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Prevention of Chemotherapy-Induced Nausea and Vomiting by Olanzapine in Japanese Female Patients with Early Breast Cancer who had Poor Control with the Standard Antiemetic Regimen

Tomomi Nishimura[1], Hiroshi Ishiguro[2*], Kosuke Kawaguchi[1], Tomoharu Sugie[3], Mariko Tokiwa[1], Megumi Takeuchi[1] and Masakazu Toi[1]

[1]Breast Surgery Department, Kyoto University Hospital, Japan

[2]Department of Target Therapy Oncology, Graduate School of Medicine Kyoto University, 54 Kawaharacho, Shogoin Sakyo-ku, Kyoto 606-8507, Japan

[3]Breast Surgery Department, Hirakata Hospital, Kansai Medical University, 2-3-1, Shinmachi, Hirakata, Osaka 573-1191, Japan

Abstract

Aim: To evaluate the antiemetic efficacy and safety of olanzapine in Japanese women with nausea and/or vomiting refractory to the standard antiemetic regimen.

Methods: We retrospectively reviewed the medical records of consecutive female patients with early breast cancer who underwent highly emetogenic chemotherapy at our hospital from January 2009 to March 2013. Patients with grade 2 or 3 nausea and/or vomiting despite receiving standard antiemetics (5-hydroxytryptamine3 receptor antagonists and dexamethasone 20 mg on day 1, and 4 mg dexamethasone on days 2 and 3) in the first chemotherapy cycle received an additional 2.5–10 mg olanzapine from days 1 to 3 in the subsequent cycles. We assessed patient characteristics, olanzapine dose, nausea and vomiting grades before and after adding olanzapine, and adverse effects.

Results: We reviewed 20 patients with poor control in the first chemotherapy cycle, despite receiving standard antiemetics, who received olanzapine from the second cycle. Nausea and vomiting improved in 75% and 70% of cases, respectively, despite poor control during the first cycle, while an additional 10% of cases achieved a complete response (no emesis, no rescue) in the second cycle. No grade 3/4 adverse events were noted, but 50% and 30% of subjects complained of grade 1/2 drowsiness and dizziness, respectively, prompting a reduction in the olanzapine dose. Efficacy was retained at the lower dose.

Conclusion: Olanzapine has excellent antiemetic efficacy in Japanese women with chemotherapy-induced nausea and vomiting refractory to standard antiemetics. The recommended dose of olanzapine for Japanese women appears to be lower than for Caucasians.

Keywords: Antiemetics; Asian Continental Ancestry Group; Breast neoplasms; Drug therapy; Olanzapine

Abbreviations: OLN: Olanzapine; APR: Aprepitant; HEC: Highly Emetogenic Chemotherapy; CINV: Chemotherapy-Induced Nausea and Vomiting; AC: Anthracycline and Cyclophosphamide Combination; IV: Intravenous; PO: Peroral; 5-HT3RA: 5-Hydroxytryptamine3 Receptor Antagonist; BMI: Body Mass Index; CR: Complete Response; PALO: Palonosetron

*Corresponding Author: Hiroshi Ishiguro, Department of Target Therapy Oncology, Graduate School of Medicine Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan; Tel: 075-751-4950; Fax: 075-751-4951; E-mail: hishimd@kuhp.kyoto-u.ac.jp

Introduction

APRepitant (APR), an Aeurokinin 1 (NK1) receptor antagonist, is currently recommended for use with Highly Emetogenic Chemotherapy (HEC) in the NCCN [1], ASCO [2], and MASCC [3] guidelines. However, its high cost and metabolic interactions with other drugs are problematic. NK1 receptor antagonists are moderate inhibitors of CYtochrome P450 3A4 (CYP3A4) [4] and can influence the pharmacokinetics of drugs metabolized by the CYP3A4 pathway, such as dexametathone [5]. The influence of NK1 receptor antagonists on the metabolism of anthracycline, which is one of the most important drugs in the treatment of breast cancer, is still unclear, and increased exposure to anthracyclines can increase the risk of heart failure, so it is desirable to carefully select the drugs for concomitant use with anthracycline.

OLaNzapine (OLN), the multi-acting receptor-targeting antipsychotic, is a weak inhibitor of CYP and might have fewer interactions with the pharmacokinetics of some drugs metabolized in liver. Several phase II trials showed OLN to have an antiemetic effect [6, 7], and a recent phase III trial showed it to be as effective as APR for achieving a Complete Response (CR; no emesis, no rescue) in HEC in Caucasian patients [8]. In addition, this trial demonstrated that not only is OLN equivalent to APR for controlling emesis, but also that OLN is better than APR for controlling nausea, especially in the delayed period (24–120 h postchemotherapy); the proportion of patients with no nausea was 69% in the OLN group and 38% in the APR group ($p < 0.01$). This and other trials of OLN (at least 10 mg/day for 4 days per cycle of chemotherapy) for the prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Caucasians (55–77% women) showed no grade 3/4 adverse events with OLN, and there was no mention of patients who required OLN dose reduction [6-8]. The NCCN guideline [1] now recommends the OLN-containing regimen (OLN + palonosetron + dexamethasone) for HEC as an alternative to the APR-containing regimen.

OLN has long been used to treat schizophrenia at a dose of 5–20 mg/day for longer treatment periods than those in the phase III trial where OLN was administered to prevent CINV. When OLN is used in patients with schizophrenia, it is known that some adverse events are known to occur (e.g., drowsiness, 20–40%; dizziness, 11–18%; and hyperglycemia, 0.1–5%), and that OLN possibly exacerbate preexisting comorbidity (e.g., diabetes mellitus, Parkinson's diseases, and epilepsy). There are also some reported severe adverse events, such as diabetic ketoacidosis especially with longer duration of exposure [9] and rare potentially fatal arrhythmias such as Torsades de points [10]. A study showed that OLN clearance was delayed in women, non-smokers, and African-Americans compared with Caucasians, and it has been suggested that such adverse events occur more often in the African-American population [11]. Though OLN had an antiemetic effect and adequate safety in trials conducted in Western countries, the safety and recommended dose of OLN as an antiemetic for non-Caucasian women have not been examined. Therefore, we performed a retrospective study to evaluate the efficacy and safety of OLN in an antiemetic regimen for Japanese women with breast cancer who underwent HEC and had poor control of CINV with the standard antiemetic regimen.

Material and methods

We retrospectively reviewed the medical records of patients who underwent highly emetogenic adjuvant or neoadjuvant chemotherapy for early breast cancer at Kyoto University Hospital from January 2009 to March 2013. A schematic of patient disposition is shown in (Figure 1). All patients who underwent HEC, consisting of an Anthracycline and Cyclophosphamide (AC) combination and/or cisplatin (>50 mg/m^2), were treated as follows according to the regimen of a phase III study comparing granisetron and palonosetron in Japanese patients [12]: A standard antiemetic regimen of

Intravenous (IV) 5-Hydroxytryptamine3 Receptor Antagonists (5-HT3RAs; 3 mg granisetron or 0.75 mg palonosetron) and IV dexamethasone 20 mg on day 1, and 4 mg dexamethasone Peroral (PO) or IV on days 2 and 3 in the first HEC cycle. For patients with poor control in the first cycle of HEC, 2.5–10 mg of OLN was added from days 1 to 3 in the second and subsequent cycles. We reviewed the patients who developed grade 2 or 3 nausea and/or vomiting despite receiving the standard antiemetic regimen in the first cycle, and took OLN additionally in the second and subsequent cycles.

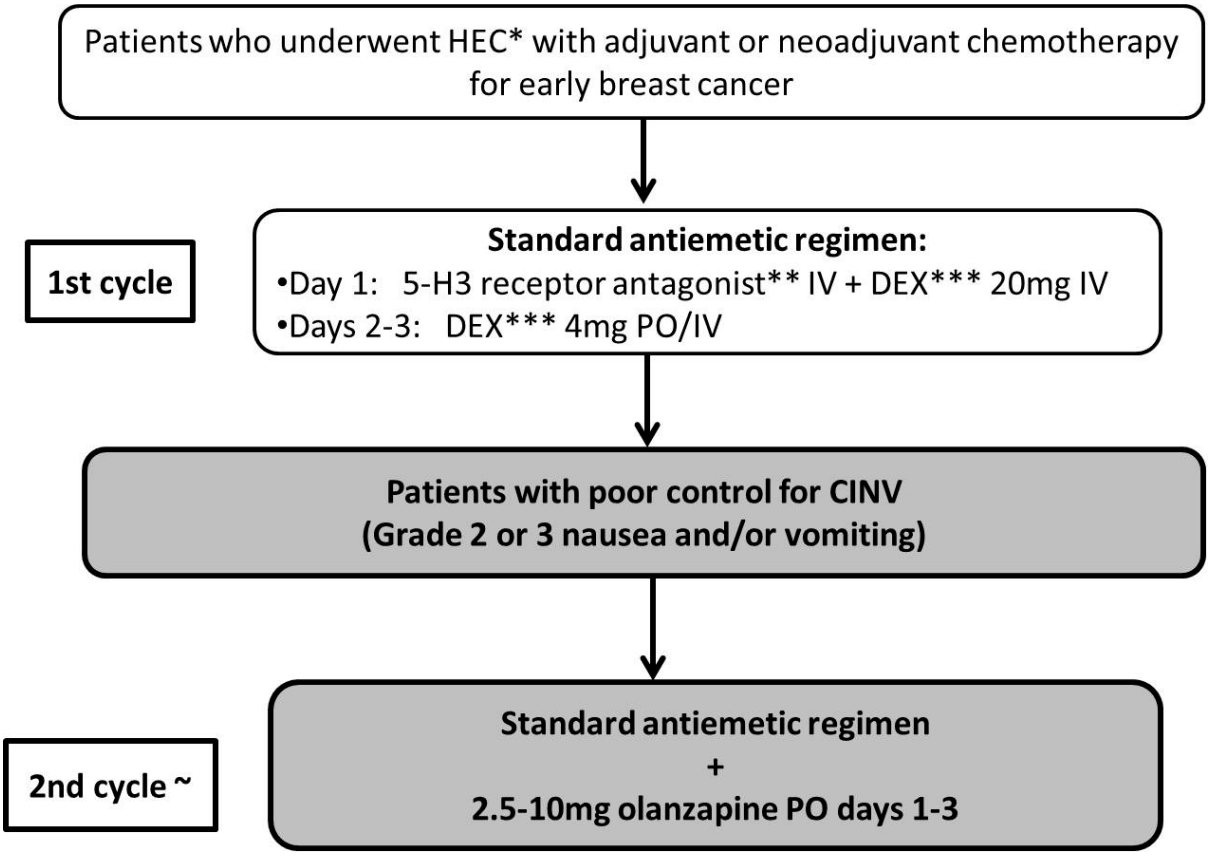

Figure 1: Patient disposition

*HEC: Highly Emetogenic Chemotherapy

**5-H3 receptor antagonist: 3 mg granisetron (2009/01–2009/06) or 0.75 mg palonosetron (2009/07–2013/03)

***DEX: Dexamethasone

The following data were obtained: patient characteristics (age, menopausal status, body weight, Body Mass Index [BMI], history of smoking, chemotherapy regimen, and type of 5-HTRA), OLN dose, grade of nausea and vomiting before and after using OLN, and adverse effects of OLN.

The primary endpoint was the CR (no emesis, no rescue) rate for the overall period (0–120 h postchemotherapy) in the second cycle of HEC, when OLN was added to the regimen. The secondary endpoints were the rates of reduction in the grades of nausea and vomiting during the acute period (0–24 h postchemotherapy) and the delayed period (24–120 h postchemotherapy) in the second HEC cycle compared with the first cycle. We evaluated the grades of nausea and vomiting in accordance with the Common Terminology Criteria for Adverse

Events (CTCAE) v3.0 [13]. We then analyzed the CR rate and the rates of reduction in the grades of nausea and vomiting in the second HEC cycle according to age, BMI, smoking status, chemotherapy regimen, the type of 5-HTRA and the starting OLN dose. In addition, we used the Chi-squared test to determine potential associations between the CR rate and patient characteristics. We also analyzed the incidence of OLN adverse events, namely, drowsiness, dizziness (both of which were evaluated in accordance with CTCAE v3.0 [13]), falling, and reduction in OLN dose (excluding patients who underwent only two cycles of HEC) in at least one HEC cycle with OLN use, according to patient characteristics such as age, BMI, smoking status, and starting OLN dose.

This retrospective observational study was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine. Because OLN is reimbursed by the Japanese health insurance system only for the treatment of schizophrenia and depression, approval by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine with respect to "Financial support for off-label prescription in patients with severe adverse drug reaction due to cancer chemotherapy" was also obtained.

Results

In total, 108 patients underwent HEC, which contained the AC combination and/or cisplatin (>50 mg/m^2). Of these patients, 20 had developed grade 2 or 3 nausea and/or vomiting during the first HEC cycle without OLN and received OLN for subsequent cycles. The medical records of these 20 consecutive patients were reviewed, and their characteristics are presented in Table 1. Of them, 25% had a past history of smoking, but all refrained from smoking during chemotherapy. None had diabetes mellitus, Parkinson's diseases and epilepsy as past medical history. With regard to 5HTRA treatment, 45% had received granisetron and the others had received palonosetron during all HEC cycles. They had also used metoclopramide and/or domperidone as rescue antiemetics, but no patient had used APR during all HEC cycles. At first, we added OLN 10 mg/day for four patients, but most of them complained of grade 1 or 2 drowsiness and needed a reduction in the OLN dose, so we reduced the starting dose of OLN to 5 mg/day for the next five patients, and then reduced it to 2.5 mg/day for the remaining 11 patients. Palonosetron became available in our hospital during the time when we reduced the starting OLN dose to 2.5 mg/day, so all patients whose starting OLN dose was 2.5 mg/day also received palonosetron as the standard antiemetic regimen.

Of the 20 patients, 3 underwent only two cycles of HEC because of progressive disease, and 7 and 10 patients underwent 3 and 4 HEC cycles, respectively, as previously scheduled. All patients received the same dose of HEC during all cycles. None of the patients stopped HEC because of CINV.

Table 1. Patient characteristics

Patients (n)		20
Median age (years)		47 (30–71)
Menopausal state†	pre- (n)	11 (55%)
	post- (n)	9 (45%)
Median weight ‡(kg)		54 (45–99)
Median BMI‡		21.5 (18.6–26.7)
Smoking history	Never- (n)	15 (75%)

	Ex- (n)	5 (25%)
Diabetes (n)		0
Chemotherapy regimen	AC combination§ (n)	12 (60%)
	Cisplatin (n)	8 (40%)
5HT3 antagonist	Granisetron (n)	9 (45%)
	Palonosetron (n)	11 (55%)
OLN (olanzapine) dose in the 2nd cycle (= first OLN use)	10 mg/day (n)	4 (20%)
	5 mg/day (n)	5 (25%)
	2.5 mg /day (n)	11 (55%)

†Menopausal state: pre-, pre-menopausal; post-, post-menopausal

‡Initial measurements

§AC: Anthracycline and Cyclophosphamide combination

BMI: body mass index

OLN: olanzapine

All the nine patients receiving granisetron started OLN at 5–10 mg/day, and 11 patients receiving palonosetron started OLN at 2.5 mg/day.

The number of patients who achieved a CR is shown in (Figure 2A).

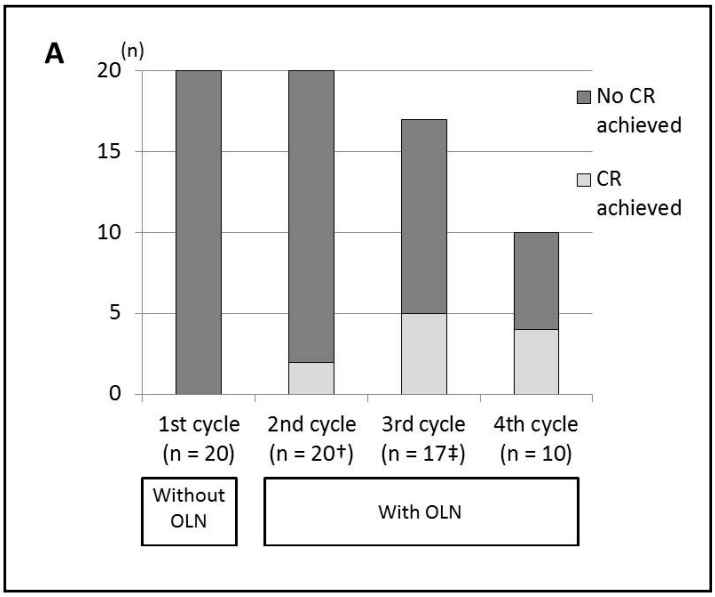

Figure 2: Patient responses to chemotherapy and nausea and vomiting grades

Figure 2A: Number of patients achieving a complete response (no emesis, no rescue) in each chemotherapy cycle. Three patients underwent only two cycles of chemotherapy because of progressive disease, and seven underwent three chemotherapy cycles as previously scheduled. All patients who achieved a CR, except for one patient who achieved a CR in the third chemotherapy cycle, maintained a CR in the subsequent cycles.

†One of the two patients who achieved a CR in the second chemotherapy cycle did not undergo the third and fourth cycles.

‡Two of the five patients who achieved a CR in the third chemotherapy cycle did not undergo the fourth cycle.

OLN: Olanzapine

CR: Complete Response (no emesis, no rescue)

Among those who did not respond to standard antiemetic treatment for HEC, two patients (10%) achieved a CR in the second cycle with OLN. The other four patients achieved a CR from the third cycle, and two achieved a CR from the forth cycle.

Figures 2B and 2C show the occurrence and grades of nausea and vomiting in the first HEC cycle without OLN and in the second cycle with OLN, respectively. Adding OLN improved the grades of nausea and vomiting in both the acute and delayed periods. The number of patients with grade 3 nausea in both periods decreased from 5 (25%) to 0, while the total number of patients with grade 2/3 nausea decreased from 14 (70%) to 12 (60%) during the acute period and from 20 (100%) to 10 (50%) during the delayed period (Figure 2B). The number of patients with grade 3 vomiting decreased from 8 (40%) to 2 (10%) during the acute period and from 10 (50%) to 2 (10%) during the delayed period. The total number of patients with grade 2/3 vomiting decreased from 13 (65%) to 5 (25%) during the acute period and from 14 (70%) to 4 (20%) during the delayed period (Figure 2C). For the overall period, 15 patients (75%) and 14 patients (70%) had an improved grade of nausea and vomiting, respectively, during the acute and/or delayed period.

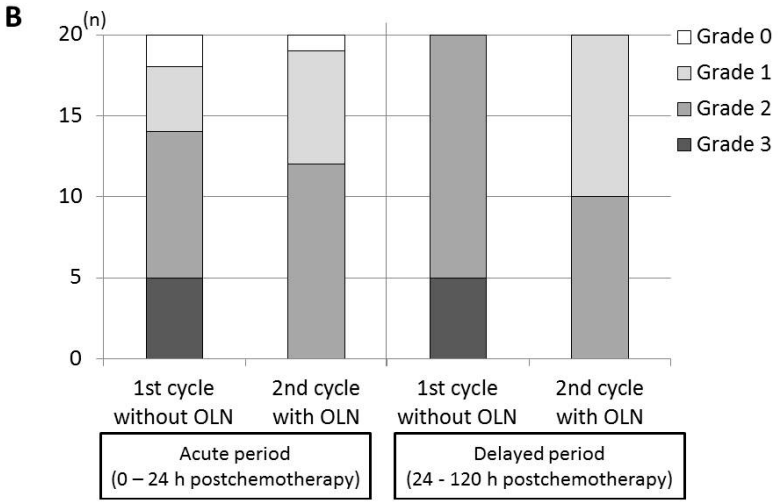

Figure 2B: Grade of nausea in the first and second chemotherapy cycles (n = 20)

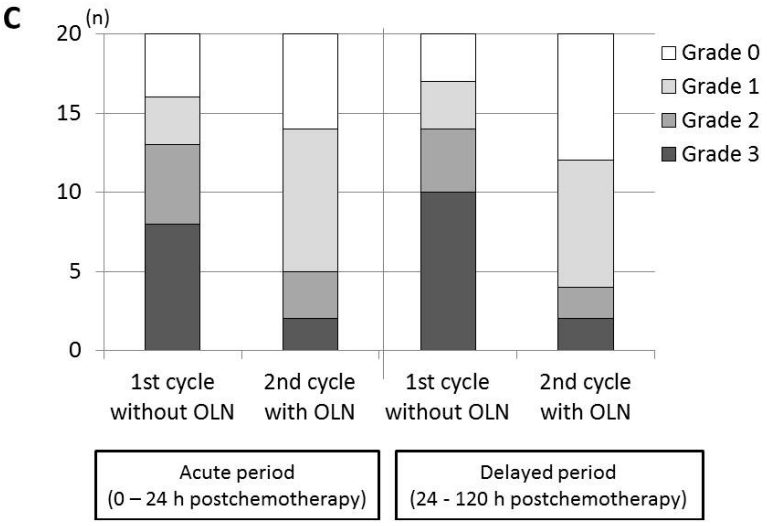

Figure 2C: Grade of vomiting in the first and second chemotherapy cycles (n = 20)

We analyzed the antiemetic effect of OLN during the acute and delayed periods in the second HEC cycle according to multiple patient characteristics (age, BMI, smoking history, chemotherapy regimen, the type of 5-HTRA, and starting OLN dose) (Table 2).

Table 2. Relationships between patient characteristics and the efficacy of OLN in the second chemotherapy cycle (n = 2)

		Acute nausea improvement† (n = 19)		Delayed nausea improvement† (n = 20)		Acute vomiting improvement† (n = 18)		Delayed vomiting improvement† (n = 17)		Achieved a CR (n = 20)		
		Yes (n)	No (n)	Yes (n)	No (n)	Yes (n)	No (n)	Yes (n)	No (n)	Yes (n)	No (n)	P value*
Total		9 (47%)	10	15 (75%)	5	12 (67%)	6	13 (76%)	4	2 (10%)	18	-
Age	≧ 50	4 (50%)	4	7 (78%)	2	6 (75%)	2	7 (88%)	1	1 (11%)	8	0.88
	< 50	5 (45%)	6	8 (73%)	3	6 (60%)	4	6 (67%)	3	1 (9%)	10	
BMI	≧ 22	3 (38%)	5	7 (78%)	2	6 (86%)	1	8 (100%)	0	1 (11%)	8	0.88
	< 22	6 (55%)	5	8 (73%)	3	6 (55%)	5	5 (56%)	4	1 (9%)	10	
Smoking	Never-	7 (50%)	7	11 (73%)	4	10 (71%)	4	10 (77%)	3	2 (13%)	13	0.38
	Ex-	2 (40%)	3	4 (80%)	1	2 (50%)	2	3 (75%)	1	0 (0%)	5	
Chemotherapy regimen	AC combination	5 (42%)	7	10 (83%)	2	9 (82%)	2	8 (89%)	1	2 (17%)	10	0.22
	Cisplatin	4 (57%)	3	5 (63%)	3	3 (43%)	4	5 (63%)	3	0 (0%)	8	
5HT3 antagonist	Granisetron	6 (67%)	3	6 (67%)	3	7 (78%)	2	7 (68%)	2	0 (0%)	9	0.18
Starting OLN dose (mg/day)	5 - 10											
5HT3 antagonist	Palonosetron	3 (30%)	7	9 (82%)	2	5 (56%)	4	6 (75%)	2	2 (18%)	9	
Starting OLN dose (mg/day)	2.5											

†Reduction in the grades of nausea and vomiting after adding OLN in the second HEC cycle (acute period: 0–24 h postchemotherapy; delayed period: 24–120 h postchemotherapy); excluding the patients who had grade 0 without the use of OLN, and maintained grade 0 after the addition of OLN

CR: Clinical Response (no emesis, no rescue)

BMI: Body Mass Index

AC: Anthracycline and Cyclophosphamide combination

OLN: Olanzapine

*Chi-squared test

Although no statistical differences were observed in antiemetic effect between these characteristics, more patients with a higher BMI (≥ 22) showed an improvement in the grade of vomiting than those with a lower BMI (< 22) in both the acute and delayed periods.

No grade 3/4 adverse events of OLN were noted, but 10 (50%) and 6 (30%) patients had grade 1 or 2 drowsiness and dizziness, respectively (Table 3). Three patients (15%) fell because of dizziness, two of whom also hit their head. Although none of the patients needed treatment for adverse events, we reduced the starting OLN dose and changed the administration time of OLN from morning to nighttime. In addition, we asked the patients to try to refrain from walking around after taking OLN. No elevation of blood glucose level was seen after taking OLN.

Regarding the adverse events of OLN in all HEC cycles, the incidence of adverse events did not differ statistically between the patients characteristics noted above. However, there appeared to be a trend of increased incidence of drowsiness that required OLN dose reduction in patients with a lower BMI (<22) compared with those with a higher BMI (≥ 22). Though the rate of drowsiness and dizziness did not differ much between never-smokers and ex-smokers, patients who fell or required an OLN dose reduction were all never-smokers (Table 3).

Six patients whose starting OLN dose was 10 mg/day (n = 2), 5 mg/day (n = 3), or 2.5 mg/day (n = 1) required an OLN dose reduction because of adverse events such as drowsiness, dizziness, and falling. Of them, two with starting OLN doses of 10 mg/day and 5 mg/day stopped taking OLN in the third and fourth cycle, respectively. After reducing or quitting OLN, all patients had less OLN-related adverse events and the same degree of good control of CINV as when they had been taking a higher dose of OLN. Patients who had started OLN at a lower dose (2.5 mg/day) also had less drowsiness and dizziness than those with a higher OLN starting dose (5–10 mg/day) (Table 3).

Table 3. Relationships between patient characteristics (BMI, smoking, and first OLN dose) and adverse effects of OLN

		Drowsiness† (n = 20)		Dizziness† (n = 20)		Fall† (n = 20)		OLN reduction‡ (n = 17)		
		Grade 0 (n)	Grade 1/2 (n)	Grade 0 (n)	Grade 1/2 (n)	No (n)	Yes (n)	No (n)	Yes (n)	P value*
Total		10	10 (50%)	14	6 (30%)	17	3 (15%)	11	6 (35%)	-
Age	≧ 50	5	4 (44%)	6	3 (33%)	7	2 (22%)	3	3 (50%)	0.35
	< 50	5	6 (54%)	8	3 (27%)	10	1 (9%)	8	3 (27%)	

BMI	≧ 22	7	2 (22%)	7	2 (22%)	8	1 (11%)	6	1 (14%)	0.13
	< 22	3	8 (73%)	7	4 (36%)	9	2 (18%)	5	5 (50%)	
Smoking	Never-	7	8 (53%)	10	5 (33%)	12	3 (20%)	6	6 (50%)	0.05
	Ex-	3	2 (40%)	4	1 (20%)	5	0 (0%)	5	0 (0%)	
Starting OLN dose (mg)	5 - 10	3	6 (67%)	5	4 (44%)	8	1 (11%)	4	5 (56%)	0.06
	2.5	7	4 (36%)	9	2 (18%)	9	2 (18%)	7	1 (13%)	

†At least one cycle of the second and subsequent cycles (i.e., with OLN use)

‡At least one cycle of the second and subsequent cycles (i.e., with OLN use), excluding patients who underwent only two cycles of chemotherapy

BMI: Body Mass Index

OLN: Olanzapine

*Chi-squared test

Discussion

We performed this retrospective observational study to evaluate the efficacy and safety of OLN as an antiemetic for Japanese female patients with early breast cancer who had poor control of CINV (defined as grade 2 or 3 nausea and/or vomiting) and were on a standard antiemetic regimen. We reviewed 20 patients, of whom two (10%) achieved a CR (no emesis, no rescue) after adding OLN in the second HEC cycle, despite poor control of CINV during the first cycle. More than 70% of patients had an improved grade of nausea and vomiting, but no significant correlations were found between patient characteristics and the antiemetic effect. In addition, no grade 3/4 adverse events were noted, but 35% of the patients needed a dose reduction of OLN in the subsequent HEC cycles because of grade 2 drowsiness or dizziness. Patients with a lower BMI (<22) and no smoking history tended to need a greater reduction in OLN dose. Patients who had the OLN dose reduced because of OLN-related adverse effects had less adverse effects without worsening of CINV, and OLN retained its antiemetic effects, even at a dose lower than that used in Caucasian patients in previous studies [6-8].

The limitations of this study are as follows. First, we cannot exclude the possibility of a placebo effect and other biases due to the study design. Second, an underreporting bias may exist because this was a retrospective study. Third, we reviewed a limited number of cases, all of which showed poor control of CINV while on the standard antiemetic regimen without APR. Therefore, we could not compare the efficacy of OLN and NK1 receptor antagonists such as APR, which are currently recommended for HEC [1-3]. Fourth, the types of 5HTRA differed completely between the patients who started OLN at a lower dose (2.5 mg/day) and those with a higher OLN starting

dose (5–10 mg/day), so we could not directly compare the antiemetic efficacy and safety between the two groups.

The superior antiemetic effects of NK1 receptor antagonists over previous antiemetic drugs were shown in many randomized trials, most of which were funded by pharmaceutical companies [14]. On the other hand, two recent trials, both of which were supported by government-affiliated organizations, failed to show the superior antiemetic effect of APR over dexamethasone during the delayed period with the use of palonosetron and prochlorperazine and/or metoclopramide [15, 16]. Most former trials did not use an effective alternative medication for delayed nausea such as prochlorperazine in the control groups [17-25], so there is a possibility that this difference contributed to some extent to the conflicting results. OLN, which is more cost-effective (in Japan, the equivalent cost of OLN per cycle as used in the phase III trial was about \2,000 (approx. 20 USD), while the cost of APR per cycle was about \15,000 (approximately 150 USD) [8]). Compared with APR, OLN, has a non-inferior antiemetic efficacy compared with APR, as well as fewer interactions with certain drugs metabolized by CYP3A4 [26], and it is now recommended as a standard antiemetic for HEC in the recently published NCCN guideline[1]. Although there were 8 cases of Torsades de points possibly related with use of OLN as antipsychotics among 2,131,688 cases spontaneously reported to US FDA Adverse Event Reporting System database [10], such severe arrhythmias haven't been observed in the patients with antiemetic OLN use in the clinical trials [6-8]. Although it was reported that use of anthracyclines, especially with higher cumulative dose, was associated with QTc-prolongation [27], cumulative dose in perioperative setting is much lower than total dose with increased cardiac risk. Furthermore, OLN is used in a lower dose and more importantly, much shorter duration as antiemetics than used as antipsychotics.

In our study, OLN also showed antiemetic efficacy in Japanese female patients with poor CINV control while on the standard antiemetic regimen, even when a dose of OLN lower than that used for Caucasians was administered. Never-smokers tended to need a greater reduction of the OLN dose because of the adverse effects such as drowsiness and dizziness, which is consistent with the results of previous studies that showed delayed OLN clearance in never-smokers compared with active smokers [11]. On the other hand, patients with a lower BMI (<22) had more adverse effects and less antiemetic effect, but the reason for this is unclear. When we administer OLN to Japanese female patients, it might be desirable to start OLN at a lower dose (<5 mg/day), especially for never-smokers and/or those with a lower BMI (<22).

Ideally, a large, double-blinded, randomized, prospective trial is needed to fully demonstrate the non-inferiority of OLN relative to NK1 receptor antagonists. However, the cheaper price of OLN and the fact that the OLN patent expired in some Western countries in 2011, and is due to expire in Japan in 2016, makes it difficult to obtain financial support from pharmaceutical companies and conduct such trials with a cost-saving strategy. Instead, we should at least conduct a phase II dose-determining study for OLN as an antiemetic for Japanese patients.

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