

A Randomized Trial to Compare the Efficacy and Safety of Antiemetic Treatment with Ondansetron and Ondansetron Zydis in Patients with Breast Cancer Treated with High-dose Epirubicin

D. PECTASIDES¹, U. DAFNI², G. ARAVANTINOS³, E. TIMOTHEADOU⁴, D.V. SKARLOS⁵,
N. PAVLIDIS⁶, A. GAGLIA¹, H.P. KALOFONOS⁷ and G. FOUNTZILAS⁴

¹Second Department of Internal Medicine, Oncology Section, Attikon University General Hospital Haidari, Athens;

²Laboratory of Biostatistics, University of Athens School of Nursing, Athens;

³Third Department of Medical Oncology, Agii Anargiri Cancer Hospital, Athens;

⁴Department of Medical Oncology, Papageorgiou General Hospital, Aristotle University of Thessaloniki School of Medicine, Thessaloniki;

⁵Second Department of Medical Oncology, Henry Dunant Hospital, Athens;

⁶Department of Medical Oncology, Ioannina University Hospital, Ioannina;

⁷Department of Medicine, Division of Oncology, University Hospital of Patras, Greece

Abstract. *Objective:* The objective of this study was to compare the efficacy of a disintegrating tablet of ondansetron (ODT) and the conventional tablet formulation of ondansetron (OT) in controlling nausea and vomiting in breast cancer patients. *Patients and Methods:* A total of 134 breast cancer patients receiving high-dose epirubicin participated in a randomized trial comparing the antiemetic efficacy and safety of an 8 mg OT given twice daily to an 8 mg orally ODT given twice daily, both for 3 days. *Results:* OT was significantly better in the complete control of emesis (72% versus 52%, $p=0.020$) and marginally better in the complete control of nausea (66% versus 48%, $p=0.054$) induced by high-dose epirubicin over days 1-3 compared to ODT. However, no differences were found in major control of emesis (0 to 2 emetic episodes, 76% versus 70%, $p=0.28$) over days 1-3. *Conclusion:* OT was significantly better in the complete control of emesis and marginally better in the complete control of nausea, but not in the major control of emesis and nausea induced by high-dose epirubicin compared to ODT. ODT may be an effective alternative to OT, particularly in patients who have difficulties in swallowing a conventional tablet.

Correspondence to: D. Pectasides, Second Department of Internal Medicine, Propaedeutic, Oncology Section, Attikon University Hospital, Rimini 1, Haidari, Athens, Greece. Tel: +30 210 5831691, +30 210 6008610, Fax: +30 210 5831690, +30 210 6008610, e-mail: pectasid@otenet.gr

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Moderately emetogenic regimens, such as anthracycline-based chemotherapy regimens, are effective in the treatment of various malignancies, including breast cancer, and are usually administered on an outpatient basis. These regimens cause emesis in approximately 70% to 80% of patients, even when doxorubicin is administered as a slow continuous infusion and accompanied by conventional antiemetic therapy (1). Prevention of nausea and vomiting in patients receiving these regimens is very important since nausea and vomiting are the most distressing side-effects of chemotherapy occurring in patients not receiving antiemetic treatment (2). In addition nausea and vomiting may limit a patient's tolerance to and compliance with the treatment.

Several studies have shown the efficacy of 5-HT₃ during the acute phase of emesis. Ondansetron is a highly effective and well-tolerated anti-vomiting agent in patients receiving chemotherapy and radiotherapy. Both the *i.v.* and oral formulations have been extensively used for the prevention of nausea and vomiting associated with cisplatin or non-cisplatin chemotherapy (3, 4). In order to control nausea and vomiting in an outpatient basis, anti-vomiting regimens should be effective, well-tolerated, simple and convenient. Oral administration of an antiemetic may be the route of choice in an outpatient basis.

Oral treatment with ondansetron has been shown to control nausea and vomiting induced by moderately emetogenic chemotherapy regimens (3-6). Ondansetron has also been shown to be superior to placebo, metoclopramide, alizapride and other conventional antiemetic regimens (3, 5-7). The conventional tablet

formulation of ondansetron (OT) may not be suitable for all patients, especially for those who have difficulty in swallowing. Therefore, an orally disintegrating ondansetron tablet (ODT), a novel formulation, has been developed by GlaxoSmithKline Beecham. The ODT is a freeze-dried tablet product which disperses rapidly when placed onto the tongue. It does not require water to facilitate swallowing and therefore would be especially useful for patients who have difficulty in swallowing and is also likely to enhance patient compliance due to ease of administration. When it is put into the mouth, the freeze-dried structure disintegrates instantaneously releasing the drug which dissolves and disperses in the saliva. The saliva contains the effective ondansetron which is swallowed and absorbed from the gastrointestinal mucosa.

The purpose of the study was to compare the ODT preparation given twice daily at a dose of 8 mg to OT given twice daily at a dose of 8 mg over 3 days, in terms of emesis and nausea control in breast cancer patients receiving high-dose epirubicin as adjuvant treatment.

Patients and Methods

The Hellenic Cooperative Oncology Group conducted a phase II trial comparing two antiemetic treatment strategies in chemotherapy breast cancer patients receiving their first course of high-dose epirubicin as part of a dose-dense sequential chemotherapy consisting of epirubicin (110 mg/m²), paclitaxel (200 mg/m²) and Mega-CMF (cyclophosphamide, 840 mg/m²; methotrexate, 57 mg/m²; and fluorouracil, 840 mg/m²) every two weeks *versus* epirubicin (110 mg/m²), Mega-CMF every two weeks and weekly docetaxel (35 mg/m²) *versus* epirubicin (110 mg/m²), Mega-CMF every two weeks and weekly paclitaxel (80 mg/m²). Patients were randomly allocated to receive either ODT or OT. The efficacy and safety were evaluated during the first cycle of high-dose epirubicin. Patients were randomized to receive one of the following study treatments for three consecutive days during the first cycle of epirubicin. Arm 1: 8 mg ODT tablet twice daily for three consecutive days, or Arm 2: 8 mg OT twice daily for three consecutive days. Ondansetron was given 1 h before chemotherapy and 8 h after chemotherapy on day 1, followed by 8 mg every 12 h for the next 2 days. Rescue administration was allowed but such patients were considered failures. Informed consent was obtained by all patients participating in the study.

Chemotherapy patients were eligible for inclusion if they were receiving the first course of high-dose epirubicin. Patients were excluded from the study if they presented with any underlying illness causing emesis (signs of gastrointestinal obstruction, increased intracranial pressure due to verified CNS tumor or metastases, hypercalcemia, active peptic ulcer), or they had received medications with known or potential antiemetic activity, or medications which could confound the efficacy evaluation in the 24 h prior to inclusion or during the study, or had experienced emesis or moderate or severe nausea in the 24 h prior to the first dose of study drug, or were regarded as having a very high alcohol uptake, or had moderate or severe impaired liver function. The use of dexamethasone was permitted.

Efficacy and safety assessment. The clinical team recorded episodes of nausea or vomiting during the 3-4 h post-chemotherapy administration during the stay in the outpatient clinic. After completion of the three-day period, all patients were interviewed on the number of emetic episodes, the intensity of nausea they experienced and the use of any additional antiemetic drug they used. In addition, patients were given diary cards to record emesis and nausea episodes on days 1 through 3, with day 1 starting at the time of completion of epirubicin infusion and ending at midnight, and days 2 and 3 being the next two consecutive 24 h periods. The patient would record the following information on each day of the 3-day study period: Day and time of each emetic episode, assessment of the worst experience of nausea (grade) on that day, time of taking the study medication, and time of taking the rescue medication (if any). Regarding the adverse events, a post-treatment assessment was carried out as soon as possible after completion of the study treatment (no sooner than 24 h after completion of the study treatment but no later than 28 days after the beginning of any treatment). The following events led to patient withdrawal: Patients removed from the study by the investigator at any time if the treatment was considered detrimental to the patient if continued, or patients choosing to withdraw from the study at any time without prejudice to the subsequent treatment, or patients experiencing more than 3 emetic episodes in any 24-hour period or who had persistent severe nausea, or patients who had received rescue medication (record day, time and agent of rescue).

Response evaluation. An event corresponded to any single event of vomiting or retching. For nausea, each new occurrence was recorded as an episode if its duration was less than 1h, while if nausea continued for longer than 1h, every hour was counted as a supplementary episode. The result of treatment was evaluated as follows: *Complete emesis control:* Absence of any episode of vomiting, no rescue medication, no treatment discontinuation. *Major emesis control:* 0-2 or 1-2 vomiting events, no rescue medication, no treatment discontinuation. *Partial emesis control:* 3-4 vomiting events. *Failure:* 5 or more vomiting events, or rescue medication, or treatment discontinuation.

The intensity of nausea was recorded as mild, moderate or severe and separately analysed.

Statistical analysis. For this analysis, complete emesis control was defined as no emetic episode, while major emesis control was defined as ≤ 2 emetic episodes, given that the patient had not received any rescue antiemetic medication and had not discontinued the treatment in the three-day period of the study. Analysis was conducted following the intent-to-treat principle. The primary endpoint of this study was to compare the major emesis control rate in the two treatment arms. Secondary endpoints were the comparison of complete emesis and nausea control between the two treatment arms.

To detect a difference of 20% at a baseline rate of 70%, with power 80% for a two-sided test at a 5% level of significance, 60 patients per group needed to be registered. Taking into account a 3% withdrawal rate, 126 patients were required to enter the study.

Distributions of complete and major responses in the two treatment arms were compared using Fisher's exact test. Differences on the distribution of continuous variables were assessed by the Mann-Whitney test. Logistic regression analysis was performed for both complete and major emesis control.

Table I. Patient characteristics with respect to treatment arm.

	ODT N=66	OT N=68
Disease stage		
Early	64 (97)	65 (96)
Advanced	2 (3)	3 (4)
Age (years)		
Median	53	53
Range	29-78	25-78
BSA (m ²)		
Median	1.7	1.7
Range	1.5-2.1	1.3-2.0
Systolic blood pressure (mmHg) (baseline evaluation)		
Median	132	130
Range	100-170	110-160
Diastolic blood pressure (mmHg) (baseline evaluation)		
Median	76	75
Range	60-110	60-100
Heart rate (bpm) (baseline evaluation)		
Median	74	72
Range	60-110	60-100

Variables included in the analysis were patient's age, height, weight and treatment arm. The backwards selection procedure was used to choose the variables that had a significant effect on the response. The exclusion criterion for this procedure was set at 0.10. For all statistical tests, the significance level was $\alpha=0.05$. Statistical analysis was performed using SPSS 11.0 system (SPSS, Inc, Chicago, IL, USA).

Results

One hundred and thirty-four patients were registered in the study. Sixty-six patients were randomized to receive ODT, while 68 patients were randomized to receive OT. Nevertheless, one patient randomized to ODT was administered OT, while one patient randomized to OT never started the protocol treatment. These two patients are included in the analysis in the group they were randomized. Fifty-nine patients returned their diary card completed.

None of the participants had experienced nausea or vomiting in the 24-h period before treatment initiation. The age distribution was similar in the two treatment groups [median age 53 years (range, 29-78 years) in the ODT group *versus* median 53 years (range, 25-78) in the OT group, $p=0.75$]. Two patients in the ODT group (3%) and 3 patients in the OT group (4%) suffered from advanced breast cancer when randomized. The patient characteristics are shown in Table I. There were no significant differences in terms of baseline characteristics between the two groups.

Results of the assessment of emetic control are shown in Table II, which demonstrates the distribution of the number

Table III. Emesis control on the worst day (N=59) following treatment with high-dose epirubicin.

	ODT N=33 (%)	OT N=26 (%)
No emesis	18 (55)	17 (65)
1-2 emetic episodes	5 (15)	0 (0)
>2 emetic episodes	2 (6)	5 (19)
Rescue medication	8 (24)	4 (15)

Table II. Number (%) of emetic episodes on days 1-3 of treatment with high-dose epirubicin.

	ODT N=66	OT N=68
No emesis	34 (52)	49 (72)
1-2 emetic episodes	12 (18)	3 (4)
>2 emetic episodes	6 (9)	9 (13)
Rescue medication	13 (20)	6 (9)
Withdrawal	0 (0)	1 (1.5)
Not recorded ^a	1 (1.5)	0 (0)

^aThis patient experienced at least one episode of emesis. Exact number of emetic episodes is not recorded.

of emetic episodes in each treatment group through days 1-3. Complete or major control of emesis (0-2 emetic episodes, no rescue medication, no withdrawal) was achieved by 70% (46/66) of ODT patients and 76% (52/68) of OT patients. This difference was not statistically significant ($p=0.28$). However, there was a statistically significant difference in the rate of complete emesis control (no emesis, no rescue medication, no withdrawal) for days 1 through 3 between the treatment arms (52% for ODT *versus* 72% for OT, $p=0.020$). More patients in the ODT group (20%) needed rescue medication compared to those in the OT group (9%). The emesis control on the worst day according to the data based on the diary cards completed by 59 patients during the 3-day study period is shown in Table III. Complete control of emesis was recorded in 18/33 (54.5%) patients in the ODT group and in 17/26 (65%) patients in the OT group ($p=0.44$). Similarly, no statistically significant difference for the major control of emesis on the worst day was found between the two treatment groups (23/33 (70%) *versus* 17/26 (65%) respectively, $p=0.78$). There was also no statistically

Table IV. Control of emesis on day 1, in the subgroup of 59 patients who completed a diary card following treatment with high-dose epirubicin.

	ODT N=33 (%)	OT N=26 (%)
No emesis	22 (67)	17 (65)
1-2 emetic episodes	5 (15)	4 (15)
>2 emetic episodes	2 (6)	4 (15)
Rescue medication	4 (12)	1 (4)

significant difference between the two treatment groups for the complete or major control of emesis on the first day according to the data based on the diary cards completed by 59 patients (22/33 (67%) versus 17/26 (65%) respectively, $p>0.99$ and 27/33 (82%) versus 21/26 (80%) respectively, $p>0.99$, for both comparisons; Table IV). Figure 1 shows the antiemetic response to treatment.

Table V shows the distribution of nausea grades. Complete nausea control rates differed marginally between the two groups during days 1 through 3 (32/66, (48%) versus 45/68 (66%), $p=0.054$). Rates of no or mild nausea differed significantly between the two groups (41/66 (62%) for ODT versus 54/68 (79%) for OT, $p=0.036$). Figure 2 shows the response of nausea to treatment.

Figure 3 shows the complete nausea control on days 1, 2 and 3. The rate of complete nausea control did not differ significantly (Day 1: 39% in the ODT group versus 50% in the OT group, $p=0.44$; Day 2: 42% in the ODT group versus 42% in the OT group, $p>0.99$; and Day 3: 45.5% in the ODT group versus 54% in the OT group, $p=0.60$).

Logistic regression analysis showed that older age (hazard ratio (HR): 1.04, 95% confidence interval (CI) 1-1.07, $p=0.030$), lower weight (HR: 0.97, 95% CI 0.94-1, $p=0.055$) and conventional OT (HR: 3.02, 95% CI 1.40-6.53, $p=0.005$) were significant predictors for complete emesis control. On the contrary, none of these variables was found to be significant for major emesis control.

Safety. ODT and OT were both well tolerated, with no statistically significant difference in the overall rate of adverse effects attributed to protocol treatment between the two treatment groups (9% for ODT versus 10% for OT, $p>0.99$). The majority of adverse events were judged by the investigators as not related to the study medication. The most frequently reported drug-related adverse effects were headache (ODT 4.5% versus OT 4%) and constipation (ODT 3% versus OT 6%). No serious adverse events occurred during treatment.

Table V. Worst intensity of nausea on days 1-3 following treatment with high-dose epirubicin.

	ODT N=66	OT N=68
No nausea	32 (48)	45 (66)
Mild	9 (14)	9 (13)
Moderate	6 (9)	1 (1.5)
Severe	6 (9)	5 (7)
Rescue medication	13 (20)	6 (9)
Withdrawal	0 (0)	1 (1.5)
Not recorded	0 (0)	1 (1.5)

Discussion

Patients assigned to chemotherapy express fear mainly of two side-effects: loss of hair and vomiting. The fact is that chemotherapy regimens differ considerably with respect to these unwanted events (2). The clinical use of 5-HT₃ antagonists has been associated with a remarkable emesis control in the routine chemotherapy treatment of cancer patients. Even with the highly emetogenic regimens containing cisplatin, it is now possible to prevent acute vomiting in most patients. The role of 5-HT₃ antagonists in the control of emesis induced by moderately emetogenic regimens has been also extensively investigated (4-7). The efficacy of ondansetron when taken orally has proven highly effective and well-tolerated for the prophylaxis of emesis induced by these less emetogenic treatments (4-8). The ease of administration along with a low side-effect profile of oral ondansetron enables the use of the drug in an outpatient setting. ODT, an orally disintegrating ondansetron tablet, is a freeze-dried tablet product which disperses rapidly when placed onto the tongue and does not require water to facilitate swallowing. It is therefore especially useful for patients who have difficulty in swallowing and may improve compliance of these patients (9-13). Seager *et al.* (9) reported on the freeze-dried ODT form and underlined its easy administration and good tolerability. Only few reports on fast dissolving ondansetron have been published to date (9-13). However, neither the efficacy of these formulations on the control of emesis in breast cancer patients receiving high-dose epirubicin nor the behavior of high-dose epirubicin in causing emesis is known.

ODT was found to be significantly inferior in complete emesis control during days 1 through 3 compared to OT

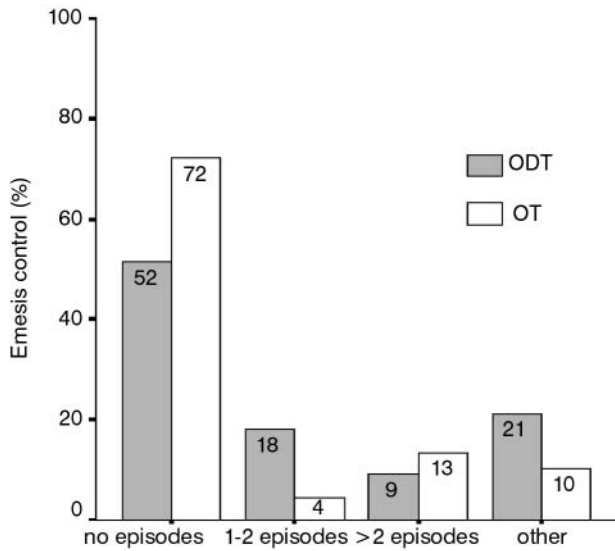


Figure 1. Response to protocol treatment. Other includes withdrawal, rescue medication or unknown number of emesis events.

(52% versus 72%, $p=0.02$). However, ODT and OT did not differ in terms of complete and major control of emesis during days 1 through 3 achieved in 70% of ODT and 76% of OT. These efficacy rates are in the range previously recorded with ODT or OT tablets (6, 9-12, 14, 15). Similarly, rates of complete or major control of emesis on the worst day during the 3-day study period and on day 1 did not differ significantly between the two treatment groups. However, a marginally significant difference was found in the rates of complete control of nausea, with no nausea experienced over days 1 through 3 (48% of ODT patients and 66% of OT patients). These response rates are little higher than previously reported by Dicato *et al.* (6) with OT (44%) and Davidson *et al.* (10) with OT (37%) or ODT (43%), respectively. Moreover, a statistically significant difference was found in favour of OT with respect to no or mild nausea (62% for ODT versus 79% for OT, $p=0.03$). These results are in contrast with those reported by Davidson *et al.* (10).

The generally administered dose of OT is 8 mg b.i.d and the average complete control of emesis on day 1 is 64% (10, 14-16). The combined treatment of oral OT (at a dose of 16 or 24 mg) with dexamethasone (12 or 20 mg) resulted in better complete control of emesis in the range of 76%-100% (17-19).

The fast dissolving tablets were introduced as antiemetics in moderately emetogenic regimens and radiotherapy protocols. Moreover, reports are still rare on this new form of ondansetron. Davidson *et al.* (10) conducted a multicentre, randomized phase III trial, with 427 patients receiving cyclophosphamide-containing chemotherapy, comparing 8 mg

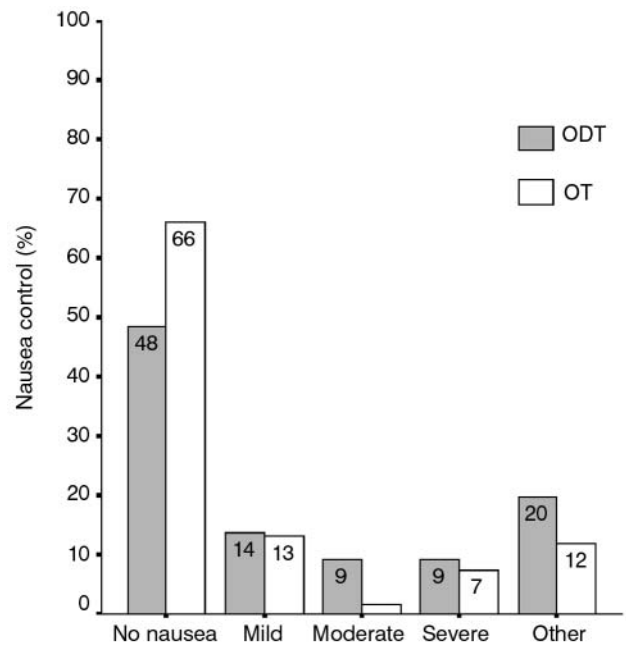


Figure 2. Nausea control according to treatment. 'Other' corresponds to withdrawal, rescue medication or no data on patient status.

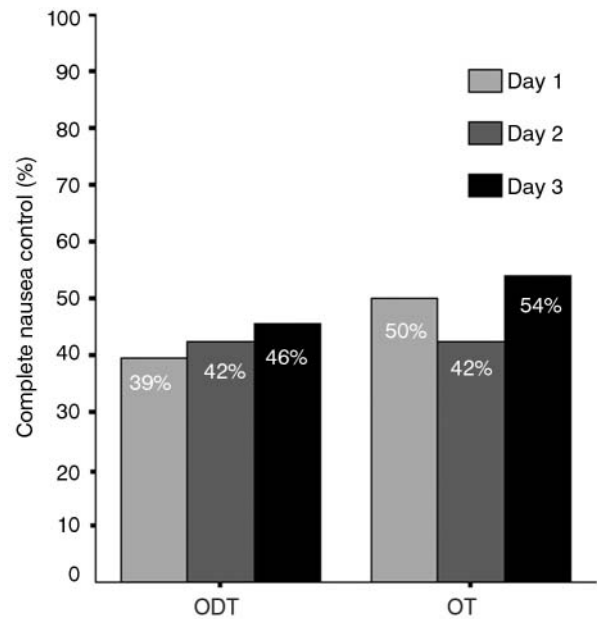


Figure 3. Complete nausea control on days 1, 2, and 3 following treatment with high-dose epirubicin.

b.i.d. of ODT with 8 mg b.i.d. of OT for 3 consecutive days. There were no differences in complete control of emesis over days 1 through 3 between the two groups of treatment (63% versus 64%). Similarly, no difference was found in major

response (0-2 emetic episodes) for either drugs in the first 24 h of chemotherapy. Both drugs were well tolerated. Ariyoshi *et al.* (20) reported on the efficacy of the fast dispersing ondansetron pill GG032X on cisplatin-induced nausea and emesis. Sixty-three of 119 patients (53%) showed complete and/or major response in the first 24 h of chemotherapy. Major adverse effects included headache, fever, atrial fibrillation and increases in total bilirubin, Aspartate Aminotransferase (GOT) and Alanine Aminotransferase (GPT) values. None of these was serious and the affected patients recovered without any treatment. At lower multiple doses of cisplatin (a single dose of 10 mg/m² or more, administered intravenously for 3-5 consecutive days), the inhibitory effect was 70.6% (12/17 cases). They concluded that GG032X tablets had the same inhibitory effect as the already-approved ondansetron tablets against cisplatin-induced nausea and emesis, and were considered safe and clinically useful. Lehoczyk *et al.* (11) evaluated the antiemetic efficacy of ODT (2x8 mg) in 36 patients with gynaecological malignancies treated with cisplatin (50 mg/m²). Most patients displayed complete response (75%) to ODT. A major response was recorded in 11%. They concluded that fast dissolving ondansetron is a new and effective preparation that enriches the panel of available supporting drugs. LeBourgeois *et al.* (13) studied the fast dissolving oral ondansetron in patients receiving fractionated radiotherapy. Two doses of ODT, 8 mg and 16 mg, were compared with placebo. The study showed that ODT was clinically superior to placebo in treating emesis and nausea successfully over a 12-hour period after taking the medication. There were no statistically significant differences between the two doses of ODT. In the 2 hours after taking the study medication, patients who received ODT (8 mg and 16 mg) had significantly fewer emetic episodes compared with those who received placebo. ODT at 8 mg is effective in the treatment of radiotherapy-induced emesis and nausea and provides an effective alternative to the conventional ondansetron tablet.

In our study, the adverse event rates were similarly low in both groups and no local oral adverse events occurred in the ODT group. The most common side-effects at similar rates in both groups were headache and constipation.

In conclusion, OT and ODT at 8 mg, given twice daily for 3 days, were both well-tolerated. OT was significantly better in the complete control of emesis and marginally better in the complete control of nausea induced by a high-dose of epirubicin over days 1 through 3 compared to ODT. However, neither form of ondansetron was significantly different in preventing high-dose epirubicin-induced emesis and nausea on the worst day or in the first 24 h of chemotherapy. ODT is as effective as OT in the treatment of high-dose epirubicin-induced emesis and nausea and provides an effective alternative to the conventional ondansetron tablet, particularly in patients with difficulties in swallowing a conventional tablet.

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