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Prevention Strategy of Chemotherapy-Induced Nausea and Vomiting (CINV) with Olanzapine: Alternative Option

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Abstract: Chemotherapy-induced nausea and vomiting (CINV) is a major problem for patients who use chemotherapy and can lower the quality of life for many cancer patients. If the patient is continuing chemotherapy treatment, then the patient can be certain to experience CINV. Current CINV prevention strategies primarily use 5-hydroxytryptamine-3 receptor antagonists (5HT3-RAs), dexamethasone, and/or neurokinin-1 receptor antagonists (NK-1 RAs). However, these preventive therapies have not been fully implemented, especially the use of NK-1 RAs because of the high cost. In addition, a standard therapy for CINV prevention is still not effective in controlling CINV symptoms. One alternative CINV preventive therapy option is to use olanzapine. It is an antipsychotic drug that can be used as a preventive therapy for CINV off-label. The purpose of this study is to explain the utilization of olanzapine as alternative choice of antiemetic therapy in preventing CINV.

Keywords: Chemotherapy, Nausea, Olanzapine, Prevention, Vomiting

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is one of the symptoms due to the use of chemotherapy which is characterized by nausea and vomiting. It will be able to affect adherence in undergoing chemotherapy and lower the quality of life of patients (Piko & Bassam, 2009; Burke et al., 2011; Russo et al., 2014). CINV is the leading cause of morbidity and the only significant predictor of decreased health of life for cancer patients undergoing chemotherapy (Molassiotis et al., 2008; Dinis et al., 2009; Hawkins & Grunberg, 2009; Perwitasari et al., 2011; Haiderali et al., 2011).

The pathophysiology of CINV begins when chemotherapy is given. Chemotherapy drugs or their metabolites activate neurotransmitter receptors in the chemoreceptor trigger zone (CTZ) (sending afferent impulses to the vomiting center), GI channels (via vagal afferent fibers to the vomiting center), or directly to the vomiting center (Chisholm-Burns et al., 2016). The main receptors involved in the emetic response are serotonin (5-hydroxytryptamine [5-HT3]) and NK1 receptors (Rao & Faso, 2012) (Figure 1). 5-HT3 receptors are associated with acute emesis through peripheral pathways. Acute emesis arises

within 24 hours after chemotherapy (Herrstedt et al., 2011; Kawecki & Krzakowski, 2018). Other receptors involved in emesis include acetylcholine, cannabinoid receptors, corticosteroids, dopamine, histamine, neurokinin-1 (NK1) and opioids, which are located in the vomit and vestibular center of the brain. The NK1 receptor is associated with delayed emesis through a central pathway. Delayed emesis occurs after one day of chemotherapy use and usually lasts until 5 days post-chemotherapy (Aapro et al., 2015; Adel, 2017). Some antiemetic agents can inhibit different neuronal pathways. When utilized at certain concentrations, every dominant antiemetic agent obstructs only one type of receptor. Olanzapine is known to have an antiemetic mechanism of action on many receptors involved in the emetic pathway (Chiu et al., 2016a).

Several meta-analysis studies report that olanzapine is alternative choice for preventing CINV (Chelkeba et al., 2017; Yang et al., 2017). Olanzapine also has efficacy similar to other classes of drugs such as aprepitant, so it can be considered for the prevention of cancer patients with nausea and vomiting (Yang et al., 2017). This study aims to explain the utilization of olanzapine as an antiemetic therapy option in preventing CINV and its safety.

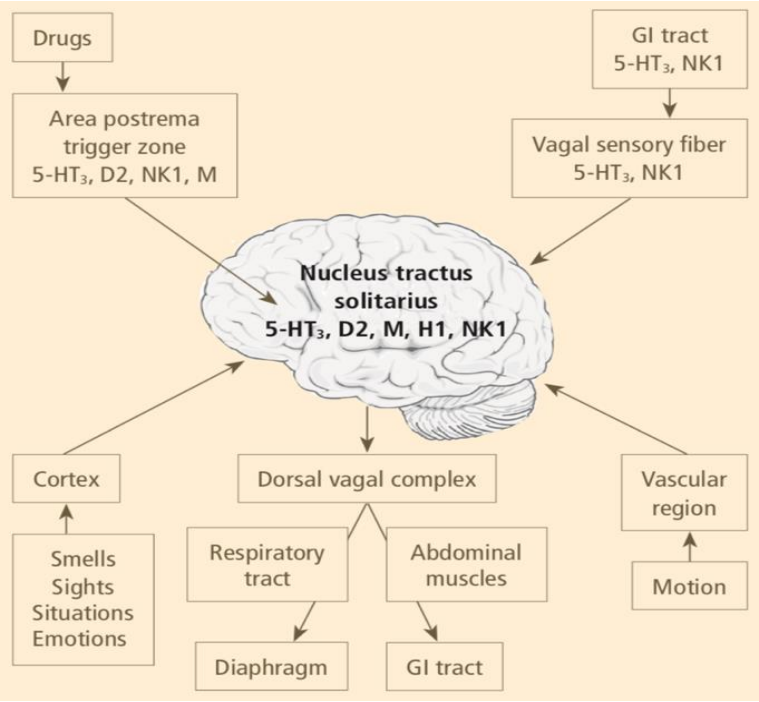

Figure 1. Pathophysiology of CINV (Hawkins & Grunberg, 2009)

OVERVIEW OF OLANZAPINE

Structure Characteristics and Pharmacology

Olanzapine is a second-generation antipsychotic drug compound with another name thienobenzodiazepine (Martel et al., 2016). These antipsychotics were introduced in the 90s and were widely spread because they had wider efficacy, especially in schizophrenia patients with negative symptoms, slight occurence of extrapyramidal effects, and minimal interactions with other drugs compared to previous generations (Malhotra et al., 2015). These antipsychotics have also been approved to treat patients with depressive episodes with bipolar disorder especially type 1. This drug has a very imminent similarity to first-generation such as clozapine and only differs from two extra metal truss and the lack of a chloride truss (Figure 2) (Schatzberg & Nemeroff, 2017).

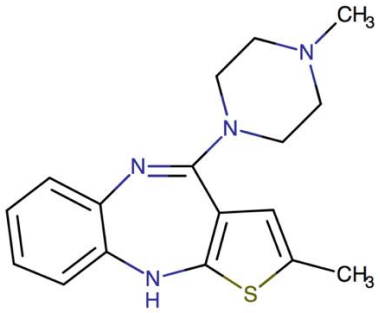

Figure 2. The chemical structure olanzapine

Olanzapine is one of the atypical antipsychotic drugs that plays a role in inhibiting dopaminergic receptors D1, D2, D3, D4, 5-HT2A, 5-HT2C, 5-HT3, and 5-HT6 receptors and muscarinic acetylcholine receptors M1, M2, M3, M4, M5, and M6 (Brafford & Glode, 2014; Hocking & Kichenadasse, 2014; Navari, 2014). The effects of olanzapine on D2 receptors, 5-HT3 receptors, and 5-HT2C receptors are known to play a significant role for inhibiting the effects of CINV or controlling CINV symptoms (Bymaster et al., 1996; Srivastava et al., 2003; Licup & Baumrucker, 2010; Chiu et al., 2016; Chelkeba et al., 2017; Al-Quteimat et al., 2019). Figure 3 shows the mechanism of action of olanzapine in preventing and controlling CINV.

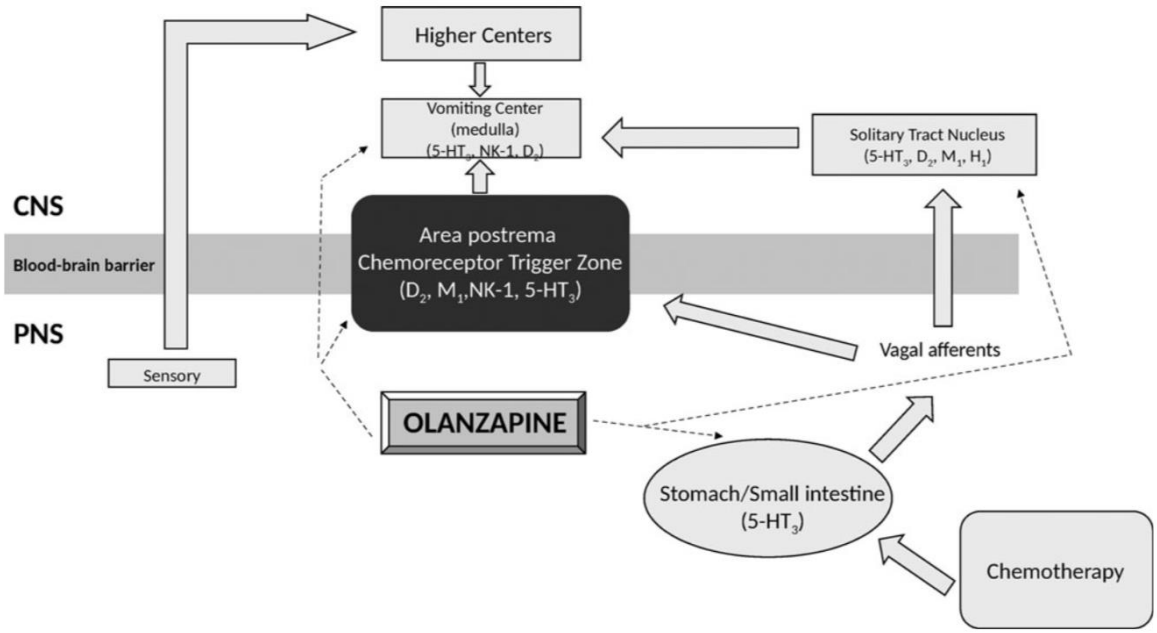

Figure 3. Action mechanism of olanzapine for prevention CINV (DeRemer et al., 2016)

Pharmacokinetics

Olanzapine has a linear and dose-proportional pharmacokinetic profile throughout the clinical dose range. After administering the drug every day, it can reach a steady-state state within a week (Callaghan et al., 1999). Under normal olanzapine doses, stable plasma concentration is not appear to get beyond 150 ng/ml together with area under curve of 333 ng/h/ml (Chue & Singer, 2003).

Olanzapine absorption is not affected by simultaneous feeding. The bioavailability of oral olanzapine is 60% (Table 1) (Kassahun et al., 1997). The pharmacokinetic profile of its is signified by achieving a high plasma concentration of 156.9 ng/ml about six hours after

orally use. Its distribution volume is notified to be 1000 liters which indicates a major distribution thru the body. Olanzapine is mostly bound to plasma proteins. Plasma proteins for binding are albumin (90%) and alpha-1 glycoprotein acid (77%) (Callaghan et al., 1999).

Table 1: Pharmacokinetics profile of olanzapine (Callaghan et al., 1999; Schatzberg & Nemeroff, 2017)

Pharmacological Properties	PK Parameters
Absorption	Tmax, oral: 6 hours Bioavailability, oral: Well-absorbed with first-pass metabolism (60%) Effects of food: No affect on the rate or extent of absorption
Distribution	Protein binding: albumin (90%), alpha 1-acid glycoprotein (77%) Volume of distribution: 1000 L
Metabolism	Hepatic: Extensive Metabolite: 10-N-glucuronide, 4'-N-desmethyl olanzapine (inactive)
Excretion	Renal excretion: 57-60% changed; 7% Fecal excretion: 30% Renal clearance: 25 L/h Half-time: 21 to 54 hours

Olanzapine is widely metabolized in the liver, especially by the activity of the glucuronide enzyme. This drug is also metabolized by the CYP system (mainly with CYP1A2 and CYP2D6) (Na Takuathung et al., 2019). About 50-60% of phase I metabolism, the main metabolites of olanzapine are 4'-N-desmethyl and 10-N-glucuronide which are formed by CYP1A2 activity and are clinically inactive. Otherwise, CYP2D6 catalyzes the formation of flavin-containing monooxygenase and 2-hydroxide responsible for N-oxide of olanzapine. In phase II olanzapine metabolism, UGT1A4 is an important gene by producing conjugation form of olanzapine directly (Callaghan et al., 1999).

Olanzapine has a half-life ranging from 21 to 54 hours with an average half-life of 30 hours. Most olanzapine is excreted through urine in the form of metabolites around 57-60%. Only 7% of the drug removed can be found as an unchanging form. Whereas 30% are excreted through feces (Prommer, 2013; Mauri et al., 2018). The average clearance rate of olanzapine is 29.4 L/hr, however, several studies have found the clearance level about 25 L/hr (Schatzberg & Nemeroff, 2017).

EFFICACY AND SAFETY OF OLANZAPINE:

Several studies regarding the addition of olanzapine to standard antiemetic regimens have been studied previously (Table 2). Passik et al (2004) state that olanzapine has effectiveness against delayed emesis caused by high or moderate emetogenic chemotherapy (Passik et al., 2004). According to Tan et al (2009), administration of olanzapine 10 mg/day for 5 days is known to increase complete response (CR) of delayed nausea and vomiting in patients receiving highly or moderately emetogenic chemotherapy combined with azacetron and dexamethasone compared to standard therapy antiemetics without using olanzapine, as well as improving the quality of life of cancer patients which is significantly seen in emotional function, insomnia, and loss of appetite that improves during chemotherapy. The most frequent side effect is drowsiness which can effectively relieve insomnia and agitation caused by dexamethasone. No serious side effects during olanzapine administration were reported (Tan et al., 2009). Lv et al (2013) mentioned that olanzapine 5 mg/day can increase CR in acute CINV. Side effects can still be well tolerated (Lv et al., 2013). Two other studies found that the incidence of acute and delayed vomiting was significantly lower in patients given a combination of olanzapine, dexamethasone, and ondansetron compared to the group without olanzapine (Wang et al., 2015; Wang et al., 2018). Similar results were obtained by Meng et al (2016) and James et al (2017) that olanzapine has the effectiveness of both acute

and delayed CINV in patients given highly and moderately emetogenic chemotherapy. There are no reports of serious side effects (Meng et al., 2016; James et al., 2017). Two other studies found that CR in the group given olanzapine was better when compared to the control group without using olanzapine. Both of these studies favored olanzapine to be superior to delayed CINV compared with acute CINV. Side effects associated with the use of olanzapine are sedation, somnolence, and loose motion, tremor. But side effects between groups were not significant (Mukhopadhyay et al., 2016; Osman et al., 2018). No patient stopped using olanzapine because of sedation or had life-threatening consequences (grade 4 toxicity) (Osman et al., 2018). A recent report found that olanzapine has the ability to prevent acute and delayed CINV better than standard antiemetic regimens without olanzapine administration (Yeo et al., 2020).

Most studies have found that olanzapine has a good effectiveness in preventing CINV symptoms when compared to placebo (Table 3 and Table 4). A randomized controlled trial study conducted by Mizukami et al (2014) in Japan reported that oral administration of olanzapine at a dose of 5 mg/day added to standard antiemetic therapies (such as dexamethasone, 5HT3-RAs, and aprepitant) can reduce the frequency of delayed CINV and improve the quality of life of patients receiving highly or moderately emetogenic chemotherapy. Sleepiness is a side effect found. There were no serious side effects, including extrapyramidal symptoms (Mizukami et al., 2014). Three other studies report that the combination of olanzapine 10 mg with three other antiemetics (dexamethasone, 5HT3-RAs, and NK-1 RAs) significantly increases the prevention of nausea and CR in the acute and delayed phases when compared with placebo in patients given highly emetogenic chemotherapy . The side effect of olanzapine found was sedation (severe at 5%) which was significantly different from placebo on the second day. However, no patients stopped the study because of unwanted sedation (Navari et al., 2016a; Clemmons et al., 2018; Saldanha et al., 2019). Jeon et al (2019) mentioned that CR did not differ significantly between the groups that were intervened by olanzapine and those given the placebo. However, patients who experience nausea are found to have fewer olanzapine regimens. In addition, the olanzapine group showed a better quality of life (Jeon et al., 2019). Another study conducted by Tienchaiananda et al (2019) revealed that 10 mg of olanzapine combined with ondansetron and dexamethasone was more effective than placebo in preventing acute CINV. Sleepiness was significantly more common in the group given olanzapine. No serious side effects were reported (Tienchaiananda et al., 2019).

Recent research shows that administration of olanzapine 5 mg in the standard antiemetic regimen (5HT3-RAs, dexamethasone, and aprepitant) can prevent CINV in patients given highly emetogenic chemotherapy (Abe et al., 2015; Nakashima et al., 2017; Hashimoto et al., 2020; Iihara et al., 2020). Adding a dose of olanzapine 5 mg or 10 mg to the standard antiemetic regimen (5HT3-RAs and dexamethasone) can both prevent CINV (Mukhopadhyay et al., 2017; Yanai et al., 2018). There was no significant difference between the 5 mg and 10 mg doses. However, the incidence of somnolence is lower when administering olanzapine at a dose of 5 mg (Yanai et al., 2018). A retrospective study conducted by Chiu et al (2016b) on olanzapine as a prophylactic and rescue CINV suggests that olanzapine 2.5 mg is also recommended to prevent CINV (Chiu et al., 2016b). However, most studies prefer dosages of 5 to 10 mg to be used in preventing CINV.

Phase II clinical studies conducted by Navari et al (2007) reported that the combination of olanzapine, dexamethasone, and palonosetron had CR in the acute, delayed, and similar overall phases among patients given highly emetogenic chemotherapy compared with moderately emetogenic chemotherapy. However, the number of patients experiencing delayed nausea on emetogenic chemotherapy is higher than that of moderately emetogenic chemotherapy (Navari et al., 2007).

Several studies on the comparison of olanzapine with other antiemetics, especially NK1-RAs, have been widely studied (Table 5 and Table 6). Shumway et al (2009) mentioned the group of patients given olanzapine was more effective in increasing CR in acute CINV when compared to the group that received aprepitant (Shumway et al., 2009). Phase III randomized studies followed by Navari et al (2011) show that olanzapine combined with dexamethasone and palonosetron can reduce the incidence of acute and delayed CINV in patients given highly emetogenic chemotherapy (Navari et al., 2011). CR levels were not significantly significant in the group of patients who received aprepitant, dexamethasone, and palonosetron (Navari et al., 2011; Shumway et al., 2015; Babu et al., 2016; Navari et al., 2016b). However, nausea is more effectively controlled by administering olanzapine regimens compared to regimens that use aprepitant (Navari et al., 2011; Navari et al., 2016b; Trifilio et al., 2017). Olanzapine is given orally in the form of tablets which dissolves quickly in the mouth, making it easy for patients to take it. In addition, olanzapine is cheaper than aprepitant, which is considered the most effective agent in treating CINV (Navari et al., 2011; Babu et al., 2016; Akshay & Basavanna, 2018; Chanthawong et al., 2019; Dhanushkodi, 2019) . Side effects found were sedation and sleepiness. Both studies reported no grade 3 or 4 toxicity or extrapyramidal symptoms, hyperglycemia, or weight gain (Navari et al., 2007; Navari et al., 2011; Babu et al., 2016).

A study conducted by Maeda et al (2016) reported that olanzapine combined with palonosetron and dexamethasone did not prevent CINV in patients induced by highly emetogenic chemotherapy (Maeda et al., 2016). According to the American Society of Clinical Oncology (2017) and the National Comprehensive Cancer Network (2020), the use of 3-drug or 4-drug regimens containing olanzapine may be the best alternative choice for patients who get HEC and MEC based on clinical trial data (Hesketh et al., 2017; NCCN, 2020). Olanzapine combined with dexamethasone and palonosetron is effective in preventing acute and delayed CINV (Passik et al., 2004; Navari et al., 2007; Tan et al., 2009; Navari et al., 2015; Chiu et al., 2016b) . The combination of olanzapine with dexamethasone, 5HT3-RAs, and NK-1 RAs has a superior effect for preventing acute and delayed CINV (Navari et al., 2016a; Tanaka et al., 2019).

Common side effects of olanzapine include orthostatic hypotension, fatigue, drowsiness, dry mouth, and dizziness (Muench & Hamer, 2010; Kaneishi et al., 2012; Alldredge et al., 2013; MacKintosh, 2016; Navari, 2016c; Katzung et al. , 2019). Olanzapine can also cause an increase in appetite that leads to hyperphagia with consequent weight gain (Kast & Foley, 2007; De Hert et al., 2012; Kasper et al., 2015; Hou et al., 2018). Therefore, the drug must be used with caution in obese patients (Meyer & Stahl, 2009; Huang et al., 2018). Another side effect of olanzapine is hyperglycemia which can be caused due to reduced insulin sensitivity (Li et al., 2018; Nicol et al., 2018). Olanzapine can also cause extrapyramidal symptoms. However, the risk of these side effects is lower than first generation antipsychotics due to rapid dissociation of olanzapine with D2 receptors (Carison et al., 2003; Papadakis et al., 2015; Whalen et al., 2015; Tollens et al., 2018). Olanzapine must also be used with caution in elderly patients (Morita et al., 2004). Elderly patients diagnosed with dementia with symptoms of psychosis should not be given olanzapine because of an increased risk of death (Kim et al., 2011).

SUMMARY:

Olanzapine is one of the latest antiemetic drugs and is considered an effective drug in preventing CINV in patients with highly and moderately emetogenic chemotherapy. In addition, olanzapine can also improve the quality of life of cancer patients who are routinely chemotherapy. The addition of this drug proved effective when combined with other class antiemetic agents. The most common side effect that occurs is somnolence. There are no

reports of SAE on short-term administration of olanzapine. However, further research is needed regarding the use of olanzapine which is associated with pharmacoeconomics when compared with other antiemetic combination therapies to control CINV.

ABBREVIATIONS

5HT, 5-hydroxytryptamine; APR, aprepitant; AZA, azasetron; bid, twice a day; CINV, chemotherapy-induced nausea and vomiting; CR, complete response; D, dopamine; DEX, dexamethasone; DHD, diphenhydramine; FOS, fosaprepitant; HEC, highly emetogenic chemotherapy; i.m., intramuscularly; i.v., intravenously; GRA, granisetron; MEC, moderate emetogenic chemotherapy; M, muscarinic; MP, methylprednisolone; N/A, not available; NK1, neurokinin-1; OLN, olanzapine; OND, ondansetron; p.o., orally; PAL, palonosetron; RAs, receptor antagonists; SAE, serious adverse effect; TRO, tropisetron.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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Table 2: Complete Response With Olanzapine Compared Without Olanzapine in The Acute, Delayed, and Overall Phase

Author	Population	Antiemetic Regimen	Complete Response			Safety
			Acute	Delayed	Overall	
Tan et al., 2009	n = 229; 18-74 yr received HEC or MEC	OLN 10 mg p.o. days 1-5 AZA 10 mg i.v day 1 DEX 10 mg i.v. day 1	AN w/o OLN: 86.96% (HEC) OLN: 94.64% (HEC) w/o OLN: 93.54% (MEC) OLN: 98.46% (MEC) AV w/o OLN: 89.13% (HEC) OLN: 91.07% (HEC) w/o OLN: 96.77% (MEC) OLN: 96.92% (MEC) p > 0.05 (all)	DN w/o OLN: 30.43% (HEC) OLN: 69.64% (HEC) w/o OLN: 58.06% (MEC) OLN: 83.07% (MEC) DV w/o OLN: 56.52% (HEC) OLN: 78.57% (HEC) w/o OLN: 75.80% (MEC) OLN: 89.23% (MEC) p < 0.05 (all)	NC w/o OLN: 28.26% (HEC) OLN: 69.64% (HEC) w/o OLN: 56.45% (MEC) OLN: 83.07% (MEC) VC w/o OLN: 56.52% (HEC) OLN: 78.57% (HEC) w/o OLN: 75.80 (MEC) OLN: 89.23% (MEC) p < 0.05 (all)	Somnolence no SAE
Lv et al., 2013	n = 60; 31-72 yr received HEC or MEC	OLN 2,5 mg bid or 5 mg p.o. day 1 DHD 20 mg i.m. day 1 DEX 5-10 mg i.v. day 1 TRO 5 mg i.v. day 1	w/o OLN: 36.7% OLN: 73.3% p < 0.05	N/A	N/A	Somnolence (not significant, p > 0.05) no SAE
Meng et al., 2016	n = 60; <60 yrs vs. ≥60 yrs received MEC or HEC	OLN 2,5 mg bid days 1-5 GRA 3 mg day 1 DEX 5 mg i.v. day 1	w/o OLN: 37.9% (HEC) OLN:48.5% (HEC) p = 0.01 (p < 0.05) w/o OLN: 45.2% (MEC) OLN: 63.0% (MEC) p = 0.008	w/o OLN: 20.7% (HEC) OLN: 35.5% (HEC) p = 0.04 (p < 0.05) w/o OLN: 22.6% (MEC) OLN: 37.0% (MEC) p = 0.02	N/A	Somnolence, fatigue no SAE
Mukhopadhyay et al., 2016	n = 100; ≥18 up to 80 yr received HEC	OLN 10 mg p.o days 1-5 PAL 0,25 mg i.v. day 1 DEX 8 mg i.v. day 1	w/o OLN: 94.4% (HEC) OLN: 97.2% (HEC) p = 0.5 w/o OLN: 92.9% (MEC) OLN: 100.0% (MEC) p > 0.9	w/o OLN: 38.9% (HEC) OLN: 94.4% (HEC) p < 0.0001 w/o OLN: 50% (MEC) OLN: 100.0% (MEC) p < 0.0001	w/o OLN: 36.1% (HEC) OLN: 91.7% (HEC) p < 0.0001 w/o OLN: 50% (MEC) OLN: 100.0% (MEC) p < 0.0001	Sedation, somnolence, tremor, loose motion (not significant, p > 0.02), No SAE
Osman et al., 2018	n = 131; 17-76 yr received MEC or HEC	OLN 10 mg p.o. days 1-4 (HEC) OLN 10 mg p.o. days 1-3 (MEC) OND 8-16 mg i.v. day 1 OND 8 mg bid p.o. days 1-5 DEX 8-16 mg i.v. day 1	w/o OLN: 71.6% OLN: 86.0% p = 0.086	w/o OLN: 30.9% OLN: 72.0% p < 0.01	w/o OLN: 25.9% OLN: 66% p < 0.01	Sedation (grade 1-3), somnolence (grade 1-2) No SAE
Yeo et al., 2020	n = 120; 32-71 yr received HEC	OLN 10 mg p.o. days 1-5 OND 8 mg p.o. or i.v. day 1 DEX 12 mg p.o. or i.v. day 1 APR 125 mg p.o. day 1 APR 80 mg p.o. days 2-3	Cycle 1 with higher rates w/o OLN: 51.7% OLN: 70.0% p = 0.0397 (p < 0.05)	Cycle 1 with higher rates w/o OLN: 74.2% OLN: 92.9% p = 0.0254 (p < 0.05)	Cycle 1 with higher rates w/o OLN: 38.3% OLN: 65.0% p = 0.0035 (p < 0.05)	Somnolence, fatigue, dizziness No SAE

AN, acute nausea; AV, acute vomiting; AZA, azasetron; bid, twice a day; DEX, dexamethasone; DHD, diphenhydramine; DN, delayed nausea; DV, delayed vomiting; GRA, granisetron; HEC, highly emetogenic chemotherapy; i.m, intramuscularly; i.v, intravenously; MEC, moderate emetogenic chemotherapy; N/A, not available; NC, nausea of whole period of chemotherapy; OLN, olanzapine; OND, ondansetron; p.o, orally; PAL, palonosetron; SAE, serious adverse effect; TRO, tropisetron; VC, vomiting of whole period of chemotherapy; w/o, without.

Table 3: Complete Response With Olanzapine Compared With Placebo in The Acute, Delayed, and Overall Phase

Author	Population	Antiemetic Regimen	Complete Response			Safety
			Acute	Delayed	Overall	
Mizukami et al., 2014	n = 44; 22-78 yr received HEC or MEC	OLN 5 mg p.o. days 0-5 DEX 9,9 mg i.v. day 1 DEX 6,6 mg i.v. days 2-4 APR 125 mg p.o day 1 APR 80 mg p.o days 2-3 5-HT_3 receptor antagonist day 1	Placebo: 86.0% OLN: 100.0% p = 0.233	Placebo: 73% OLN: 100.0% p = 0.021 (p < 0.05)	Placebo: 68.0% OLN: 100.0% p = 0.009 (p < 0.05)	Drowsiness No SAE
Navari et al., 2016 (nejm)	n = 380; 28-89 yr received HEC	OLN 10 mg p.o. days 1-4 DEX 12 mg p.o. day 1 DEX 8 mg p.o. days 2-4 5-HT_3 receptor antagonist day 1 NK1 receptor antagonist day 1-3	Placebo: 65.0% OLN: 86.0% p < 0.001 (p < 0.05)	Placebo: 52.0% OLN: 67.0% p = 0.007 (p < 0.05)	Placebo: 41.0% OLN: 64.0% p < 0.001 (p < 0.05)	Sedation (severe in 5%) on day 2 No SAE
Clemmons et al., 2018	n = 101; 22-74 yr received HEC	OLN 10 mg p.o. (on each day and 3 additional days after chemotherapy) OND 8-16 mg p.o. or i.v. DEX 8-20 mg p.o. or i.v. (on each day of chemotherapy) FOS 150 mg i.v. day 1 OND 8 mg p.o. DEX 4 mg p.o. (on days of total body irradiation)	Placebo: 62.0% OLN: 76% p = 0.13	Placebo: 30.0% OLN: 60.8% p = 0.001 (p < 0.05)	Placebo: 26.0% OLN: 55.0% p = 0.003 (p < 0.05)	N/A
Jeon et al., 2019	n = 56; 30-79 yr received MEC	OLN 10 mg p,o. days 1-5 PAL 0,25 mg i.v. day 1 DEX 12 mg i.v. day 1	Placebo: 88.0% OLN: 96.5% p = 0.326	Placebo: 48.0% OLN: 69.0% p = 0.118	Placebo: 48.0% OLN: 69.0% p = 0.118	Somnolence, fatigue No SAE
Tienchaiananda et al., 2019	n = 39; 27-67 yr received HEC	OLN 10 mg p.o. days 1-4 OND 8 mg i.v. day 1 DEX 20 mg i.v. day 1 DEX 10 mg p.o. days 1-4	Placebo: 36.8% OLN: 75.0% p = 0.016 (p < 0.05)	Placebo: 26.3% OLN: 50.0% p = 0.129	Placebo: 21,1% OLN: 50% p = 0.060	Somnolence (p < 0.001) No SAE
Hashimoto et al., 2020	n = 710; 22-75 yr received HEC	OLN 5 mg p.o days 1-4 DEX 12 mg i.v. or p.o. day 1 DEX 8 mg i.v. or p.o. days 2-4 PAL 0.75 mg i.v. day 1 NK1 receptor antagonist day 1-3	Placebo: 89.0% OLN: 95.0% p = 0.0021	Placebo: 66.0% OLN: 79.0% p < 0.0001	Placebo: 64.0% OLN: 78.0% p < 0.0001	Constipation, hiccups, somnolence, insomnia, dizziness, dry mouth No SAE

5HT3, 5-hydroxytryptamine-3; APR, aprepitant; DEX, dexamethasone; FOS, fosaprepitant; HEC, highly emetogenic chemotherapy; i.v., intravenously; MEC, moderate emetogenic chemotherapy; N/A, not available; NK1, neurokinin-1; OLN, olanzapine; OND, ondansetron; p.o., orally; PAL, palonosetron; SAE, serious adverse effect.

Table 4: Patients Without Nausea With Olanzapine Compared With Placebo in The Acute, Delayed, and Overall Phase

Author	Population	Antiemetic Regimen	Patients with Nausea			Safety
			Acute	Delayed	Overall	
Mizukami et al., 2014	n = 44; 22-78 yr received HEC or MEC	OLN 5 mg p.o. days 0-5 DEX 9,9 mg i.v. day 1 DEX 6,6 mg i.v. days 2-4 APR 125 mg p.o day 1 APR 80 mg p.o days 2-3 5-HT_3 receptor antagonist day 1	N/A	N/A	N/A	Drowsiness No SAE
Navari et al., 2016 (nejm)	n = 380; 28-89 yr received HEC	OLN 10 mg p.o. days 1-4 DEX 12 mg p.o. day 1 DEX 8 mg p.o. days 2-4 5-HT_3 receptor antagonist day 1 NK1 receptor antagonist day 1-3	Placebo: 45.0% OLN: 74.0% p = 0.002 (p < 0.05)	Placebo: 25.0% OLN: 42.0% p = 0.002 (p < 0.05)	Placebo: 22.0% OLN: 37.0% p = 0.002 (p < 0.05)	Sedation (severe in 5%) on day 2 No SAE
Clemmons et al., 2018	n = 101; 22-74 yr received HEC	OLN 10 mg p.o. (on each day and 3 additional days after chemotherapy) OND 8-16 mg p.o. or i.v. DEX 8-20 mg p.o. or i.v. (on each day of chemotherapy) FOS 150 mg i.v. day 1 OND 8 mg p.o. DEX 4 mg p.o. (on days of total body irradiation)	Placebo: 50.0% OLN: 68.0% p = 0.05	Placebo: 18.0% OLN: 42.5% p = 0.011 (p < 0.05)	Placebo: 13.0% OLN: 39.0% p = 0.006	N/A
Jeon et al., 2019	n = 56; 30-79 yr received MEC	OLN 10 mg p,o. days 1-5 PAL 0,25 mg i.v. day 1 DEX 12 mg i.v. day 1	N/A	N/A	Placebo: 17.2% OLN: 44% p = 0.002 (p < 0.05)	Somnolence, fatigue No SAE
Tienchaiananda et al., 2019	n = 39; 27-67 yr received HEC	OLN 10 mg p.o. days 1-4 OND 8 mg i.v. day 1 DEX 20 mg i.v. day 1 DEX 10 mg p.o. days 1-4	Placebo: 10.5% OLN: 50.0% p = 0.008 (p < 0.05)	Placebo: 15.8% OLN: 35.0% p = 0.170	Placebo: 0,0% OLN: 30.0% p = 0.009 (p < 0.05)	Somnolence (p < 0.001) No SAE
Hashimoto et al., 2020	n = 710; 22-75 yr received HEC	OLN 5 mg p.o days 1-4 DEX 12 mg i.v. or p.o. day 1 DEX 8 mg i.v. or p.o. days 2-4 PAL 0.75 mg i.v. day 1 NK1 receptor antagonist day 1-3	N/A	N/A	N/A	Constipation, hiccups, somnolence, insomnia, dizziness, dry mouth No SAE

5HT3, 5-hydroxytryptamine-3; APR, aprepitant; DEX, dexamethasone; FOS, fosaprepitant; HEC, highly emetogenic chemotherapy; i.v., intravenously; MEC, moderate emetogenic chemotherapy; N/A, not available; NK1, neurokinin-1; OLN, olanzapine; OND, ondansetron; p.o., orally; PAL, palonosetron; SAE, serious adverse effect.

Table 5: Complete Response With Olanzapine Compared With Nk1-Receptor Antagonists In The Acute, Delayed, and Overall Phase

Author	Population	Antiemetic Regimen	Complete Response			Safety
			Acute	Delayed	Overall	
Shumway et al., 2009	n = 17; 24-71 yr received HEC	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v day 1 DEX 12 mg i.v. day 1 DEX 4 mg bid p.o days 2-4	APR: 44.0% OLN: 75.0%	APR: 55.6% OLN: 62.5%	N/A	Drowsiness No SAE
Navari et al., 2011	n = 241; 39-81 yr received HEC	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v. day 1 DEX 20 mg i.v. day 1	APR: 87.0% OLN: 97.0% p > 0.05	APR: 73.0% OLN: 77.0% p > 0.05	APR: 73.0% OLN: 77.0% p > 0.05	Sedation, feeling drowsy (not significant, p > 0.05) No SAE
Shumway et al., 2015	n = 19; median 54/61 yr received HEC	OLN 5 mg p.o. days -1 to -2 OLN 10 mg p.o. days 1-4 DEX 12 mg i.v. day 1 DEX 4 mg bid p.o. days 2-4 PAL 0,25 mg i.v. day 1	APR: 33.3% OLN: 62.5%	APR: 55.6% OLN: 66.7%	N/A	Drowsiness No SAE
Babu et al., 2016	n = 100; average 43,3/44,7 yr received HEC	OLN 10 mg p.o. day 1 OLN 5 mg bid p.o days 2-4 PAL 0,25 mg i.v day 1 DEX 20 mg i.v. day 1 DEX 4 mg bid p.o. days 2-4	APR: 86.0% OLN: 84.0% p > 0.05	APR: 86.0% OLN: 88.0% p > 0.05	APR: 80.0% OLN: 78.0% p > 0.05	Sedation, drowsiness, fatigue, dizziness (not significant, p > 0.05) No SAE
Navari et al., 2016	n = 101; 52-76 yr received HEC and radiotherapy	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v. day 1 DEX 20 mg i.v. day 1	FOS: 84.0% OLN: 88.0% p > 0.01	FOS: 74.0% OLN: 76.0% p > 0.01	FOS: 74.0% OLN: 76.0% p > 0.01	Sedation, drowsiness (significant, p < 0.01), weight gain, fatigue (not significant, p > 0.01)
Trifilio et al., 2017	n = 117; 42-74 yr received HEC	OLN 5 mg bid p.o. days 1-5 OND 16 mg i.v. day 1 MP 125 mg day -1 DEX 10 mg day 0 DEX 4 mg bid days +1 to +2	APR: 59.0% OLN: 81.0% p = 0.0267 FOS: 75.0% OLN: 81.0% p = 0.473	APR: 35.0% OLN: 66.0% p = 0.0043 FOS: 35.0% OLN: 66.0% p = 0.251	N/A	Sedation, orthostatic hypotension, fatigue, extrapyramidal No SAE

APR, aprepitant; bid, twice a day; DEX, dexamethasone; FOS, fosaprepitant; HEC, highly emetogenic chemotherapy; i.v, intravenously; MP, methylprednisolone; N/A, not available; OLN, olanzapine; p.o, orally; PAL, palonosetron; SAE, serious adverse effect.

Table 6: Patients Without Nausea With Olanzapine Compared With Nk1-Receptor Antagonists in The Acute, Delayed, and Overall Phase

Author	Population	Antiemetic Regimen	Patients with Nausea			Safety
			Acute	Delayed	Overall	
Shumway et al., 2009	n = 17; 24-71 yr received HEC	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v day 1 DEX 12 mg i.v. day 1 DEX 4 mg bid p.o days 2-4	APR: 44.4% OLN: 62.5%	APR: 66.7% OLN: 62.5%	N/A	Drowsiness No SAE
Navari et al., 2011	n = 241; 39-81 yr received HEC	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v. day 1 DEX 20 mg i.v. day 1	APR: 87.0% OLN: 87.0% p > 0.05	APR: 38.0% OLN: 69.0% p ≤ 0.01	APR: 38.0% OLN: 69.0% p ≤ 0.01	Sedation, feeling drowsy (not significant, p > 0.05) No SAE
Shumway et al., 2015	n = 19; median 54/61 yr received HEC	OLN 5 mg p.o. days -1 to -2 OLN 10 mg p.o. days 1-4 DEX 12 mg i.v. day 1 DEX 4 mg bid p.o. days 2-4 PAL 0,25 mg i.v. day 1	N/A	N/A	N/A	Drowsiness No SAE
Babu et al., 2016	n = 100; average 43,3/44,7 yr received HEC	OLN 10 mg p.o. day 1 OLN 5 mg bid p.o days 2-4 PAL 0,25 mg i.v day 1 DEX 20 mg i.v. day 1 DEX 4 mg bid p.o. days 2-4	APR: 88.0% OLN: 84.0% p > 0.05	APR: 84.0% OLN: 88.0% p > 0.05	APR: 84.0% OLN: 84.0% p > 0.05	Sedation, drowsiness, fatigue, dizziness (not significant, p > 0.05) No SAE
Navari et al., 2016	n = 101; 52-76 yr received HEC and radiotherapy	OLN 10 mg p.o. days 1-4 PAL 0,25 mg i.v. day 1 DEX 20 mg i.v. day 1	FOS: 78.0% OLN: 86.0% p > 0.01	FOS: 40.0% OLN: 71.0% p < 0.01	FOS: 40.0% OLN: 71.0% p < 0.01	Sedation, drowsiness (significant, p < 0.01), weight gain, fatigue (not significant, p > 0.01)
Trifilio et al., 2017	n = 117; 42-74 yr received HEC	OLN 5 mg bid p.o. days 1-5 OND 16 mg i.v. day 1 MP 125 mg day -1 DEX 10 mg day 0 DEX 4 mg bid days +1 to +2	APR: 65.0% OLN: 98.0% p < 0.0001 FOS: 80.0% OLN: 98% p = 0.0318	APR: 37.0% OLN: 75.0% p = 0.0004 FOS: 55.0% OLN: 75.0% p = 0.1519	N/A	Sedation, orthostatic hypotension, fatigue, extrapyramidal No SAE

APR, aprepitant; bid, twice a day; DEX, dexamethasone; FOS, fosaprepitant; HEC, highly emetogenic chemotherapy; i.v, intravenously; MP, methylprednisolone; N/A, not available; OLN, olanzapine; p.o, orally; PAL, palonosetron; SAE, serious adverse effect.