A modified olanzapine regimen for the prevention of chemotherapy-induced nausea and vomiting

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Background At Kaiser Permanente Antioch and Walnut Creek Cancer Centers, a modified olanzapine regimen is used to prevent chemotherapy-induced nausea and vomiting (CINV) in patients who receive highly emetogenic chemotherapy (HEC).
Objective To determine if an olanzapine, ondansetron, dexamethasone (OOD) regimen is noninferior to a fosaprepitant, ondansetron, dexamethasone (FOD) regimen in preventing CINV in patients receiving HEC.
Methods This retrospective cohort study compared the rates of CINV in patients who were treated with HEC and received either the OOD or FOD regimen. Electronic medical records were assessed for documented reports of CINV. 148 patients were included in this study.
Results Complete response (CR), defined as no emesis after Cycle 1 of HEC, in patients receiving the OOD regimen was 95.7% in the acute phase, 94.3% in the delayed phase, and 92.9% overall. CR in patients receiving the FOD regimen was 98.7% in the acute phase, 89.7% in the delayed phase, and 89.7% overall. The percentage of patients who had no nausea on the OOD regimen was 87.1 in the acute phase, 75.5 in the delayed phase, and 71.4 overall, compared with 78.2 in the acute phase, 62.8 in the delayed phase, and 62.7 overall in patients on the FOD regimen.
Limitations This study was limited by its retrospective, nonrandomized design, and short follow-up period. This study did not assess adverse effects from the antiemetic regimens.
Conclusions A modified olanzapine regimen is noninferior to a standard fosaprepitant regimen in regard to CR in showing improved control of CINV. In addition, the use of the olanzapine regimen reduces patient exposure to corticosteroids and the risk of associated side effects, and it is significantly more cost effective, compared with the fosaprepitant regimen.

Many patients with cancer receive treatment with highly emetogenic chemotherapy (HEC). Nausea is a serious adverse effect that is anticipated and can lead to emesis, which can impair performance status.[1] The National Comprehensive Cancer Network guidelines for antiemesis recommend 3 regimens based on aprepitant, fosaprepitant, or olanzapine in conjunction with a 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist and corticosteroid.[1] Previous studies have compared olanzapine and aprepitant in conjunction with palonosetron and dexamethasone.[2] At Kaiser Permanente Antioch and Walnut Creek, olanzapine and fosaprepitant are used in conjunction with ondansetron and dexamethasone. The olanzapine, ondansetron, and dexamethasone (OOD) regimen was implemented at the 2 centers in August of 2012. Prior to that implementation, a fosaprepitant, ondansetron, and dexamethasone (FOD) regimen had been used.

Although studies comparing palonosetron with ondansetron have concluded that palonosetron is superior in the delayed phase of nausea, a single dose of ondansetron on Day 1 may not be the best comparison because its half-life is shorter than that of palonosetron.[3] Palonosetron is only available as a brand medication and is not cost effective for many facilities. One study comparing 4 doses of dexamethasone found that a 20-mg dose is more effective in controlling CINV than a 12-mg dose, but the difference was not statistically significant.[4] Dexamethasone has known adverse effects including insomnia, hyperglycemia, and immunosuppression and limiting its use may result in improved outcomes for oncology patients.[5] From these studies, modifications to the olanzapine regimen include substitution of palonosetron with ondansetron, continued until Day 4, and a reduction of dexamethasone on Day 1 from 20 mg to 12 mg. At the Antioch and Walnut Creek centers, oncology pharmacists manage supportive care regimens that include selection and prescribing of antiemetics under protocol.

All patients on HEC receive the OOD regimen unless olanzapine is not tolerated or contraindicated as determined by the pharmacist, in which case the FOD regimen is used. The objective of this study is to determine if a modified olanzapine regimen is noninferior to a standard fosaprepitant regimen in preventing CINV and justify use of this new, cost-effective regimen that reduces patient exposure to corticosteroids.

Methods

Patient selection
Patients at the 2 centers were included in the study if they received HEC – defined as cisplatin ≥50 mg/m^2 or cyclophosphamide ≥500 mg/m^2 and doxorubicin ≥50 mg/m^2 as per the American Society of Clinical Oncology guidelines – and were treated with the OOD or FOD regimen during the delineated time periods. Patients in the OOD arm received treatment during August 1, 2012-December 31, 2013, and patients in the FOD arm received treatment during August 1, 2011-July 31, 2012. The cut-off for the OOD arm was originally July 31, 2013, but was extended because of an insufficient sample size to achieve power.

Study design and treatment regimen
This study was a retrospective cohort study testing for noninferiority of a modified olanzapine regimen to a standard fosaprepitant regimen. The FOD and OOD treatment regimens are shown in Tables 1 and 2, respectively. The primary endpoint was complete response (CR), defined as no

emesis after Cycle 1. The secondary endpoint was no report of nausea after Cycle 1. A cost analysis was also conducted.

Assessment procedures
Patients at the 2 centers are followed up with a phone call from one of our clinic nurses within 24-72 hours after the last dose of chemotherapy of Cycle 1, and an assessment of CINV in the patient's electronic medical record (EMR) is documented. This follow-up assessment was used to capture data for the acute phase of CINV, defined as nausea or vomiting within the first 24 hours after chemotherapy. The primary and secondary endpoints were binary – any documentation of the presence of nausea or vomiting was considered treatment failure. To capture any reports of CINV in the delayed phase, documentation from all office visits, telephone encounters, or patient secure messages in the patients EMR were evaluated. Patients were excluded if they had documented nausea or vomiting within 24 hours before receiving chemotherapy or if there was no documentation of CINV assessment in the EMR.

Statistical methods
It was determined that if there was a true difference of 4% in favor of the experimental treatment (based on outcomes of a randomized phase 3 trial[2]), then 130 patients would be required to be 80% sure that the upper limit of a 1-sided 95% confidence interval (CI) will exclude a difference in favor of the standard group of more than 15%. The 15% tolerance limit was selected to mirror that of the randomized phase 3 trial.[2]

TABLE 1 Fosaprepitant, ondansetron, dexamethasone (FOD) treatment regimen

Drug	Day 1	Day 2	Day 3	Day 4
Fosaprepitant	150 mg IV	-	-	-
Ondansetron	16-24 mg PO or 8-16 mg IV	8 mg PO BID	8 mg PO BID	8 mg PO BID
Dexamethasone	12 mg PO or IV	8-16 mg PO	8-16 mg PO	8-16 mg PO
Prochlorperazine or metoclopramide	As needed	As needed	As needed	As needed

BID, twice a day; IV, intravenously; PO, by mouth

TABLE 2 Olanzapine, ondansetron, dexamethasone (OOD) treatment regimen

Drug	Day 1	Day 2	Day 3	Day 4
Olanzapine	10 mg PO	10 mg PO	10 mg PO	10 mg
Ondansetron	16-24 mg PO or 8-16 mg IV	8 mg PO BID	8 mg PO BID	8 mg PO BID
Dexamethasone	12 mg PO or IV	-	-	-
Prochlorperazine	As needed	As needed	As needed	As needed

BID, twice a day; IV, intravenously; PO, by mouth

A 1-sided confidence interval was selected because the value of interest was the lower limit to determine noninferiority and not superiority. Statistical Analysis System (SAS) was used to test for noninferiority of 2 proportions, and a 95% CI was determined for the difference between 2 proportions for the primary and secondary outcomes.

Results

Ninety-five patients who received fosaprepitant were assessed for eligibility, and 17 patients were excluded. Of those patients who were excluded, 7 did not receive the specified HEC, 7 had nausea within 24 hours prior to treatment, 1 had no documented assessment of CINV, 1 died before follow-up, and 1 was already on daily dexamethasone for spinal cord compression prior to treatment. Eighty-seven patients who received olanzapine were assessed for eligibility, and 17 patients were excluded. Of those patients who were excluded, 4 did not receive the specified HEC, 6 received additional doses of dexamethasone, 3 also received fosaprepitant, and 4 had nausea within 24 hours prior to treatment. In all, 78 patients were included in the FOD arm and 70 were included in the OOD arm. The sample sizes in each arm met the specified power requirements.

Patient characteristics

Demographic data and patient characteristics are presented in Table 3. Risk factors for CINV including age, gender, type of chemotherapy, and use of radiation were assessed. There were no statistically significant differences between the 2 treatment arms.

Efficacy parameters

The CR for the acute phase, delayed phase, and overall phase in the FOD and OOD treatment arms are shown in Figure 1. The difference between the treatment arms was 3% (95% CI, -0.03, 0.11) in the acute phase, 4.6% (95% CI, -0.05, 0.14) in the delayed phase, and 3.2% (95% CI, -0.07, 0.13) overall. The percentage of patients reporting no nausea for the acute, delayed, and overall phases in the FOD and OOD treatment arms are shown in Figure 2. The difference between the treatment arms was 8.9% (95% CI, -0.04, 0.21) in the acute phase, 12.9% (95% CI, -.02, 0.27) in the delayed phase, and 8.6% (95% CI, -0.07, 0.23) overall. For the primary and secondary outcomes, a noninferiority analysis for the differences in proportions with a prespecified tolerance of 15% was statistically significant ($P < .001$) for all phases. By rejecting the null hypothesis that the OOD regimen is not noninferior to the FOD regimen, we accept the alternative, which is that the OOD regimen is noninferior to the FOD regimen. In addition, the 95% CIs for the differences between the 2 regimens in both the primary and secondary outcomes did not cross the noninferiority limit of 15%.

TABLE 3 Demographic data and patient characteristics

Characteristic	FOD	OOD	P value
Patients, n	78	70	–
Average age, y (range)	58.53 (21-81)	58.4 (33-77)	0.970 –
Female, n (%)	49 (63)	45 (64)	0.853
Cisplatin ≥50 mg/m^2, n (%)	52 (67)	38 (54)	0.292
Doxorubicin ≥50 mg/m^2 and cyclophosphamide ≥500 mg/m^2, n (%)	26 (33)	32 (45)	0.123
Radiation, n (%)	27 (35)	17 (24)	0.170

FOD, fosaprepitant, ondansetron, dexamethasone; OOD, olanzapine, ondansetron, dexamethasone
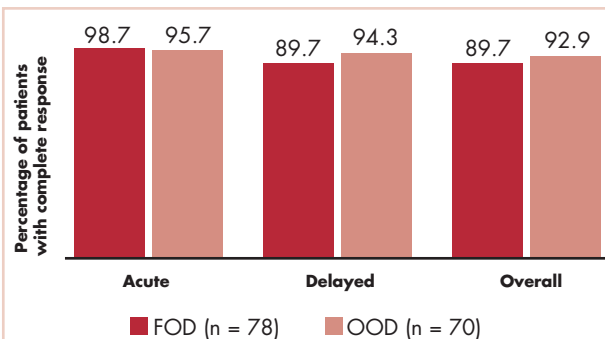

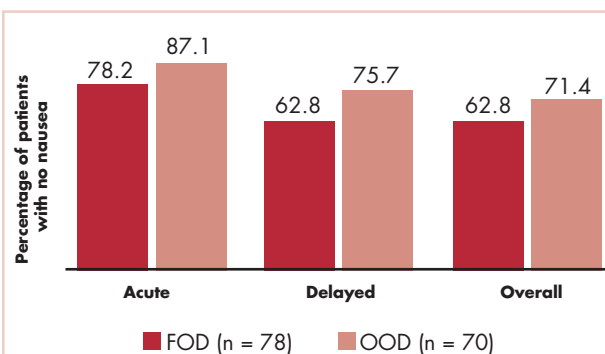**FIGURE 1** FOD vs OOD: percentage of patients with complete response.

FIGURE 2 FOD vs OOD: percentage of patients with no nausea.

Cost

Comparing wholesale acquisition cost (WAC) from Redbook for medications in each regimen, the OOD regimen is less than 4% of the cost of the FOD regimen ($8.58 vs $265.59), and about 2% of the cost of the standard olanzapine, palonosetron, dexamethazone (OPD) regimen ($8.58 vs $420.26) per patient for 1 cycle of chemotherapy.[6]

Discussion

A key difference between this study and previous studies is that in this study patients were prescribed antiemetics for breakthrough CINV and the therapies were readily available to the patient.[1] Options for breakthrough in the FOD arm included prochlorperazine and metoclopramide. Only prochlorperazine was given to patients receiving the OOD regimen because of the risk of extrapyramidal side effects when adding the antidopaminergic activity of metoclopramide to that of olanzapine. No documentation of the use of breakthrough medication was made so the endpoints of no nausea and no vomiting may have been helped by prochlorperazine and/or metoclopramide; however, this treatment scenario reflects what would occur in a real clinic-based setting where patients are able to self-manage breakthrough nausea.

Because this is a retrospective study, determination of the outcomes relied on thorough documentation. A limitation to this study is the variability between providers making the assessment with the patient as well as their interpretation and documentation practices. However, the nurse assessment at 24-72 hours consistently documented whether or not the patient reported nausea or vomiting when asked. Only 1 patient was excluded for lack of documentation, and we did not assume that no documentation equated to a complete response. Nausea is a subjective outcome, but we did not use a scale to determine grade of nausea because any complaint of nausea was categorized as treatment failure.

This study was limited by its short follow-up of 1 cycle and the study did not assess adverse effects, However, a randomized phase 3 trial followed patients for up to 6 cycles of HEC and found that there were no significant changes between an OPD regimen and an aprepitant, palonosetron, dexamethasone regimen, and no grade 3 or 4 toxicities.[2] Significant side effects noted in the OPD arm were problems remembering, drowsiness, and dry mouth which increased over days in some individual cycles but did not increase with additional cycles.

This study found that olanzapine in combination with a single oral dose of dexamethasone 12 mg and repeat dosing of ondansetron was very effective in controlling acute and delayed CINV in patients receiving HEC. The results demonstrate that the modified olanzapine regimen was as effective as a standard regimen consisting of fosaprepitant, ondansetron, and dexamethasone within the Kaiser Permanente Diablo Service Area. When focusing on nausea, which is more difficult to control in the delayed phase, the modified olanzapine regimen resulted in improved outcomes over the fosaprepitant regimen. The trend of results is consistent with the findings of previous studies, with more patients achieving a complete response and having no nausea when using olanzapine. The results of this retrospective study indicate that further randomized trials should be conducted to confirm these results.

The benefits of the OOD regimen over the FOD regimen include improved control of CINV, a reduction of dexamethasone use, reduction in infusion time since all medications are administered orally and are available as orally disintegrating tablets, and significant cost avoidance. The study period for the OOD regimen included patients up to January 1, 2014 which was when the 2 centers added acupuncture referrals in addition to the OOD regimen to control CINV in patients who were receiving HEC. This OOD with acupuncture regimen may be the subject of future investigations.

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