# Use of Low Dose Olanzapine for the Control of Nausea and Vomiting in Patients Receiving Highly Emetogenic Chemotherapy in a Rural Medical College in Etawah District, Uttar Pradesh, India

Kailash Kumar Mittal[1], Parveen Mendiratta[2], Nishu Bala[3]

[1]Department of Radiation Oncology, Uttar Pradesh University of Medical Sciences, Etawah, Uttar Pradesh, India.
[2]Department of Oncosurgery, Uttar Pradesh University of Medical Sciences, Etawah, Uttar Pradesh, India.
[3]Department of Radio-diagnosis, Uttar Pradesh University of Medical Sciences, Etawah, Uttar Pradesh, India.

**ABSTRACT**

**BACKGROUND**

Chemotherapy-induced nausea and vomiting (CINV) is a frequent and feared adverse effect of cancer chemotherapy. International guidelines recommend combinations of 5-hydroxytryptamine type 3 (5-$HT_3$) receptor antagonists, dexamethasone, and/or neurokinin-1 ($NK_1$) receptor antagonists for the control of CINV in patients receiving highly emetogenic chemotherapy (HEC) as a part of their treatment. Even though, nausea in delayed period is less controlled and poses a major concern for these patients.

**METHODS**

This open label, prospective study was conducted in a rural medical college in Etawah District in Uttar Pradesh, India from November 2017 to November 2018 over a period of 1 year to observe the efficacy of low dose (5 mg OD) olanzapine in combination with standard anti-emetic regimen for the prevention of CINV. Olanzapine is a food and drug administration (FDA) approved antipsychotic drug that has anti-emetic activity and has shown to improve CINV. Low dose olanzapine along with a standard combination of ondansetron, dexamethasone and aprepitant was given to patients receiving highly emetogenic chemotherapy (Cisplatin >70 mg/m2 or doxorubicin-cyclophosphamide combination). CINV was assessed using common toxicity criteria of adverse events (CTCAE) version 5.0.

**RESULTS**

Complete response to nausea was observed in 90.90 %, 60.60 % and 54.54 % in acute, delayed and overall period respectively. Complete response to vomiting was observed in 96.96 %, 69.69 % and 66.66 % in acute, delayed and overall period respectively. Complete response to Grade-2 (or above) nausea was observed in 96.96 %, 93.93 % and 90.90 % in acute, delayed and overall period, respectively. Daytime Grade -3 somnolence which was seen in 2/33 patients (6.06 %) was attributable to olanzapine. Patients receiving olanzapine were more likely to have complete response of nausea and emesis in the early, late, and overall assessment periods especially of higher grade (G2 and G3).

**CONCLUSIONS**

The authors concluded that low dose olanzapine 5 mg OD combined with an $NK_1$-receptor antagonist, a 5-$HT_3$–receptor antagonist, and dexamethasone is safe and efficacious in the prevention of CINV in patients receiving HEC.

**KEYWORDS**

Olanzapine, Low Dose, CINV, HEC

*Corresponding Author:*
*Dr. Parveen Mendiratta,*
*Assistant Professor,*
*Department of Oncosurgery*
*Uttar Pradesh University of Medical Sciences, Saifai, Etawah - 206130,*
*Uttar Pradesh, India.*
*E-mail: oncologydeptt@yahoo.com*

*DOI: 10.18410/jebmh/2021/584*

*How to Cite This Article:*
*Mittal KK, Mendiratta P, Bala N. Use of low dose olanzapine for the control of nausea and vomiting in patients receiving highly emetogenic chemotherapy in a rural medical college in Etawah District, Uttar Pradesh, India. J Evid Based Med Healthc 2021;8(34):3211-3216. DOI: 10.18410/jebmh/2021/584*

*Submission 22-06-2021,*
*Peer Review 28-06-2021,*
*Acceptance 26-07-2021,*
*Published 23-08-2021.*

## BACKGROUND

Chemotherapy induced nausea and vomiting is a frequent and feared side effect of anti-neoplastic chemotherapy. CINV may impact the quality of life, completion and outcome of cancer chemotherapy. Without prophylaxis, more than 90 % of patients who receive highly emetic chemotherapy endure CINV. Up to two thirds of patients experience CINV despite standard prophylaxis with anti-emetics.[1]

The concomitant administration of a combination of 5-hydroxytryptamine type 3 (5-$HT_3$) receptor antagonists, dexamethasone, and/or neurokinin-1 ($NK_1$) receptor antagonists has significantly improved the control of CINV in patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) over a 120-h period following chemotherapy administration.[2,3]

International guidelines recommend combinations of these agents to prevent chemotherapy-induced nausea and vomiting in patients receiving moderately or highly emetogenic chemotherapy. Although emesis has been improved in the acute period with the use of the 5-$HT_3$ receptor antagonists and in the delayed period with the use of the NK-1 receptor antagonists, many of these studies have measured nausea as a secondary endpoint and have demonstrated that nausea has not been well controlled. Even though, nausea remains a major problem for many patients.[4]

Clinical trials have demonstrated that with the use of guideline-directed prophylactic antiemetics, in patients receiving HEC or MEC, the control of emesis and nausea is 65 – 75 % and 35 – 50 %, respectively, over the 120-h period post-chemotherapy. Dexamethasone and aprepitant are not very effective anti-nausea agents and that nausea remains a persistent patient issue.[5]

Over the last few years, there has been a growing interest in the use of Olanzapine for control of CINV. Olanzapine may have significant potential in controlling nausea.[6]

Earliest studies of use of olanzapine in CINV as early as 2000s opened the drug for further evaluation.[7] Data from RCTs support the use of an olanzapine containing combination regimen as an option for CINV prophylaxis and single agent olanzapine for the treatment of breakthrough CINV. The currently recommended dose of olanzapine for this off-label use in CINV is 10 mg which causes daytime sedation.[4,6]

It was therefore very intriguing to evaluate the efficacy of a cheap cost and easily available drug low dose olanzapine (5 mg) in Indian rural setting to control CINV without or less sedation.

The primary objective of the current trial was to assess the efficacy of low dose olanzapine along with standard triplet anti-emetic combination for preventing CINV in patients receiving highly emetogenic cancer chemotherapy, with CINV prevention assessed during three periods. The secondary objective was to assess the intensity of CINV in all three periods and any major adverse effects.

### The Primary End Points Were

1. To record the efficacy in terms of complete response of vomiting (No vomiting, no rescue therapy) in early, delayed and overall period.
2. To record the efficacy in terms of complete response of nausea (No nausea, no rescue therapy) in early, delayed and overall period.

### The Secondary End Points Were

1. To record different grades of CINV in all three periods
2. To records major adverse effects with different grades

Early (Acute): 0 - 24 hours (Day 1), Delayed (Late): 25 - 120 hours (Day 2 - 4), and Overall: 0 - 120 hours (Day 1-5), post chemotherapy. Complete response (No nausea, no emesis and no rescue therapy) was recorded in the three periods, as well as the daytime somnolence and any other significant side effect (if any).

## METHODS

The open label, prospective, single arm observational study was conducted on randomly selected thirty-three histopathological proven cancer patients who attended the Department of Radiation Oncology, UPUMS, Saifai, Etawah (Uttar Pradesh), India over a period of 1 year from November 2017 to November 2018 for purpose of treatment. Informed written consent was obtained from all eligible patients. CINV assessment in these patients was done for only first chemotherapy cycle. Rescue therapy was given as per the discretion of the treating consultant in the setting of severe breakthrough vomiting, nausea, or troublesome retching, depending on the setting. The study was approved by the Institutional Ethical Committee.

### All Participants Received Anti-Emetic Therapy as Below

Inj. Ondansetron 8 mg intravenously (IV), pre and post chemotherapy on Day 1
Inj. Dexamethasone 16 mg IV, pre chemotherapy on Day 1
Cap. Aprepitant 125 mg P.O. pre chemotherapy on Day 1 and 80 mg on day 2 and 3
Tab. Dexamethasone 4 mg P.O. BID on Day 2, 3 and 4
Tab. Olanzapine 5 mg P.O. OD on Day 1 to 4

### Inclusion Criteria

1. 18 years of age or older patients who had not received previous chemotherapy.
2. Patients who are to receive highly emetogenic cancer chemotherapy (i.e. cisplatin ≥ 70 mg/$m^2$ or a combination chemotherapy of doxorubicin > 60 mg/$m^2$ with cyclophosphamide > 600 mg/$m^2$),
3. Karnofsky performance status ≥ 70,
4. Normal complete haemogram, kidney and liver function tests.

### Exclusion Criteria

1. Pregnancy or lactating females.
2. History of allergy to ondansetron, or aprepitant.
3. Received any chemotherapy in last 3 weeks.
4. Multiday chemotherapy regimens, concurrent radiotherapy.
5. Existing nausea vomiting due to other reasons.
6. Any associated medical condition causing nausea/vomiting (e.g. renal, liver, central nervous system disease or heart disease).

### Data Collection and Statistical Analysis

All baseline demographic data and patients' characteristics were recorded. Patients or relatives were trained and asked to keep daily records of numbers of episodes of nausea, vomiting or retching (number/time/severity) and if the rescue therapy was used or not, from the first day of chemotherapy to day 5 (Day 1 - 5). Adverse events were graded according to the terminology and grading categories defined in the common terminology criteria for adverse events, version 5.0 (CTCAE V5.0).[8]

On Day 1, acute nausea and vomiting was recorded at the hospital, whilst the severity, timing and frequency of delayed nausea and vomiting (day 2 - 5) were recorded by the patient himself or the attendants at home. One of the patients' attendants or relatives were explained and trained about the details of identifying symptoms and recording in the format given in local language. They were given instructions to record the severity/frequency of emetic episodes on the given proforma. The proformas were collected when the patients visited the hospital for next cycle. Complete response (CR) was defined as patients not having any nausea and vomiting in acute (< 24 hours), delayed (24 - 120 hours) and overall period (0 - 120 hours). CR was also recorded for different grades of nausea and vomiting in the three periods. In addition, every day for 5 days, sedation and daytime somnolence were also recorded.

## RESULTS

### Demographic and Clinical Characteristics

Table - 1 shows the demographic data, disease and treatment profiles of the eligible patients. Around 60 % of the patients were male. Age range was 21 - 65 years with a mean of 56 years. The median KPS was 80. The most site of cancer was head & neck and lung followed by cancer of breast. All the patients received highly emetogenic chemotherapy with ¾ patients receiving cisplatin and rest ¼ doxorubicin plus cyclophosphamide.

### Outcome

Table - 2 shows the number of patients who reported different levels of nausea and vomiting in acute, delayed and overall period as per the CTCAE v5.0. Delayed and overall nausea was observed in 39.39 % and 45.45 % patients with only one patient experiencing severe (level 3 or higher) nausea. Delayed and overall vomiting was observed in 30.30 % and 33.33 % patients respectively with none having severe vomiting.

| Characteristics | Variation | Number | Percentages |
|---|---|---|---|
| Gender | Male | 19 | 57.57 % |
| | Female | 14 | 42.43 % |
| Age (years) | Range | 21-65 | |
| | Median | 56 | |
| Mean weight (Kg) | Male | 58 | |
| | Female | 49 | |
| Mean height (cm) | Male | 155 | |
| | Female | 167 | |
| Primary cancer site | Ca lung | 10 | 33.33 % |
| | Ca breast | 6 | 18.18 % |
| | Head neck cancer | 10 | 33.33 % |
| | Lymphoma | 2 | 6.66 % |
| | Ca gall bladder | 2 | 6.66 % |
| | Genito urinary cancer | 3 | 9.09 % |
| Chemotherapy regimen | Cisplatin (>70 mg/m2) | 25 | 75.75 % |
| | Doxorubicin-cyclophosphamide | 8 | 24.24 % |
| Performance status KPS | 70 | 10 | 33.33 % |
| | 80 | 18 | 54.54 % |
| | 90 | 5 | 15.15 % |

***Table 1. Patients Demographics (N = 33, 100 %)***

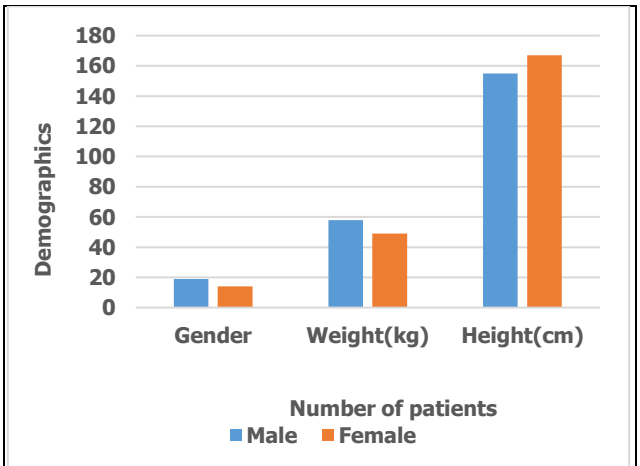


***Chart 1. Patients Demographics***

| CINV | Grades of Toxicity | Number of Patients | % |
|---|---|---|---|
| Acute nausea | G1 | 2 | 6.06 |
| | G2 | 1 | 3.03 |
| | **Total** | **3** | **9.09** |
| Acute vomiting | G1 | 1 | 3.03 |
| | **Total** | **1** | **3.03** |
| Delayed nausea | G1 | 10 | 30.30 |
| | G2 | 2 | 6.06 |
| | G3 | 1 | 3.03 |
| | **Total** | **13** | **39.39** |
| Delayed vomiting | G1 | 8 | 24.24 |
| | G2 | 2 | 6.06 |
| | **Total** | **10** | **30.30** |
| Overall nausea | G1 | 11 | 33.33 |
| | G2 | 3 | 9.09 |
| | G3 | 1 | 3.03 |
| | **Total** | **15** | **45.45** |
| Overall vomiting | G1 | 9 | 27.27 |
| | G2 | 2 | 6.06 |
| | **Total** | **11** | **33.33** |

***Table 2. Different Grades of Observed CINV in Study Patients (N = 33, 100 %)***

Table - 3 shows the complete response of olanzapine containing study regimen (Olanzapine plus Ondansetron, Aprepitant and Dexamethasone) of nausea and vomiting in acute, delayed and overall period with different levels of toxicity as well. Complete response to nausea was observed in 90.90 %, 60.60 % and 54.54 % in acute, delayed and overall period respectively. Complete response to vomiting was observed in 96.96 %, 69.69 % and 66.66 % in acute, delayed and overall period respectively. Complete response

to grade 2 (or above) nausea was observed in 96.96 %, 93.93 % and 90.90 % in acute, delayed and overall period, respectively. The CR in overall nausea was 54.54 % and with different grades was G1 - 66.66 %, G2 - 90.90 % and G3 - 96.96 % respectively, demonstrating an efficacy of low olanzapine in control of intensity of nausea in delayed and overall period.

| CINV | Grades of Toxicity | CR (%) |
|---|---|---|
| Acute nausea | G1 | 93.93 |
| | G2 | 96.96 |
| | G3 | 100.0 |
| | **Total** | **90.90** |
| Acute vomiting | G1 | 96.96 |
| | G2 | 100.0 |
| | **Total** | **96.96** |
| Delayed nausea | G1 | 69.69 |
| | G2 | 93.93 |
| | G3 | 96.96 |
| | **Total** | **60.60** |
| Delayed vomiting | G1 | 75.75 |
| | G2 | 93.93 |
| | G3 | 100 |
| | **Total** | **69.69** |
| Overall nausea | G1 | 66.6 |
| | G2 | 90.90 |
| | G3 | 96.96 |
| | **Total** | **54.54** |
| Overall vomiting | G1 | 72.72 |
| | G2 | 93.93 |
| | G3 | 100 |
| | **Total** | **66.66** |

***Table 3. Complete Response of CINV in Different Grades***

### Definition of Nausea According to CTCAE V 5.0[8]

G1: Loss of appetite without alteration in eating habits
G2: Oral intake decreased without significant weight loss, dehydration or malnutrition
G3: Inadequate oral caloric and/or fluid intake, IV fluids, tube feedings, or TPN indicated

### Definition of Vomiting According to CTCAE V 5.0[8]

G1: Intervention not indicated
G2: Outpatient IV hydration; medical intervention indicated
G3: Tube feeding, TPN, or hospitalization indicated
G4: Life-threatening consequences
G5: Death

Daytime Somnolence Grade 1 was reported in 23/33 (70 %) of patients and Grade 3 in 2/33 patients (6.06 %) which was attributable to olanzapine. One patient had grade 3 constipation. No grade 4 or 5 toxicities were observed.

## DISCUSSION

This single institution open label single arm interventional study showed that low dose olanzapine (5 mg) is efficacious when combined with a $NK_1$-receptor antagonist (Aprepitant), a 5-$HT_3$–receptor antagonist (Ondansetron), and dexamethasone for preventing nausea and vomiting in those patients who are currently receiving highly emetogenic chemotherapy. Patients receiving olanzapine were more likely to have complete response of nausea and emesis in the early, later, and overall assessment periods especially of higher grade (G2 and G3).

Other phase three trials have also suggested the benefit of olanzapine in preventing nausea and vomiting due to chemotherapy administration.[5,9] These trials showed that when olanzapine was added to guideline-directed prophylactic agents, nausea and emesis were significantly reduced. The efficacy of olanzapine for nausea control contrasts with the findings in clinical trials of $NK_1$-receptor antagonists. Although these agents (aprepitant, fosaprepitant, netupitant, and rolapitant) significantly controlled early and later emesis in patients receiving moderately or highly emetogenic chemotherapy. They appear to have been less effective in controlling nausea.[5,9]

Tan et al. reported use of olanzapine in his study and reported improved complete response in HEC in delayed and overall period. Delayed nausea improved by 39.21 % (i.e. 69.64 % versus 30.43 %, $P < 0.05$) and vomiting by 22.05 % (78.57 % versus 56.52 %, $P < 0.05$). Complete response for the whole period improved by: Nausea 41.38 % (69.64 % versus 28.26 %, $P < 0.05$) and vomiting by 22.05 % (78.57 % versus 56.52 %, $P < 0.05$). The results in our study were comparable with Tan et al. study for delayed nausea (60.60 % vs 69.64 %), delayed vomiting (69.69 % vs 78.57 %), overall nausea (54.54 % vs 69.64 %) and overall vomiting (66.66 % vs 78.57 %) in patients receiving HEC. CR of grade 2 nausea and vomiting in acute period was 96.96 vs 97.52 and 100 vs 99.17 respectively. CR of grade 2 nausea and vomiting in delayed period was 93.93 vs 94.21 and 93.93 vs 96.70 respectively.[10]

A randomized phase III trial compared olanzapine, palonosetron and dexamethasone to aprepitant, palonosetron, and dexamethasone in patients receiving HEC. The olanzapine regimen was significantly better than the aprepitant regimen in the control of nausea in the delayed and overall periods (no nausea, overall period: 69 % versus 55 % in our study olanzapine group; 38 % aprepitant group) suggesting that olanzapine is an effective agent for the control of nausea. The dose of olanzapine in our study was lower (5 mg vs 10 mg).[5]

The study done by Osman et al. included 131 patients (olanzapine-containing: 50 patients; ondansetron /dexamethasone: 81 patients). CR and nausea control were higher in the olanzapine-containing than in the ondansetron/dexamethasone regimen (CR: acute phase, 86 % v 71.6 %; $P = .086$; delayed phase, 72 % v 30.9 %; $P < .001$; overall phase, 66 % v 25.9 %; $P < .001$; nausea control: acute phase, 86 % v 74.1 %; $P = .127$; delayed phase, 76 % v 34.6 %; $P < .001$; overall phase, 72% v 29.6%; $P < .001$). The significant side effect of olanzapine was grade 1 and 2 sedation which was observed in 25 patients. This data is consistent with our study and hence olanzapine is helpful in nausea control.

This study showed the olanzapine-containing regimen to be slightly better with higher percentages of CR (in vomiting) and nausea control in the acute period as compared to the non-olanzapine regimen ($P > .05$); this was so because both arms used ondansetron and the 5-HT3 receptor antagonists are known to be effective in preventing acute emesis, because they block 5-HT3 i.e. serotonin, which is an

important neuro-mediator of acute vomiting and nausea. In the delayed period, the olanzapine-containing schedule was superior to the non–olanzapine schedule in CR (vomiting) and nausea control (P < .05); this effect is again due to the use of ondansetron. Thus, 5-HT3RA agents are not very effective in preventing delayed emesis, because it occurs via different mechanisms and involve neurotransmitters other than serotonin.[11] On the other hand, olanzapine has the property of blocking multiple receptor types involved in acute and delayed emesis, including dopamine and serotonin receptors.[11] The results in our study are in line with this study using olanzapine along with standard antiemetic regimen and shows that olanzapine is better in controlling CINV in delayed phase. Thus, we conclude that our study is comparable with the previous study.

Navari et al. conducted an analysis. In the study, he included three hundred eighty patients who were available to be evaluated (192 in olanzapine group, and 188 in placebo group).[12] Olanzapine group had higher proportion of patients without chemotherapy induced nausea than placebo group in the first 24 hours (early period) post chemotherapy (74 % versus 45 %, P = .002), the late period from 25 to 120 hours post chemotherapy (42 % versus 25 %, P = .002), and in the 120-hour overall period (37 % versus 22 %, P = .002). The complete response of (no vomiting and no rescue) rate was significantly higher in olanzapine group during all the three periods; 86 % vs. 65 %, 67 % vs. 52 % and 54 % vs. 41 %.[12] This is consistent with our study finding in which it is concluded that olanzapine is helpful in nausea control and complete response rate.

Study by Hocking et al. included four hundred eighty-eight (488) patients from three trials of olanzapine CINV prophylaxis and three hundred (323) patients from three trials of olanzapine in breakthrough settings.[6] Regimens including olanzapine were associated with significant improvements in CINV prevention with both HEC and MEC. Single agent olanzapine for break through nausea was superior to standard alternative option.[6] Hence olanzapine is efficacious in controlling CINV even in breakthrough setting.

Study by Bosnjak et al. has shown two phase III clinical studies which observed superior CINV efficacy of olanzapine as comparison to substance-P blocking neurokinin-1 receptor antagonists (aprepitant, fosaprepitant) in the prevention of nausea after highly emetogenic chemotherapy. He opined that olanzapine is inexpensive replacement of NK1RA and can significantly reduce the costs of CINV prevention, which is important in resource strained countries. The addition of olanzapine to aprepitant containing combination regimens for the prevention of CINV was also investigated, and has the potential to further improve the prevention of CINV after highly emetogenic chemotherapy or moderately emetogenic chemotherapy, without substantial increase in costs. In the treatment of uncontrolled ('breakthrough') CINV, olanzapine was more effective than metoclopramide.[13] This is consistent with our study.

Hashimoto et al. in his study used low dose 5 mg olanzapine along with standard anti-emetic regimen and reported a completed response of overall vomiting in 79 % versus 66.66 % in our study.[14] A comparison of results with other studies is presented in Table-4.

| Study | Complete Response (Nausea/Vomiting) | | |
|---|---|---|---|
| | Acute | Delayed | Overall |
| TAN et al. | 94.6 % / 91 % | 69.6 % / 78 % | 69.6 % / 78 % |
| Osman et al. | 86 % / 86 % | 76 % / 72 % | 72 % / 66 % |
| Navari et al. | 74 % / 86 % | 42 % / 67 % | 37 % / 54 % |
| This Study | 90.9 % / 96.9 % | 60.6 % / 79.59 % | 54.5 % / 66.7 % |

***Table 4. Comparison of CINV Control in All Periods***

Thus, clinical data shows that olanzapine can relieve a plethora of gastrointestinal symptoms in advanced cancer patients (chronic anorexia, nausea & vomiting).[13] Olanzapine is well tolerated and major dose-limiting adverse effect was sedation. Among the adverse events comparable grade 3 somnolence was reported by Navari et al. (5% vs 6% in our study) which is also as par with other studies.[12]

## CONCLUSIONS

In conclusion, our study showed that low dose olanzapine (5 mg OD) combined with an $NK_1$-receptor antagonist, a 5-$HT_3$–receptor antagonist, and dexamethasone is efficacious and safe for the prevention of nausea and vomiting in patients who are receiving highly emetogenic chemotherapy and results comparable to other studies were achieved. Olanzapine in low dose can provide a cheap alternative to prevalent schedules especially in a rural setting.

### Limitations of This Study

A limitation of our study is that it is a single arm study with few numbers of patients in a rural institution in India. Lower or higher doses may impact efficacy, adverse events, or both. We have not studied the efficacy of 5-mg olanzapine in multiple and multiday chemotherapy cycles. These potential issues should be addressed in future studies with high number of patients.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.

## REFERENCES

[1] Jordan K, Sippel C, Schmoll HJ. Guidelines for antiemetic treatment of chemotherapy-induced nausea and vomiting: past, present, and future recommendations. Oncologist 2007;12(9):1143–1150.
[2] Navari RM. Palonosetron for the prevention of chemotherapy-induced nausea and vomiting in patients with cancer. Future Oncol 2010;6(7):1074-84.
[3] Curran MP, Robinson DM. Aprepitant: a review of its use in the prevention of nausea and vomiting. Drugs 2009;69(13):1853-1878.
[4] Navari RM. Treatment of chemotherapy-induced nausea. Community Oncol 2012;9:20-26.

[5] Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol 2011;9(5):186-195.
[6] Hocking CM, Kichenadasse G. Olanzapine for chemotherapy-induced nausea and vomiting: a systematic review. Support Care Cancer 2014;22(4):1143-1151.
[7] Passik SD, Lundberg J, Kirsh KL, et al. A pilot exploration of the antiemetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. J Pain Symptom Manage 2002;23(6):526-532.
[8] Common terminology criteria for adverse events (CTCAE) version 5. US department of Health and Human Services, National Institute of health, National Cancer Institute. Published November 27, 2017.
[9] Mizukami N, Yamauchi M, Koike K, et al. 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 Manage 2014;47(3):542-550.
[10] Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for the prevention of chemotherapy-induced nausea and vomiting. J Exp Clin Cancer Res 2009;28(1):131.
[11] Gyawali B, Poudyal BS, Iddawela M. Cheaper options in the prevention of chemotherapy-induced nausea and vomiting. J Glob Oncol 2016;2(3):145-153.
[12] Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy induced nausea and vomiting. N Engl J Med 2016;375(2):134-142.
[13] Bosnjak SM, Dimitrijevic J, Djordjevic F. Cancer and chemotherapy-induced nausea and vomiting: a focus on olanzapine. Curr Opin Support Palliat Care 2016;10(2):180-188.
[14] Hashimoto H, Abe M, Tokuyama O, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21(2):242-249.