (30 mg/m^2/d for pirarubicin or 45 mg/m^2/d for epirubicin) and cyclophosphamide adjuvant chemotherapy, along with either the standard therapy (dexamethasone and tropisetron) or the combined aprepitant therapy (aprepitant plus dexamethasone and tropisetron). The results of the observation between groups were presented by complete response in the overall phase (OP, 0-120 hours), acute phase (AP, 0-24 hours) and delay phase (DP, 25-120 hours). The Kaplan-Meier curves were plotted to exhibit the first time of vomiting, Functional

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Living Index-Emesis of patients' quality of life, and therapy-related adverse effects (AEs).

Results: The complete response of OP, AP, and DP were statistically different between aprepitant group and standard group (80.0% vs 48%, $P = 0.001$; 92.0% vs 74%, $P = 0.017$; 80.0% vs 48%, $P = 0.001$). The aprepitant group held a longer time reaching the first emesis after the relevant treatment than the standard group. The Functional Living Index-Emesis increased significantly in the aprepitant group compared with the standard group (24% vs 8.3%, $P = 0.029$). Fatigue and constipation were the only AEs of aprepitant, since no significant differences were observed in fatigue between the 2 groups (72% vs 70%, $P = 0.826$), while the incidence of constipation of aprepitant group was higher than the standard group (48% vs 28%, $P = 0.039$).

Conclusion: Combined aprepitant therapy is efficient and safe in the multiple-day anthracycline chemotherapy-induced nausea and vomiting control and is recommended for the clinical use.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most devastating problems confronted by the cancer patients, lowering their quality of life, discouraging them from further chemotherapy.[1,2] However, adjuvant high-dose chemotherapy was shown to be beneficial both in nonsmall cell lung cancer and breast cancer maintaining treatment.[3,4] Breast cancer was labeled as the most prevalent cancer among women around the world, as a result of which the combination use of anthracycline with cyclophosphamide (AC), a standard treatment for breast cancer is commonly seen in all kinds of related therapy.[5] However, the AC chemotherapy is alleged to be a high-emetic risk chemotherapy (HEC), confirmed by the American Society of Clinical Oncology,[6] the National Comprehensive Cancer Network,[7] the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology.[8] So, it is evidently important for us to better control the CINV. Aprepitant, a neurokinin 1 receptor antagonist, is an antiemetic drug, which demonstrated powerful antiemetic effects combined with dexamethasone (DXM) in anthracycline chemotherapy.[9,10] Both National Comprehensive Cancer Network and European Society for Medical Oncology guideline referred principles for nausea and vomiting induced by multiple-day cisplatin chemotherapy, but recommended no precise antiemetic regimen for each day during HEC multiple-day chemotherapy (MDC), since acute and delayed emesis may overlap during the whole course.[7,8] To overcome the CINV, we carried out the present study, evaluating the effectiveness and safety of aprepitant in conjunction with the standard therapy on patients taking 2-day chemotherapy based on anthracycline.

Patients and methods

Patients

The study is a prospective randomized study performed on patients diagnosed with breast cancer being treated with AC adjuvant chemotherapy. With the institutional review board ap-

Table 1
Patients' baseline characteristics [n(%)].

Characteristics	Aprepitant regimen(n = 50)	Standard regimen(n = 50)	*P*
Age (years)			
>50	51.74 ± 7.082	47.46 ± 8.180	0.317
History of motion sickness	7 (14.0)	4 (8.0)	0.338
History of nausea with pregnancy in female	28 (56.0)	19 (39.6)*	0.071
Alcohol use			0.646
No consumption	47 (94.0)	48 (96.0)	
<4 drinks per week	3 (6.0)	2 (4.0)	
Smoking Index			0.295
No Smoking	44 (88.0)	47 (94.0)	
0-400	6 (12.0)	3 (6.0)	
Chemotherapy Cycle			0.465
First-Cycle	11 (22.0)	18 (36.0)	
Second-Cycle	14 (28.0)	10 (20.0)	
Third-Cycle	14 (28.0)	12 (24.0)	
Fourth-Cycle	11 (22.0)	10 (20.0)	

Notes: P values were generated using Fisher's exact test for characteristics with two groups and with the chi-square test for characteristics with mutiple groups.
* Two female patients without pregnancy history.

Table 2
The medication procedures.

	Day 1	Day 2	Day 3	Day 4
Aprepitant group	Aprepitant 125 mg po Tropisetron 5 mg iv Dexamethasone 6 mg po	Aprepitant 80 mg po Tropisetron 5 mg iv Dexamethasone 3.75 mg po	Aprepitant 80 mg po Dexamethasone 3.75 mg po	 Dexamethasone 3.75 mg po
Standard group	Tropisetron 5 mg iv Dexamethasone 10.5 mg po	Tropisetron 5 mg iv Dexamethasone 7.5 mg po	 Dexamethasone 7.5 mg po	 Dexamethasone 7.5 mg po

proved, and written informed consent from all participants obtained, patients beyond 18 years old acquired a Karnofsky performance ≥70, without previously treatment of aprepitant, were scheduled to receive a 2-day anthracycline-based chemotherapy (30 mg/m^2/d for pirarubicin or 45 mg/m^2/d for epirubicin). Females of childbearing age were given a human chorionic gonadotropin test. Exclusion criteria were as follow: (1) alcohol abuse; (2) central nervous system metastasis; (3) advanced or metastasis breast cancer; (4) the administration of sensitized chemotherapy over last 10 days; (5) schemed radiation therapy before enrollment; (6) had vomited in 24 hours before treatment day 1; (7) incontrollable diseases; (8) abnormal laboratory values including: white blood cell count less than 3000/mm^3 and absolute neutrophil count less than 1500/mm^3, platelet count less than 100,000/mm^3, alanine transaminase more than 2.5 × upper limit of normal (ULN), aspartate aminotransferase exceed 2.5 × ULN, creatinine more than 1.5 × ULN or bilirubin exceed 1.5 × ULN. Patients were subdivided by clinical characteristics (Table 1).

Study design and medications

This was a prospective study carried out at Ordos Central Hospital in Inner Mongolia, China. Patients meet the criteria were consecutively included from June 2015 to February 2018 at the Medical Oncology Department of, and randomly divided into aprepitant group and control group.

The control group was injected with tropisetron hydrochloride (Beijing Shuanglu Pharmaceutical Co. Ltd., China) and Dexamethasone. The aprepitant group had a half dosage of Dexamethasone besides tropisetron hydrochloride and aprepitant (EMEND, MSD Sharp & Dohme, Haar,

Germany), since the function of CYP3A4 in DXM pharmacokinetics could be exhibited by aprepitant[11] (Table 2).

Procedures and assessments

The times and dates of vomiting or retching episodes were reported by patients and recorded by inspector every day. From the starting point of chemotherapy to sixth day, patients received with rescue therapy and were contacted ensuring compliance. Functional Living Index-Emesis (FLIE) questionnaire scoring, a validated emesis- and nausea-specific survey with 18 questions,[12,13] was accomplished on the last day, directly following the final self-evaluations.[14] Getting a 6 out of 7-point scale symbolize "no impact of CINV on daily life."

To observe the aprepitant related adverse events (AE), patients were followed on days 6-8 and days 19-21.

Statistical analysis

The analysis of this study was carried out by the sponsor. Complete response (CR) during the overall phase (OP, 0-120 hours following chemotherapy), no vomiting or use of rescue therapy, was the primary endpoint for the efficacy analysis. The CR in the acute phase (AP, 0-24 hours following chemotherapy), delay phase (DP, 24-120 hours following chemotherapy), and the time to first vomiting, FLIE questionnaire scoring composed the secondary endpoints. The complete control defined as no vomiting and no nausea which also among the secondary endpoints.

The comparisons of treatment and characteristics of patients were analyzed by using logistic regression models with a 2-sided significance level of 5%. The significance of tests was reported in terms of *P* values. The time to first emesis was constructed using the Kaplan-Meier curves. The evaluation of CR achievements and aprepitant-related AEs between the two groups were performed using Fisher's exact test.

Results

Patients

Among the 100 breast cancer patients who completed the whole clinical trail, 50 of which were given an aprepitant therapy (aprepitant plus tropisetron and dexamethasone), and the remaining received the control therapy (tropisetron and dexamethasone). Patients of 2 groups had similar rates of alcohol use, motion sickness, or vomiting related to pregnancy.

Efficacy

The CR during the OP exhibited a proportion of 80.0% (40/50) in aprepitant group while a 48.0% (24/50) in the control group ($P = 0.001$; Fig 1). The rate of CR in AP and DP, in the aprepitant group and control group, were 92% (46/50) vs 74% (37/50), 80.0% (40/50) vs 48.0% (24/50), respectively ($P = 0.017$, $P = 0.001$).

Comparison of FLIE index

Patients exempted from vomiting during the OP were more in the aprepitant group than in the control group, which was 80.0% (41/50) vs 52.0% (26/50) ($P = 0.003$), respectively. Fewer

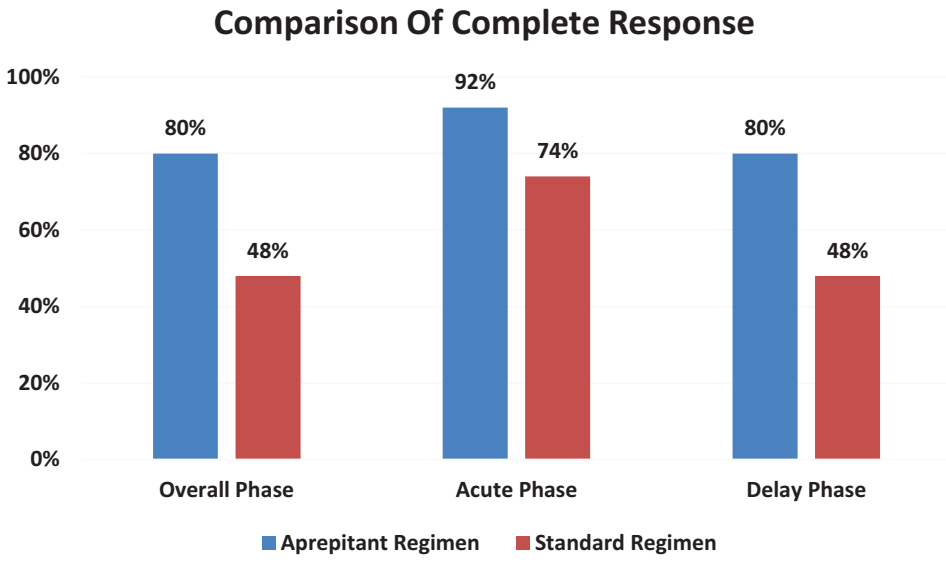

Fig. 1. Comparison of complete response between 2 groups.

Table 3
Comparison of FLIE index.

Items	Aprepitant regimen	Standard regimen	*P*
Nausea FLIE Score	41.43 ± 11.83	37.17 ± 11.27	0.069
Vomiting FLIE Score	48.79 ± 12.44	41.58 ± 13.21	0.006
FLIE Score	90.22 ± 23.12	78.76 ± 23.83	0.016

Notes: FLIF, functional living index-emesis.

patients were reported using the rescue treatment in the aprepitant group compared with the control group 16.0% (8/50) vs. 26.0% (13/50), respectively, $P = 0.220$, during the OP. The ratio of patients had no vomiting as well as no nausea were similar between the 2 groups during the OP (8.0% (4/50) vs 2.0% (1/50), $P = 0.169$).

According to the results of FLIE, the patients without impact of CINV impact on daily life were 24.0% (12/50) of aprepitant group, significant more than that of control group which was 8.3% (4/48) ($P = 0.029$). In the control group, 2 of these questionnaires were eliminated as they failed to meet the criteria (Table 3).

Comparison of time to first vomiting

The time to first vomiting of the 2 groups was exhibited by Kaplan-Meier curves. Patients in aprepitant group enduring a longer time to first emesis than in the control group ($P = 0.003$) (Fig 2).

Tolerability

Fatigue and constipation, according to adequate observations, were the most common AEs of aprepitant treatment, which happened 72.0% (36/50) and 48.0% (24/50) in the aprepitant group vs 70.0% (35/50) and 28% (14/50) in the control group ($P = 0.826$, $P = 0.039$). The aprepitant

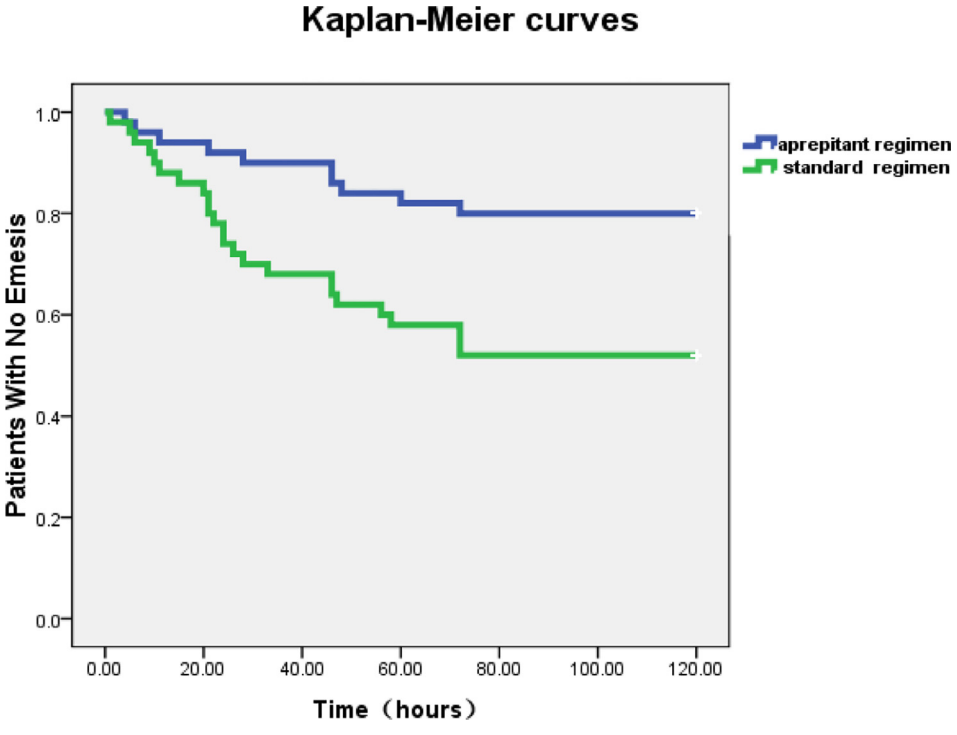

Fig. 2. Comparison of time to first vomiting between 2 groups.

group had a higher rate of constipation in comparison with control group, while the occurrence of fatigue was similar between the groups.

Discussion

Actually, the antiemetic therapy has long been recommended for patients undertaking HEC (highly emetogenic chemotherapy) by means of MDC (multiple-day chemotherapy), according to clinical guidelines from the Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology and the National Comprehensive Cancer Network.[7,8] Most of the trials have observed that vomiting cases happened a lot among patients taking the first-round single-day chemotherapy, however, MDC has always been neglected in the majority of antiemetic researches. The 2-day anthracycline-based chemotherapy has been little focused since most of the researchers were more interested in the multiple-day cisplatin chemotherapy.[15-17] Breast cancer was the most frequently diagnosed cancer in females has an incidence of $42.55/10^5$ in China.[18] It is highly recommended for patients to receive 2-day anthracycline-based AC adjuvant chemotherapy which was frequently reported to bring the CINV. As reported by our previous study that a neurokinin-1 antagonist demonstrated high efficacy in releasing nausea and vomiting caused by multiple-day cisplatin therapy.[16] The present study assessed the efficiency and safety of aprepitant in preventing the CINV caused by the multiple-day anthracycline treatment.

The results of the present study, to a great extent, were identical with Dr. Warr's multicenter trial, both defined no vomiting or use of rescue therapy during 0-120 hours (CR) as the primary endpoint, the CR in the AP, DP, and FLIE index composed the secondary endpoints.[19] The aprepitant group in the present study achieved a higher level of overall benefit (32.0%) in relation to the relevant differences of previous clinical trials (10%-15%).[19,20] The 48.0% CR

during OP of control group was similar to the 42.0%-47.1% in the standard regimen group reported by David G.Warr et al and Bernardo L. et al, while the 80.0% CR in OP of aprepitant group was obviously higher than the 51.0% and 62.8% according to them.[19,20] This implying that combined neurokinin-1 antagonist aprepitant could further improved the CINV control level when receiving 2-day anthracycline-based AC adjuvant chemotherapy. Considering the drug accessibility and medical insurance, we chose tropisetron out of all kinds of the 5-HT3 inhibitors such as ondansetron and dolasetron to prevent nausea and vomiting in this clinical trial.[21] Comparing to single-day AC chemotherapy in preventing CINV, the aprepitant regimens adding tropisetron achieved better CR rates in preventing CINV during the OP following 2-day anthracycline chemotherapy and improved life quality.[19,20]

Conversely, part of the current findings was different from the previous study. Dr. Yeo reported that the aprepitant group had similar complete response rates with the control group, in a Chinese breast cancer study.[22] Although the smaller samples may decrease the statistical power to reach primary end point in the Hong Kong single center study but they both demonstrated improved life quality involve vomiting domain.[22] Furthermore, the CR rates during AP were both elevated by aprepitant in the multiple-day cisplatin-induced and the multiple-day anthracycline-induced nausea and vomiting study, with significant differences(94.3% vs 75.5%, $P = 0.011$).[23] More noteworthy of our study is that compared with nearly 900 samples in previous trials, we had a relatively small sample sizes, as a result of which leading a relatively higher CR rate.[19,20] Additionally, the MDC exerted stronger power in alleviating acute nausea and vomiting, under the background of same dose intensity, than the single-day treatment.[24] Furthermore, the time cut-off points ranged from AP to DP also led to differences upon the other studies. Actually, Ng T. et al found that the variety of trial endpoint played an important role in reporting CINV control rates and could strongly influence the interpretation of the outcomes.[25] Furthermore, the different category of 5-HT3 and DXM dosages used in our study may be one of reasons that the current results differed from the previous studies. As is widely known that the dosage of drugs could strongly influence the interpretation of the outcomes.[24,25]

Patients undertaken aprepitant therapy had significantly higher life quality in comparison to those taken standard therapy, the patients without impact of CINV on daily life were 24.0% (12/50) vs 8.3% (4/48) ($P = 0.029$), respectively. This finding was in accordance with the clinical research results in the Caucasian population that the FILE index comparison between the aprepitant and control groups reached statistical significance, although differed from the results in Chinese population which only get statistical significance in vomiting domain.[19,22] Which demonstrated that aprepitant could better enhance the quality of life which defined as FLIE index $\geq$108 in a 2-day anthracycline chemotherapy model. However, the secondary endpoints complete control which defined as no vomiting and no nausea was only 8.0%(4/50) vs 2.0%(1/50) ($P = 0.169$).It indicated that nausea is a major challenge induced by AC chemotherapy and this finding was also identical with the results of prospective registry study in Japan reported by Kazuo Tamura et al.[26] As we know, nausea and vomiting seem to appear and respond in parallel, they are not the same phenomenal, so it is also important to find a suitable combination with others medications, such as anxiolytics or antidepressants adminnistered before chemotherapy.[6,27]

Kaplan-Meier curves separated early after initiative chemotherapy at the analysis of time to first emesis. The apparent superiority of aprepitant happened around fifth hour compared with the control regimen, and the disparity continued to widen over the 120-hour period. The trend of 2 curves differed from it observed in the clinical observation of 3-day cisplatin chemotherapy which separated until 72 hours.[16] Further analysis the possible reason for the different emesis curves separated trend, a peak was observed in the test of the excretion of the urinary serotonin metabolite 5-hydroxyindoleacetic acid after given cisplatin chemotherapy where it was not observed after FEC chemotherapy.[28,29] It indicated that 5-HT pathway play a different role in CINV induced by cisplatin or anthracycline and this may be explained the different curves trend in some degree. On the other hand, receptor cross-talk occurs between serotonergic 5-HT (3)- and tachykinergic NK (1)-receptors may also one of possible mechanism, because their combined doses were 4-20 times more potent against vomiting caused by each emetogen compared with single inhibitor.[30]

Clinically, researchers discovered that patients enduring long time nausea and vomiting usually get depressed. Low quality of life, insomnia, and anorexia promote their anxiety. There exists study found that olanzapine had well effectiveness in control of delayed CINV.[31] From this point of view, it is a trend to prevent the chemotherapy related nausea and vomiting by combining some anxiolytics or antidepressants medications to improve the quality life of patients.

Fatigue and constipation were the main AEs in relation to aprepitant during the 2-day anthracycline chemotherapy. The aprepitant group had a higher rate of constipation in comparison with control group due to cross-talk between 5-HT (3) and NK (1) signal pathway which was demonstrated to lead decreased bowel peristalsis.[30] Besides, the aprepitant was generally well tolerated.

Conclusion

Taken together, neurokinin-1 antagonist aprepitant in conjunction with the traditional regimen of a 5-HT3 inhibitor especially tropisetron and DXM could better control the multiple-day anthracycline chemotherapy related CINV, as well as improve the life quality of patients. Moreover, the aprepitant regimen brings no more related AEs. However, nausea induced by AC chemotherapy is a major challenge, how to combine with anxiolytics or antidepressants medications to improve control level warrants further exploration.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2019.01.003.

References

1. Fernández-Ortega P, Caloto MT, Chirveches E, et al. Chemotherapy-induced nausea and vomiting in clinical practice: impact on patients' quality of life. *Support Care Cancer*. 2012;20:3141–3148. https://doi.org/10.1007/s00520-012-1448-1.
2. Grunberg SM. Obstacles to the implementation of antiemetic guidelines. *J Natl Compr Canc Netw*. 2009;7:601–605. https://doi:10.6004/jnccn.2009.0040.
3. K Ramsden K, Laskin J, Ho C. Adjuvant chemotherapy in resected stage II non-small cell lung cancer: evaluating the impact of dose intensity and time to treatment. Clin Oncol. 2015;27:394–400. https://doi.org/10.1016/j.clon.2015.03.001.
4. Bonadonna G, Valagussa P, Moliterni A. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med*. 1995;332:901–916. https://doi.org/10.1056/NEJM199504063321401.
5. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med*. 2006;355:1851–1862. https://doi.org/10.1056/NEJMoa052084.
6. Hesketh PJ, Bohlke K, Lyman GH. Antiementics: American Society of clinical oncology focused guideline update. *J Clin Oncol*. 2016;34:381–386. https://doi.org/10.1200/JOP.2015.009282.
7. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology (NCCN guidelines®). Antiemesis Version 1. https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf; 2017.
8. Herrstedt J, Roila F, et al. Updated MASCC/ESMO consenus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. *Support Care Cancer*. 2016. https://doi.org/10.1007/s00520-016-3313-0.
9. Warr David G, Hesketh Paul J, Gralla Richard J. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. *Clin Oncol*. 2005;23:2822–2830. https://doi.org/10.1200/JCO.2005.09.050.
10. Yeo W, Mo FKF, et al. 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 ReTreat*. 2009;113:529–535. https://doi.org/10.1007/s10549-008-9957-9.
11. McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin-1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther*. 2003;74:17–24. https://doi.org/10.1016/S0009-9236(03)00066-3.
12. Martin AR, Pearson JD, Cai B, et al. Assessing the impact of chemotherapy-induced nausea and vomiting on patients' daily lives: a modified version of the functional living index-emesis (FLIE) with 5-day recall. *Support Care Cancer*. 2003;11:522–527. https://doi.org/10.1007/s00520-003-0482-4.

13. Decker GM, DeMeyer ES, Kisko DL. Measuring the maintenance of daily life activities using the functional living index-emesis (FLIE) in patients receiving moderately emetogenic chemotherapy. *J Support Oncol*. 2006;4:35–41 52PMID:16444851.
14. Martin AR, Carides AD, Pearson JD, et al. Functional relevance of antiemetic control: experience using the FLIE questionnaire in a randomized study of the NK-1 antagonist aprepitant. *Eur J Cancer*. 2003;39:1395–1401. https://doi.org/10.1016/S0959-8049(03)00299-5.
15. Gao HF, Liang Y, Zhou NN, et al. Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. *Intern Med J*. 2013;43:73–76. https://doi:10.1111/j.1445-5994.2011.02637.x.
16. Li Q, Wang W, Chen G, et al. Evaluation of a neurokinin-1 antagonist in preventing multiple-day cisplatin-induced nausea and vomiting. *Open Med (Wars)*. 2018;13:29–34. https://doi.org/10.1515/med-2018-0005.
17. Rehabilitation and Palliative Care Committee. Antineoplastic drugs safety management committee of CSCO. Cancer therapy related vomiting guidelines. (2014). *Chin Clin Oncol*. 2014;19:263–273.
18. Chen W, Zheng R, Zhang S, et al. Report of incidence and mortality in China cancer registries, 2009. *Chin J Cancer Res*. 2013;25:10–21. https://doi:10.3978/j.issn.1000-9604.2012.12.04.
19. Warr DG, Hesketh PJ, Gralla RJ. Efficacy and tolerability of aprepitant for the prevention ochemotherapy-induced nausea and vomiting in patients with breast cancer after moderately metogenicchemotherapy. *Clin Oncol*. 2005;23:2822–2830. https://doi:10.1200/JCO.2005.09.050.
20. Rapoport BL, Jordan K, Boice JA. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumortypes: a randomized, double-blind study. *Support Care Cancer*. 2010;18:423–431. https://doi.org/10.1007/s00520-009-0680-9.
21. Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for postoperative nausea and vomiting prophylaxis. *Clin Ther*. 2012;34:282–294. https://doi.org/10.1016/j.clinthera.2012.01.007.
22. Yeo W, Mo FK, Suen JJ. 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*. 2009;113:529–535. https://doi.org/10.1007/s10549-008-9957-9.
23. Li QF, Jin GW, Wang WJ, et al. Clinical observation of neurokinin-1 antagonist preventing multiple-day chemotherapy-induced nausea and vomiting. *Cancer Res Prev Treat*. 2017;44:290–294. (In Chinese). https://doi:10.3971/j.issn.1000-8578.2017.04.011.
24. Dong S, YU SY. A study of chemotherapy-induced nausea and vomiting involving different dosage regimen of cisplatin. *Cancer Res Prev Treat*. 2013;40:890–893. (In Chinese). https://doi:10.3971/j.issn.1000-8578.2013.09.016.
25. Ng T, Mazzarello S, Wang Z, et al. Choice of study endpoint significantly impacts the results of breast cancer trials evaluating chemotherapy-induced nausea and vomiting. *Breast Cancer Res Treat*. 2016;155:337–344. https://doi.org/10.1007/s10549-015-3669-8.
26. Tamura K, Aiba K, Saeki T. Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV Study Group of Japan. *Int J Clin Oncol*. 2015;20:855–865. https://doi:10.1007/s10147-015-0786-7.
27. Chelkeba L, Gidey K, Mamo A, et al. Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. *Pharm Pract (Granada)*. 2017;15:877. https://doi:10.18549/PharmPract.2017.01.877.
28. Wilder-Smith OHG, et al. Urinary serotonin metabolite excretion during cisplatin chemotherapy. *Cancer*. 1993;72:2239–2241. https://doi.org/10.1002/1097-0142(19931001)72:7⟨2239::AID-CNCR2820720729⟩3.0.CO;2-5.
29. Du Bois A, Vach W, Holy R. 5-Hydroxyindoleacetic acid excretion following combination chemotherapy with cyclophosphamide,epirubicin and 5-fluorouracil plus ondansetron compared to ondansetron alone. *Support CareCancer*. 1996;4:384–389. https://doi.org/10.1007/BF01788846.
30. Darmani NA, Chebolu S, Amos B, et al. Synergistic antiemetic interactions between serotonergic 5-HT3 and tachykininergic NK1-receptor antagonists in the least shrew (Cryptotis parva). *Pharmacol Biochem Behav*. 2011;99:573–579. https://doi:10.1016/j.pbb.2011.05.025.
31. Chelkeba L, Gidey K, Mamo A, et al. Olanzapine for chemotherapy-induced nausea and vomiting: systematic review and meta-analysis. *Pharm Pract (Granada)*. 2017;15:877. https://doi:10.18549/PharmPract.2017.01.877.