



Alliance 221602: Olanzapine with or without Fosaprepitant for the Prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in Patients Receiving Highly Emetogenic Chemotherapy (HEC): A Phase III Randomized, Double Blind, Placebo Controlled Trial

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Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in quality of life and is perceived by patients as a major adverse effect of the treatment [1]. The use of 5-hydroxytryptamine₃ (5-HT₃) receptor antagonists plus dexamethasone has significantly improved the control of acute CINV [1,2]. Studies have demonstrated additional improvement in the control of acute CINV and also delayed CINV with the use of palonosetron, a second generation 5-HT₃ receptor antagonist [3], neurokinin-1 (NK-1) receptor antagonists [4,5], and olanzapine, an antipsychotic which blocks multiple neurotransmitters in the central nervous system [6-11].

Olanzapine is an FDA-approved antipsychotic that blocks multiple neurotransmitters: dopamine at D₁, D₂, D₃, D₄ brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT₃, 5-HT₆ receptors, catecholamines at α 1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H₁ receptors [12,13]. Common side effects are sedation and weight gain [14, 15], as well as an association with the onset of diabetes mellitus [16]. Olanzapine's activity at multiple receptors, particularly at the D₂, 5-HT_{2c}, and 5-HT₃ receptors which appear to be involved in nausea and emesis, suggests that this drug may have significant anti-emetic properties.

While it is clear that olanzapine has definite efficacy for the prevention of chemotherapy-induced nausea and vomiting, it is clear that the full utility of this drug in this situation has not been realized. The study of olanzapine, a generic agent in this clinical

trial is very cost effective when compared to a number of other available antiemetic agents that have been the objects of pharmaceutical company-sponsored clinical trials.

Now that it has been established that olanzapine decreases nausea and vomiting in patients receiving highly emetogenic chemotherapy, when given with an expensive NK-1 receptor antagonist, how would it perform without the use of the expensive NK-1 receptor antagonist?

We now have data from two different clinical trial designs that support that olanzapine-containing regimens performed better than regimens that did not include olanzapine. The first of these is from our recent manuscript that demonstrated that olanzapine added to the previous standard NK-1 receptor antagonist-based regimen was more effective than placebo for the prevention of nausea and vomiting [11]. The second of these clinical trial designs consists of the above-noted randomized, controlled (but not definitive) trials that support that olanzapine is better than a standard NK-1 receptor antagonist-based regimen [6,10]. Additionally, as noted above, a recent randomized controlled (but not patient blinded) trial involving 100 patients receiving a variety of platinum-based treatments, reported that olanzapine, when added to palonosetron and dexamethasone (without an NK-1 receptor antagonist), led to a complete response rate of 96%, compared to 42% in a control group ($p < 0.0001$), with a corresponding improvement in nausea control ($p < 0.0001$) [32].

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Primary

- To compare between the two study arms the proportion of patients with no nausea for the overall (0-120 hours post-chemotherapy), acute (0-24 hours post-chemotherapy), and delayed periods (24-120 hours post-chemotherapy) for patients receiving HEC. The overall period is the efficacy period of primary interest and will be used as the primary endpoint to design the study.

Secondary

- To compare between the two study arms the complete response (CR) rates (no emetic episodes and no use of rescue medication) in the acute, delayed, and overall periods
- To compare between the two study arms, the incidences of potential toxicities that have been ascribed to olanzapine.
- To perform an economic evaluation of olanzapine and fosaprepitant vs. olanzapine in patients receiving HEC (noting that all patients will also receive dexamethasone and a 5HT3 receptor antagonist).
To explore the efficacy of olanzapine in chemotherapy cycles two to four, for patients who elect to continue on the same antiemetic regimen received in cycle one, in chemotherapy cycles two to four (continuation phase), by documenting nausea and complete response
- To explore the safety of olanzapine in chemotherapy cycles two to four, for patients who elect to continue on the same antiemetic regimen received in cycle one, in chemotherapy cycles two to four (continuation phase), by recording any adverse events or drug related toxicities.



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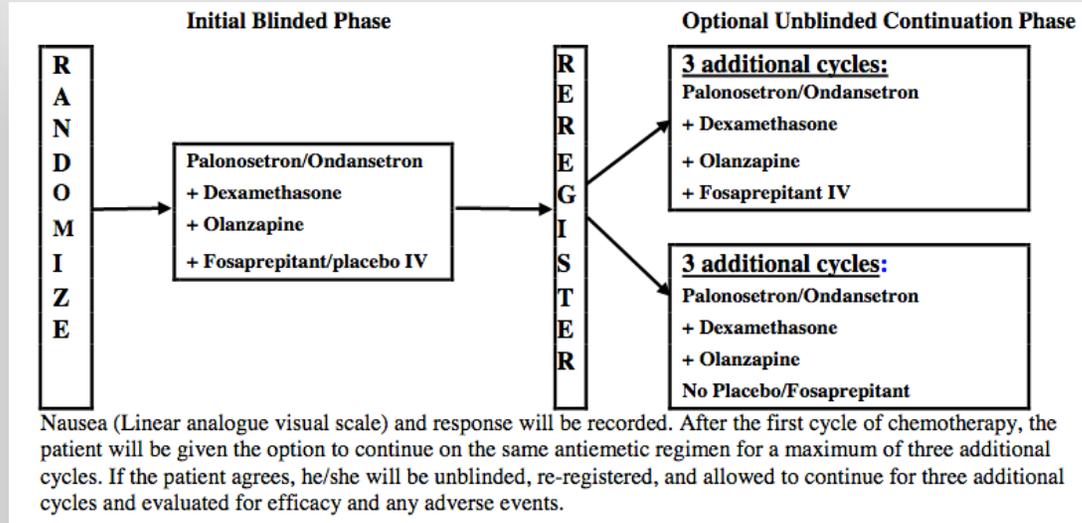
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Intervention

Experimental: Arm I (fosaprepitant dimeglumine, olanzapine)

Patients receive palonosetron hydrochloride IV over 30 seconds or ondansetron hydrochloride IV over 2-5 minutes or PO on day 1, dexamethasone PO on days 1-4, fosaprepitant dimeglumine IV over 20-30 minutes on day 1, and olanzapine PO on days 1-4. Treatment may repeat every 21 days for up to 3 courses in the absence of disease progression or unacceptable toxicity.

Active Comparator: Arm II (placebo, olanzapine)

Patients receive palonosetron hydrochloride IV over 30 seconds or ondansetron hydrochloride IV over 2-5 minutes or PO on day 1, dexamethasone PO on days 1-4, placebo IV over 20-30 minutes on day 1, and olanzapine PO on days 1-4. Treatment (with no placebo) may repeat every 21 days for up to 3 courses in the absence of disease progression or unacceptable toxicity.

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Eligibility Criteria

- Diagnosis of malignant disease.
- No prior history of chemotherapy for any malignancy
- Scheduled to receive HEC (either cisplatin-containing AST or ALT ≤ 3 x upper limit of normal (ULN) regimen or doxorubicin and cyclophosphamide [AC])
- No nausea or vomiting ≤ 24 hours prior to registration
- Negative pregnancy test (serum or urine) done ≤ 7 days prior to registration
- No known diagnosis of dementia.
- No known history of CNS disease (e.g., seizure disorder)
- No treatment with another antipsychotic agent
- No chronic phenothiazine administration as an antipsychotic agent
- No use of amifostine within 7 days prior to registration
- No radiotherapy within 7 days prior to registration or planned for one week after the current dose of chemotherapy
- No use of quinolone antibiotic therapy within 7 days prior to registration
- No chronic alcoholism (as determined by the investigator)
- No known hypersensitivity to olanzapine
- No known cardiac arrhythmia, uncontrolled congestive heart failure or acute myocardial infarction within the previous six months
- No history of uncontrolled diabetes, i.e., no diabetic ketoacidosis
- Age ≥ 18 years
- ECOG Performance Status 0, 1 or 2
- Patients must be able to read and comprehend English



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