Olanzapine 10 mg versus Olanzapine 5 mg in Treatment for HECINV: A Double-Blind Randomized Phase II Dose-Finding Study

BACKGROUND:

- Highly emetic chemotherapy induced nausea and vomiting in the delayed phase (24-120 hours) has been shown in a previous study to be controlled in 67.2% of patients receiving the standard three-drug regimen of a neurokinin-1 receptor antagonist (aprepitant), a serotonin receptor antagonist (palonosetron) and dexamethasone; which, is not considered to be optimally controlled in the delayed phase.
- Olanzapine 10 mg PO daily in HEC patients has shown effectiveness in reducing HECINV but has also been associated with higher incidence of somnolence in patients receiving this therapy.

OBJECTIVE

- To evaluate the doses of olanzapine (10 or 5 mg) as an add-on therapy to a standard antiemetic treatment in treating CINV in the late phase in patients receiving highly emetogenic chemotherapy.

METHODS

- **Design**: Multicenter (6), double-blind, stratified block randomized; Duration: 4 days
- **Inclusion criteria**: age 20-75 years old, presence of solid tumor, Eastern Cooperative Oncology Group performance status of 0-2, receiving first course of highly emetogenic chemotherapy with a regimen based on cisplatin (≥50 mg/m^2) or previously received the last dose of a course of highly emetogenic chemotherapy with regimen based on cisplatin (≥50 mg/m^2) ≥3 months ago, adequate major organ function (aspartate aminotransferase and alanine aminotransferase <100 IU/L, bilirubin <0.2 mg/dL, creatinine clearance ≥60 mL/min), written informed consent
- **Exclusion criteria**: hypersensitivity to olanzapine, aprepitant, palonosetron, or dexamethasone; serious concurrent disease; symptomatic brain metastasis, a history of diabetes or HbA1c ≥6.5%, or scheduled to receive radiotherapy to the abdomen region.
- **Primary outcome measure**: The complete response rate, defined as no emesis and no use of rescue medications, in the delayed phase (24-120 hours).
- **Secondary outcome measures**: The complete response rate in the acute phase (0-24 hours), rates of complete control defined as no emetic episodes, no use of rescue medications, and no or only mild nausea; rates of total control, defined as no emetic episodes, no use of rescue medications, and no nausea; and time to treatment failure, defined as the time to first emetic episode or use of rescue medication.
- **Number of patients enrolled:** 153 patients enrolled
    - 76 Olanzapine 10 mg
        - 76 completed the efficacy analysis
        - 75 completed the safety analysis (1 ineligible due to treatment not delivered)
    - 77 Olanzapine 5 mg
        - 77 completed both the efficacy and safety analysis
- **Drug regimens/dosages used:**
    - Olanzapine 10 mg or 5 mg by mouth once daily after supper on days 1-4
    - Standard prophylactic antiemetic treatment
        - Aprepitant (NK_1RA): Day 1: 125 mg PO; Day 2-3: 80 mg PO Or Fosaprepitant 150 mg IV on day 1
        - Palonosetron (5-HT RA) 0.75 mg IV on day 1
        - Dexamethasone Day 1: 12 mg IV or PO; Day 2: 8 mg IV or PO; Day 3-4: 16 mg IV or PO

- **Power:** Power was greater than 75% with a normal approximation at a 10% level of significance. A Bayesian predictive power was used to asses the primary hypothesis test for olanzapine 10 mg; if the predictive power was less than 1% the study was to be discontinued.
- **Data handling method:** intent-to-treat

RESULTS

- 152 of 153 patients completed the study, 1 drop out due to diagnosis of diabetes
- **Primary outcome measure**: There was a significant complete response rate in the delayed phase for both arms of the study. The CR rate in the delayed phase for the 10 mg group was 77.6% (80% CI, 70.3-83.8, P = 0.01) and for the 5 mg group it was 85.7% (80% CI, 79.2-90.7, P<0.001)
- **Secondary outcome measures**: The secondary measures were not reported with p-values so it is difficult to determine statistical significance, but the 5 mg group had higher percentages in complete control, total control and complete response when compared to the 10 mg group. When looking at somnolence presentation during therapy, 52% of patients in the 10 mg group reported grade 1 somnolence, while 44.2% of patients in the 5 mg group reported somnolence. Both groups had 1.3% of patients report an incidence of grade 2 somnolence.
- **Author's conclusion:** Olanzapine 10 mg and 5 mg have a satisfactory antiemetic effect in the delayed phase when administered with a standard three-drug antiemetic regimen.

STRENGTHS

- Only 1 drop out - No adverse events that led to discontinuation of therapy
- Similar characteristics among the two groups
- Unlikely that there was unblinding

LIMITATIONS

- 80% confidence intervals used over 95% confidence intervals and 10% level of significance
- Administered higher dose of palonosetron than what is standard
- Significantly less females than males 22-23% female versus 54% males
- No p-values for secondary endpoints
- Japanese study population
- It was not mentioned if the patients were taking other chemotherapy agents
- No breakdown of who was previously treated with a cisplatin based HEC regimen vs. those who had never been treated with a cisplatin based HEC regimen
- No comparative statistics between the 10 mg group and the 5 mg group
- Administration was after dinner, therefore potential for decreased reported incidence of somnolence
- Author bias toward Eli Lilly Co (manufacturer of Zyprexa)

CONCLUSION

Overall, based on these study results, olanzapine 10 mg and 5 mg have good antiemetic properties, but it is unknown how it compares to the standard three-drug antiemetic therapy regimen without the addition of olanzapine. I cannot recommend one dose over the other due to the lack of comparative data reported in order to indicate that the difference between the two doses was statistically significant. I am also unable to support the use of 5 mg over 10 mg on the sole basis of decreased somnolence incidence due to lack of reported p-values.

Future research:

I believe that a comparative study involving the two olanzapine doses, as an add on therapy to the standard three-drug antiemetic regimen in comparison to the three drug regimen by itself taking place in the United States with a 50/50 distribution of male to female would provide more clinically useful data to the United States. This study would assess the same primary and secondary

outcomes, but would power the study so that all outcomes have the ability to be statistically significant.

Reference: Yanai T., Iwasa S., Hashimoto H., Ohyanagi F., Takiguchi T., Takeda K., Nakao M., et al. A double-blind randomized phase II dose-fnding study of olanzapine 10 mg or 5 mg for the prophylaxis of emesis induced by highly emetogenic cisplatin-based chemotherapy. *Int J Clin Oncol.* 2017:n.p-n.p.

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