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ORIGINAL ARTICLE

Olanzapine-containing antiemetic therapy for the prevention of carboplatin-induced nausea and vomiting

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Abstract

Purpose There remains an unmet clinical need for the control of chemotherapy-induced nausea and vomiting (CINV), particularly in the prevention of nausea and the delayed phase control. We evaluated the efficacy and safety of antiemetic therapy with olanzapine, a neurokinin-1 receptor antagonist, a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist and dexamethasone in patients receiving carboplatin-containing chemotherapy. Olanzapine inhibits signalling via multiple neurotransmitter receptors involved in CINV.

Methods Chemotherapy-naïve patients with lung cancer who received carboplatin-containing chemotherapy were enrolled in this phase-II study. Patients received olanzapine, aprepitant, a 5-HT_3 receptor antagonist and dexamethasone. The primary endpoint was the complete response rate (no vomiting and no rescue therapy) during 120 h after administration of chemotherapy agents.

Results Thirty-three patients received olanzapine-containing antiemetic therapy. The overall complete response rate was 93.3% (95% confidence interval, 80.4–98.3%). The frequency of nausea was 15.2% in the delayed phase and 18.2% in the overall phase. Somnolence was observed in 16 patients.

Conclusion Adding olanzapine to antiemetic therapy with aprepitant, a 5-HT_3 receptor antagonist and dexamethasone improved CINV control in patients receiving carboplatin-containing chemotherapy.

Keywords Antiemetic · Carboplatin · Chemotherapy-induced nausea and vomiting · Olanzapine

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is among the most common and troubling event in cancer treatments [1–3]. CINV can exacerbate nutritional states, general condition and overall quality of life, which undermine the efficacy of chemotherapy [2, 4]. Because prevention of CINV is important for continuation of chemotherapy and achieving treatment success, increasing efforts have made towards improved antiemetic pharmacotherapy in recent years [2, 3]. Chemotherapy agents are categorized as "highly emetogenic chemotherapy" (HEC), "moderately emetogenic chemotherapy" (MEC) and "low or minimal emetogenic chemotherapy", depending on their vomit-inducing potency [3, 5–8]. Prophylactic antiemetic pharmacotherapy is recommended based on these categories.

Olanzapine is an antipsychotic drug that inhibits signaling via multiple neurotransmitter receptors: dopaminergic D_1, D_2, D_3 and D_4 receptors; serotonergic 5-hydroxytryptamine (5-HT) type 2a, 5-HT type 2c (5-HT_{2c}), type 3 (5-HT_3) and 5-HT type 6 receptors; catecholamine alpha$_1$ adrenergic receptors; acetylcholine muscarinic receptors and histamine H_1 receptors [5, 9, 10]. Particularly, the function of olanzapine on 5-HT_{2c} and 5-HT_3 provides a pharmacological rationale for its use in the prevention of CINV [9, 10]. For HEC regimens, triple antiemetic therapy with a 5-HT_3 receptor antagonist, dexamethasone and a neurokinin-1 (NK1) receptor antagonist has been recommended as an optimal antiemetic therapy [5, 11, 12]. However, the control of CINV, especially in the delayed phase, remains insufficient even if prophylactic treatment with these antiemetic agents is used. Several studies have demonstrated that adding olanzapine to dual therapy with a 5-HT_3 receptor antagonist and dexamethasone or triple therapy with a NK1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone can improve CINV control [13–15]. Recently, combination antiemetic therapy with olanzapine, the NK1 receptor antagonists aprepitant or fosaprepitant, a 5-HT_3 receptor antagonist and dexamethasone was evaluated in patients with cisplatin-based regimens or cyclophosphamide and anthracycline regimens [16]. Adding olanzapine reduced the proportion of patients with chemotherapy-induced nausea in the acute, delayed and overall phases. The complete response rate, as a secondary endpoint, was significantly increased when olanzapine was added. International guidelines recommend olanzapine-containing antiemetic therapy as the preferred antiemetic agent in patients with HEC [7, 8].

For MEC regimens, antiemetic therapy with a 5-HT_3 receptor antagonist and dexamethasone is recommended [6, 11, 12]. Although carboplatin was classified as a MEC agent [2, 11, 12], it is now recognized that carboplatin-containing chemotherapy has relatively strong emetic potency, particularly during the delayed phase [5, 17, 18]. At present, carboplatin is managed independently from MEC [6–8] and triple therapy with a NK1 receptor antagonist, a 5-HT_3 receptor antagonist and dexamethasone is recommended for antiemetic therapy [6–8]. Triple therapy for carboplatin-containing therapy showed a 60–80% complete response rate in the overall and delayed phases [17, 19]. However, control of nausea was not acceptable. As introduced in the antiemetic therapy for HEC regimens, olanzapine might be useful in carboplatin-containing chemotherapy, but there are few studies to demonstrate the efficacy of olanzapine in patients with carboplatin-containing regimens [13].

Here we conducted a pilot phase-II study to evaluate the efficacy and safety of antiemetic therapy with olanzapine, aprepitant, a 5-HT_3 receptor antagonist and dexamethasone, which is at present a recommended antiemetic therapy, in patients with lung cancer who received carboplatin-based first-line chemotherapy.

Patients and methods

Study design

This study was a multicenter, prospective, single arm, open-label, phase-II trial conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of each participating institution. Informed consent was obtained from all individual participants included in the study. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN ID 000,026,739).

Patient eligibility

Chemotherapy-naïve patients with pathologically confirmed inoperable stage-IIIB or -IV non-small-cell lung cancer (NSCLC) and small cell lung cancer, who were receiving carboplatin-based chemotherapy were eligible for inclusion. Additional eligibility criteria comprised age ≥ 20 years, adequate hematopoietic, renal and hepatic function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. In patients with small cell lung cancer, patients with a performance status of 2 were included. Exclusion criteria included nausea and vomiting within 24 h or use of antiemetic agents within 48 h before administration of chemotherapy, use of pimozide, and diabetes mellitus. Patients were excluded if they had symptomatic brain metastasis, gastrointestinal obstruction, or an active gastrointestinal

ulcer because these conditions were likely to induce nausea and vomiting regardless of chemotherapy.

Treatment schedule

Patients with non-squamous NSCLC were treated with pemetrexed (500 mg/m^2) and carboplatin (at an area under the curve [AUC] of 6 on day 1 of a 21 day cycle) or paclitaxel (paclitaxel 200 mg/m^2 or nanoparticle, albumin-bound at 100 mg/m^2) and carboplatin. Patients with squamous cell carcinoma were treated with paclitaxel and carboplatin or S-1 (orally 40 mg/m^2 twice per day on days 1 to 14) and carboplatin (at an AUC of 5 on day 1 of a 21 day cycle). Patients with small cell carcinoma were treated with etoposide (80 mg/m^2) and carboplatin. Bevacizumab was added in some eligible cases. The carboplatin dose was calculated according to the Calvert formula. The glomerular filtration rate was estimated from the Cockcroft–Gault formula. Patients received antiemetic therapy with a 5-HT$_3$ antagonist on day 1, dexamethasone (intravenously 4.95 mg) on day 1 and aprepitant (125 mg on day 1 and 80 mg on days 2–3). Olanzapine (5 mg) was administered on days 1–4 after the evening meal. The dose of dexamethasone was reduced according to the findings of previous studies [17, 19]. When patients took paclitaxel or pemetrexed, they received prophylactic dexamethasone, H$_1$ and H$_2$ blockers, folic acid, and vitamin B$_{12}$ according to the package insert in Japan. In the case of paclitaxel, a dose of 12 mg dexamethasone was added at day 1 to prevent anaphylactic reactions. Additional antiemetic agents and other supportive treatments were administered at the discretion of the treating physicians. Patients completed a daily questionnaire regarding the frequency of vomiting and scoring of nausea during 5 days after carboplatin administration. Physicians recorded the use of additional antiemetic therapies during the study period.

Statistical analyses

The primary endpoint was the complete response rate in the overall phase (during the 120 h immediately following administration of chemotherapy agents). Complete response was defined as the proportion of patients with no vomiting episodes and no rescue therapy. Secondary endpoints included the following: complete response rate in the acute (first 24 h after chemotherapy administration) and delayed phases (24–120 h after chemotherapy); complete control rate (no vomiting, no rescue therapy and no or mild nausea), total control rate (no vomiting, no rescue therapy and no nausea), nausea in the overall, acute, and delayed phases, and safety. Adverse events were graded using the Common Toxicity Criteria for Adverse Events, version 4.0. Based on the SWOG one-arm design, 28 patients were required to achieve 80% statistical power with a two-sided α error of 0.05, assuming an expected complete response rate of 95% and a threshold of 80% [17]. The planned sample size was 32 patients for enrolment after taking some dropouts into consideration. Efficacy analyses were based on patients who received chemotherapy, took the study drugs, and had at least one post-treatment assessment. All values were analyzed using JMP v5.0.1 (SAS Institute Japan; Tokyo, Japan).

Results

Patient characteristics

Between April 2017 and June 2018, 33 patients were enrolled. Patient characteristics are listed in Table 1.

Table 1 Patient characteristics

	All patients ($n=33$)
Age, years	75 (60–85)
Sex, male	29 (87.9)
Performance status[a]	
0	27 (81.8)
1	4 (12.1)
2	2 (6.1)
Stage	
IIIB	7 (21.2)
IV	22 (66.7)
Recurrence	4 (12.1)
Histology	
Adenocarcinoma	15 (45.5)
Squamous cell carcinoma	9 (27.3)
Small cell lung cancer	9 (27.3)
Chemotherapy regimen	
Carboplatin + pemetrexed ± bevacizumab	12 (36.4)
Carboplatin + paclitaxel[b] ± bevacizumab	10 (30.3)
Carboplatin + S-1	2 (6.1)
Carboplatin + etoposide	8 (24.2)
Carboplatin + irinotecan	1 (3.0)
5-hydroxytryptamine receptor antagonist	
Granisetron	16 (48.5)
Palonosetron	16 (48.5)
Ramosetron	1 (3.0)
Brain metastasis	2 (6.1)
Drinking habit	15 (45.5)
History of motion sickness	0 (0)
History of vomiting during pregnancy	0 (0)
Use of opioids	0 (0)

Data are given as numbers (percentage) or median (range)

[a]Performance status was determined according to the Eastern Cooperative Oncology Group Scale

[b]Paclitaxel or nanoparticle albumin-bound paclitaxel

The median age was 75 years (range 60–85 years) and 29 patients (87.9%) were male. Twenty-four (72.7%) were NSCLC and nine (27.3%) had small cell carcinoma histology. Twenty-two patients (66.7%) had stage-IV disease. Twelve (36.4%), ten (30.3%) and eight patients (24.2%) received pemetrexed-, paclitaxel- and etoposide-containing chemotherapy, respectively. Four patients (12.1%) received bevacizumab in combination with carboplatin dual therapy. Fifteen patients (45.5%) had drinking habits.

Efficacy

The olanzapine-containing therapy showed an overall complete response rate of 93.3% [95% confidence interval (CI), 80.4%–98.3%, Table 2]. The complete response rates in the acute and delayed phases were 100% (95% CI, 89.6–100%) and 93.9% (95% CI, 80.4%–98.3%), respectively. Complete control and total control rates are shown in Table 2. Strikingly, total control rates in the delayed and overall phases were 84.8% (95% CI, 69.1%–93.3%) and 81.8% (95% CI, 65.6%–91.4%), respectively. The occurrence of nausea was evaluated using patient questionnaires. The frequency of nausea was low (acute phase, 3.0%; delayed phase, 15.2%; overall phase, 18.2%).

Safety

The prevalence of major adverse events is shown in Table 3. The most common hematologic toxicity was anemia. Severe toxicities reaching grade 3 or 4 were leukopenia, neutropenia and thrombocytopenia, which were deemed to be chemotherapy related. Constipation was the most frequent non-hematologic toxicity. Somnolence was observed in 16 patients, all of which were grade 1. All adverse events were tolerated and there was no irreversible toxicity or death considered to be related to treatment.

Table 3 Adverse events

	All cases ($n=33$)	
	Grade 1–4	Grade 3–4
Hematologic toxicity		
Leukopenia	15 (45.5)	9 (27.3)
Neutropenia	16 (48.5)	12 (36.4)
Anemia	23 (69.7)	1 (3.0)
Thrombocytopenia	15 (45.5)	5 (15.2)
Non-hematologic toxicity		
Hepatotoxicity	14 (42.4)	1 (3.0)
Nephrotoxicity	3 (9.1)	0 (0)
Constipation	16 (48.5)	0 (0)
Anorexia	18 (54.5)	0 (0)
Hiccup	5 (15.2)	0 (0)
Somnolence	16 (48.5)	0 (0)

Values are given as numbers (percentage)

Discussion

Antiemetic therapy has improved during many years. However, based on the view that the ultimate goal of antiemetic management is to prevent all nausea and vomiting associated with cancer treatment, CINV remains an unresolved issue in cancer therapy. In particular, the delayed phase control and prevention of nausea are an unmet medical need. Here, we assessed the efficacy and safety of olanzapine-containing antiemetic therapy with aprepitant, a 5-HT_3 receptor antagonist and dexamethasone in lung cancer patients who received carboplatin-based chemotherapy. The control of CINV was excellent, complete response rates in overall and delayed phases were over 90%. Furthermore, nausea was markedly decreased, which was not achieved by antiemetic therapy without olanzapine. To the best of our knowledge, this is the first study to show the efficacy of adding olanzapine to triple antiemetic therapy, now a recommended therapy for carboplatin-based chemotherapy. Olanzapine-containing antiemetic therapy can be a valuable option even in patients receiving carboplatin-containing chemotherapy.

Table 2 Response rates in each phase

Phase	Acute	Delayed	Overall
Complete response rate	100 (89.6–100)	93.9 (80.4–98.3)	93.9 (80.4–98.3)
Complete protection rate	100 (89.6–100)	90.9 (76.4–96.9)	90.9 (76.4–96.9)
Total control rate	97.0 (84.7–99.5)	84.8 (69.1–93.3)	81.8 (65.6–91.4)

Data are percentages (95% confidence interval)

Complete response is defined as no vomiting and no rescue therapy. Complete protection rate is defined as no vomiting, no rescue therapy and no or mild nausea. Total control rate is defined no vomiting, no rescue therapy and no nausea

CINV in the acute and delayed phases has different physiological mechanisms [2, 3]. Acute-phase CINV occurs within 24 h after administration of chemotherapeutic agent. CINV in the delayed phase occurs between 24 h and several days after the initial administration [2, 3]. Delayed-phase CINV develops more frequently than acute-phase CINV, but clinicians are likely to underestimate delayed-phase CINV [4]. Additionally, delayed-phase CINV is less responsive to antiemetic therapy [20]. In a prospective cohort study of 1910 Japanese patients, delayed phase complete response rates for HEC and MEC regimens were 50.6 and 58.3%, respectively [21]. The control of delayed-phase CINV is necessary to improve antiemetic management and prevent all nausea and vomiting associated with cancer treatment [3].

Olanzapine has already been recommended as a viable additional antiemetic prophylaxis to supplement the accepted NK1 receptor antagonist, 5-HT_3 receptor antagonist and dexamethasone treatment for HEC regimens [7, 8]. Although the antiemetic effect of olanzapine may be applicable to MEC or carboplatin-containing regimens, few studies have assessed the efficacy of olanzapine in these regimens [13]. Navari et al. conducted a phase II trial to assess the efficacy of adding olanzapine to palonosetron and dexamethasone in patients receiving MEC and HEC regimens [14]. There was a limited number of patients receiving MEC regimens including carboplatin-containing chemotherapy. Complete responses in patients receiving MEC regimens were 100%, 75%, and 72% in the acute, delayed, and overall phases, respectively. The percentage of patients reporting no nausea was 78% in both delayed and overall phases. In another trial, multiday olanzapine was added to antiemetic therapy with a 5-HT_3 receptor antagonist and dexamethasone in patients receiving HEC and MEC regimens [22]. The complete response rate in patients receiving MEC regimens was 83.1% in the olanzapine group and 58.1% in the control group. The non-anthracycline-cyclophosphamide-based MEC regimens contained oxaliplatin and carboplatin,however, no subgroup analysis for the non-anthracycline-cyclophosphamide-based regimens was performed, therefore, the effectiveness of olanzapine for carboplatin regimens remains unknown. These studies evaluated the efficacy of olanzapine with antiemetic therapy with a 5-HT_3 receptor antagonist and dexamethasone that is no longer standardized for carboplatin.

Although carboplatin exhibits less emetic potency than cisplatin, it can induce considerable acute and delayed emesis [3, 5]. We previously evaluated triple therapy with aprepitant, a 5-HT_3 receptor antagonist and dexamethasone in patients with carboplatin-containing therapy and showed an 80.3% overall complete response rate [17]. In the present study, we evaluated the efficacy of olanzapine addition to triple antiemetic therapy in carboplatin-containing chemotherapy. The complete response rate in the acute phase was very high, which was already achievable even without olanzapine [17]. However, the complete response rate in the delayed phase was also very high, at 93.9%. To our surprise, no patients had vomiting or required rescue antiemetics until 3 days after administration of chemotherapeutic agent. Only a few patients vomited at days 4 and 5. For carboplatin, the incidence of delayed CINV increased during the latter half of the delayed phase [23] and olanzapine controlled CINV during this period. In terms of efficacy, the addition of olanzapine could enable satisfactory management of CINV during both acute and delayed phases.

Chemotherapy-induced nausea is essentially a subjective experience and involves distinct etiology from chemotherapy-induced vomiting [1]. It has a potentially negative impact on the quality of life in cancer patients [2–4] and patients typically emphasize nausea control [1]. Despite current advances in the management of chemotherapy-induced vomiting, reduction of vomiting does not always reflect control of nausea [21]. Management of nausea is difficult despite the use of triple antiemetic therapy and nausea remains a significant challenge in clinical practice [2, 3]. In our study, few patients treated with olanzapine-containing antiemetic therapy experienced nausea. Although further studies are needed to determine the optimal management of chemotherapy-induced nausea, olanzapine-containing antiemetic therapy has the potential to control nausea.

The present study had limitations. First, it was a single-arm trial with limited sample size. The number of cases was not sufficient to evaluate the risk of CINV for parameters such as age, sex, history of chemotherapy, motion sickness, emesis in pregnancy, or alcohol consumption. The study subjects were patients with NSCLC or small cell lung cancer, predominantly male and elderly, and half of the patients consumed alcohol, which are low risk factors for CINV. The efficacy of olanzapine must be applied to those with high risk of CINV and a larger population. When we started this trial, triple antiemetic therapy with aprepitant remained optional and unstandardized in Japan. At present, triple therapy is standardized for carboplatin-containing chemotherapy in Japan and a placebo-controlled comparative study between triple therapy and olanzapine-containing therapy is warranted. Second, the first-generation 5-HT_3 receptor antagonists or second-generation 5-HT_3 receptor palonosetron were used for antiemetic treatment. Palonosetron has a prolonged half-life and a greater binding affinity. Although combination of palonosetron and dexamethasone is superior to a first-generation 5-HT_3 receptor antagonist and dexamethasone in HEC [24], the superiority of palonosetron remains unknown in carboplatin regimens. Third, olanzapine has some adverse effects. Among them, somnolence is a significant problem that requires attention. In the present study, the incidence of somnolence was 48.5% and these cases were grade 1. The time to maximum concentration of olanzapine is 4.8 h and

so olanzapine was administered after the evening meal in the present study in anticipation that olanzapine levels peak during sleep, which might lower the incidence of daytime somnolence. Olanzapine was administered for 4 days. As an antiemetic agent, the use of olanzapine is limited to a short period and severe adverse events have not been reported in patients receiving olanzapine for this indication [25, 26].

In conclusion, adding olanzapine to antiemetic therapy with aprepitant, a 5-HT_3 receptor antagonist and dexamethasone is an effective and feasible prophylactic treatment in patients receiving carboplatin-containing chemotherapy. Further comparative studies are warranted to determine the benefit from such treatment.

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Conflict of interest All authors declare no actual or potential conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This trial is registered number UMIN000010018.

References

1. Roscoe JA, Morrow GR, Hickok JT, Stern RM (2000) Nausea and vomiting remain a significant clinical problem: trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain Symptom Manag 20:113–121
2. Hesketh PJ (2008) Chemotherapy-induced nausea and vomiting. N Engl J Med 358:2482–2494
3. Navari RM, Aapro M (2016) Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 374:1356–1367
4. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J (2006) Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 24:4472–4478
5. Jordan K, Jahn F, Aapro M (2015) Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. Ann Oncol 26:1081–1090
6. Roila F, Herrstedt J, Aapro M, Gralla RJ, Einhorn LH, Ballatori E, Bria E, Clark-Snow RA, Espersen BT, Feyer P, Grunberg SM, Hesketh PJ, Jordan K, Kris MG, Maranzano E, Molassiotis A, Morrow G, Olver I, Rapoport BL, Rittenberg C, Saito M, Tonato M, Warr D (2010) 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 21(Suppl 5):v232–243
7. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D, Somerfield MR, Lyman GH (2017) Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 35:3240–3261
8. Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, Brandt D, Dolan DE, Ellis G, Kim EJ, Kirkegaard S, Kloth DD, Lagman R, Lim D, Loprinzi C, Ma CX, Maurer V, Michaud LB, Nabell LM, Noonan K, Roeland E, Rugo HS, Schwartzberg LS, Scullion B, Timoney J, Todaro B, Urba SG, Shead DA, Hughes M (2017) NCCN Guidelines insights: antiemesis, Version 2.2017. J Natl Compr Canc Netw 15:883–893
9. Navari RM (2014) Olanzapine for the prevention and treatment of chronic nausea and chemotherapy-induced nausea and vomiting. Eur J Pharmacol 722:180–186
10. Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT (1996) Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 14:87–96
11. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Roscoe J, Ruhlmann CH, Walsh D, Warr D, van der Wetering M (2016) Participants of the MECCC (2016) MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol 27:v119–v133
12. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, Chesney M, Clark-Snow RA, Flaherty AM, Freundlich B, Morrow G, Rao KV, Schwartz RN, Lyman GH (2011) Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 29:4189–4198
13. Chiu L, Chow R, Popovic M, Navari RM, Shumway NM, Chiu N, Lam H, Milakovic M, Pasetka M, Vuong S, Chow E, DeAngelis C (2016) Efficacy of olanzapine for the prophylaxis and rescue of chemotherapy-induced nausea and vomiting (CINV): a systematic review and meta-analysis. Support Care Cancer 24:2381–2392
14. Navari RM, Einhorn LH, Loehrer PJ, Passik SD, Vinson J, McClean J, Chowhan N, Hanna NH, Johnson CS (2007) A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier oncology group study. Support Care Cancer 15:1285–1291
15. Mizukami N, Yamauchi M, Koike K, Watanabe A, Ichihara K, Masumori N, Yamakage M (2014) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy: a randomized, double-blind, placebo-controlled study. J Pain Symptom Manag 47:542–550
16. Navari RM, Qin R, Ruddy KJ, Liu H, Powell SF, Bajaj M, Dietrich L, Biggs D, Lafky JM, Loprinzi CL (2016) Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 375:134–142
17. Ito Y, Karayama M, Inui N, Kuroishi S, Nakano H, Nakamura Y, Yokomura K, Toyoshima M, Shirai T, Masuda M, Yamada T, Yasuda K, Hayakawa H, Suda T, Chida K (2014) Aprepitant in patients with advanced non-small-cell lung cancer receiving carboplatin-based chemotherapy. Lung Cancer 84:259–264
18. Yahata H, Kobayashi H, Sonoda K, Shimokawa M, Ohgami T, Saito T, Ogawa S, Sakai K, Ichinoe A, Ueoka Y, Hasuo Y, Nishida M, Masuda S, Kato K (2016) Efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting with a moderately emetogenic chemotherapy regimen: a multicenter, placebo-controlled, double-blind, randomized study in patients with gynecologic cancer receiving paclitaxel and carboplatin. Int J Clin Oncol 21:491–497
19. Kusagaya H, Inui N, Karayama M, Fujisawa T, Enomoto N, Kuroishi S, Nakamura Y, Matsuda H, Yokomura K, Koshimizu N, Toyoshima M, Imokawa S, Yamada T, Shirai T, Hayakawa H, Suda T (2015) Evaluation of palonosetron and dexamethasone with or without aprepitant to prevent carboplatin-induced nausea and

vomiting in patients with advanced non-small-cell lung cancer. Lung cancer 90:410–416
20. Jordan K, Sippel C, Schmoll HJ (2007) Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 12:1143–1150
21. Tamura K, Aiba K, Saeki T, Nakanishi Y, Kamura T, Baba H, Yoshida K, Yamamoto N, Kitagawa Y, Maehara Y, Shimokawa M, Hirata K, Kitajima M (2015) Japan CSGo Testing the effectiveness of antiemetic guidelines: results of a prospective registry by the CINV Study Group of Japan. Int J Clin Oncol 20:855–865
22. Tan L, Liu J, Liu X, Chen J, Yan Z, Yang H, Zhang D (2009) Clinical research of Olanzapine for prevention of chemotherapy-induced nausea and vomiting. J Exp Clin Cancer Res 28:131
23. Waqar SN, Mann J, Baggstrom MQ, Waqar MA, Chitneni P, Williams K, Gao F, Morgensztern D, Govindan R (2016) Delayed nausea and vomiting from carboplatin doublet chemotherapy. Acta Oncol 55:700–704
24. Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, Inoue K, Kitagawa C, Ogura T, Mitsuhashi S (2009) Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 10:115–124
25. Yoodee J, Permsuwan U, Nimworapan M (2017) Efficacy and safety of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis. Crit Rev Oncol Hematol 112:113–125
26. Yanai T, Iwasa S, Hashimoto H, Ohyanagi F, Takiguchi T, Takeda K, Nakao M, Sakai H, Nakayama T, Minato K, Arai T, Suzuki K, Shimada Y, Nagashima K, Terakado H, Yamamoto N (2018) A double-blind randomized phase II dose-finding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. Int J Clin Oncol 23:382–388