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EDITORIAL

Olanzapine 5 mg vs 10 mg for the prophylaxis of chemotherapy-induced nausea and vomiting: a network meta-analysis

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) can be a significant and distressing adverse event for patients undergoing cytotoxic cancer treatment [1]. It can negatively impact the quality of life of patients and also place patients at increased risk of treatment nonadherence [2]. Furthermore, poorly controlled CINV increases the risk of CINV during subsequent treatment cycles and also the risk of developing anticipatory nausea [3]. It is therefore prudent to provide effective antiemetics to patients undergoing emetogenic therapies.

At the time of this writing in mid-2021, clinical guidelines published by the American Society of Clinical Oncology (ASCO) [4] and the National Comprehensive Cancer Network (NCCN) [5] recommend a four-drug prophylactic regimen for patients receiving highly emetogenic chemotherapy (HEC), for which olanzapine is one of the drugs. Olanzapine administered at a 10 mg dosage, as it commonly has been, may be associated with fatigue, drowsiness, and reduced general activity [6]. Therefore, despite its documented superiority of olanzapine in the latest systematic review and meta-analysis [7], as well as cost-effectiveness [8], clinicians may hesitate to prescribe olanzapine at 10 mg doses. A 5 mg dose may be preferred, to reduce the likelihood of adverse events.

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There is currently a paucity of data reporting on olanzapine administered at 5 mg dose. Only 3 studies by Hasimoto et al. [9], Mizukami et al. [10], and Rumyantsev et al. [11] have compared 5 mg to placebo, while Ishimoto et al. [12] compared 5 mg to 10 mg and to placebo. In contrast, 17 studies have reported on olanzapine in the 10 mg setting.

Fundamentally, the clinical question remains whether 5 mg dosing yields equivalent efficacy as 10 mg dosing. Through a network meta-analysis, an indirect comparison between olanzapine at 5 mg and 10 mg would provide further precision in effect estimate than that provided alone, by Ishimoto et al. The aim of this article was to conduct a network meta-analysis and report on the efficacy of olanzapine administered at 5 mg, relative to when administered at 10 mg.

Methods

We used previously published data from the systematic review by Chow et al. [7], which reported on 21 trials of olanzapine on adult patients for the prophylaxis of CINV. The review reported on nine efficacy outcomes — complete response, no nausea, and no vomiting, each in the acute (0–24 h post-chemotherapy), delayed (24–120 h post-chemotherapy), and overall (0–120 h post-chemotherapy) phases. More detailed description of study selection and demographics is reported therein [7]. Due to the paucity of endpoints in trials studying olanzapine at 5 mg doses, the endpoints of interest in our network meta-analysis are (1) complete response in the acute phase and (2) complete response in the overall phase.

A multivariate network meta-analysis using a restricted maximum likelihood model was used, to compare olanzapine at 10 mg, olanzapine at 5 mg, and control, relative to each other. Risk ratios (RR) and accompanying 95% confidence intervals were calculated for each comparison. To

assess the primary underlying assumption used in network meta-analyses of consistency, we applied an inconsistency model [13]. Type I error was set at 0.05, and analyses were conducted using Stata 16.1.

Results

As previously mentioned, we only analyzed studies on adult patients reporting on complete response in the acute phase and complete response in the overall phase. Eighteen of 21 studies reported by Chow et al. [7] were included in this analysis; 3 [10, 14, 15] were excluded, as they did not report on our endpoint of interest. Study demographics for these studies have been previously reported [7]. Of the 18 studies, 15 used 10 mg doses, 3 used 5 mg doses, and 1 used a mix of 5 and 10 mg doses.

Only one study directly compared the efficacy of olanzapine at 5 mg relative to olanzapine at 10 mg. Four studies compared 5 mg olanzapine relative to control, and 18 compared 10 mg olanzapine to control. There was no significant concern for inconsistency and therefore no model violation, for either endpoints.

Acute phase

Ithimakin et al. reported 5 mg olanzapine regimens to yield similar complete response rates to 10 mg olanzapine regimens — RR 1.00, 95% CI, 0.83–1.21. This network meta-analysis also reports that the complete response rate in the acute phase is not statistically different, between 5 and 10 mg doses of olanzapine — RR 0.97, 95% CI, 0.83–1.13 (Fig. 1a).

Overall phase

In the overall phase, Ithimakin et al. also reported 5 mg olanzapine to yield similar complete response rates relative to 10 mg olanzapine — RR 0.86, 95% CI, 0.47–1.55. When estimated using network meta-analysis, 5 mg olanzapine is similarly as efficacious as 10 mg olanzapine — RR 0.95, 95% CI, 0.56–1.60 (Fig. 1b).

Discussion

To our knowledge, this is the first network meta-analysis investigating olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting and therefore the first to try to compare 5 mg olanzapine to 10 mg olanzapine regimens. Our findings suggest that 5 mg olanzapine may be equally as efficacious as 10 mg olanzapine in the prophylactic setting and support the findings by Ithimakin et al. [12].

While this network meta-analysis does give greater precision in the relative efficacy of 5 mg olanzapine to 10 mg olanzapine than the study of Ithimakin et al. alone (a confidence interval width of 0.30 compared to 0.38 in the acute phase and 1.04 relative to 1.08 for overall phase), it is important to note that there is still notable imprecision. In the 2021 meta-analysis by Chow et al. [7], the confidence interval width for 10 mg olanzapine relative to control is only 0.20 for acute phase and 0.39 in the overall phase. More studies reporting on 5 mg olanzapine may help to increase the precision of this estimate.

With the current statistical modeling intended to improve precision, 5 mg olanzapine appears to be equally efficacious. In fact, in the overall phase, the network meta-analysis suggests that 5 mg is more similar to 10 mg than reported in Ithimakin et al., as noted by the RR point estimate closer to 1.0–0.95 in the network meta-analysis, compared to 0.86 as reported by Ithimakin et al. While we caution about using these results in clinical decision-making, our results would support rationale for clinical trials studying 5 mg olanzapine regimens in a head-to-head comparison with 10 mg olanzapine regimens.

It is important to mention that this network meta-analysis did not compare the safety of 5 mg to 10 mg olanzapine. There seems to exist a greater paucity of safety data, relative to efficacy data; meta-analyzing any limited safety data at this time is uninformative in the best scenario and misleading in the worst case scenario. Future head-to-head trials should not only report one efficacy but also safety.

Under the premise that olanzapine administered at 5 mg is equally as efficacious as 10 mg and that it is likely to yield fewer adverse events, 5 mg could certainly be the preferred dosage. Its similar efficacy yet possibly better side effect profile would improve the benefit-to-risk ratio relative to non-olanzapine regimens, in terms of cost-effectiveness; the use of 5 mg olanzapine regimens may be optimal [8]. This optimistic outlook hopefully provides enthusiasm and motivation for future clinical trials on 5 mg regimens. As per the international guidelines [4, 5], olanzapine should be employed as the fourth agent in CINV prophylaxis for patient receiving highly emetogenic chemotherapy. If a 5 mg dose has equal efficacy to a 10 mg dose with fewer side effects, it may be employed by more clinicians.

Olanzapine can also be used for palliation of other symptoms such as anxiety, insomnia, delirium, and cachexia [16]. The benefit of using a lower dose could lessen the potential for toxicity, such as extrapyramidal symptoms and serotonin syndrome, all while having the potential to improve a multitude of symptoms frequently seen in patients undergoing chemotherapy. In the setting of CINV, the antiemetic action of olanzapine, compounded with the weight gain side effect, can help cancer patients slow weight loss [17, 18].

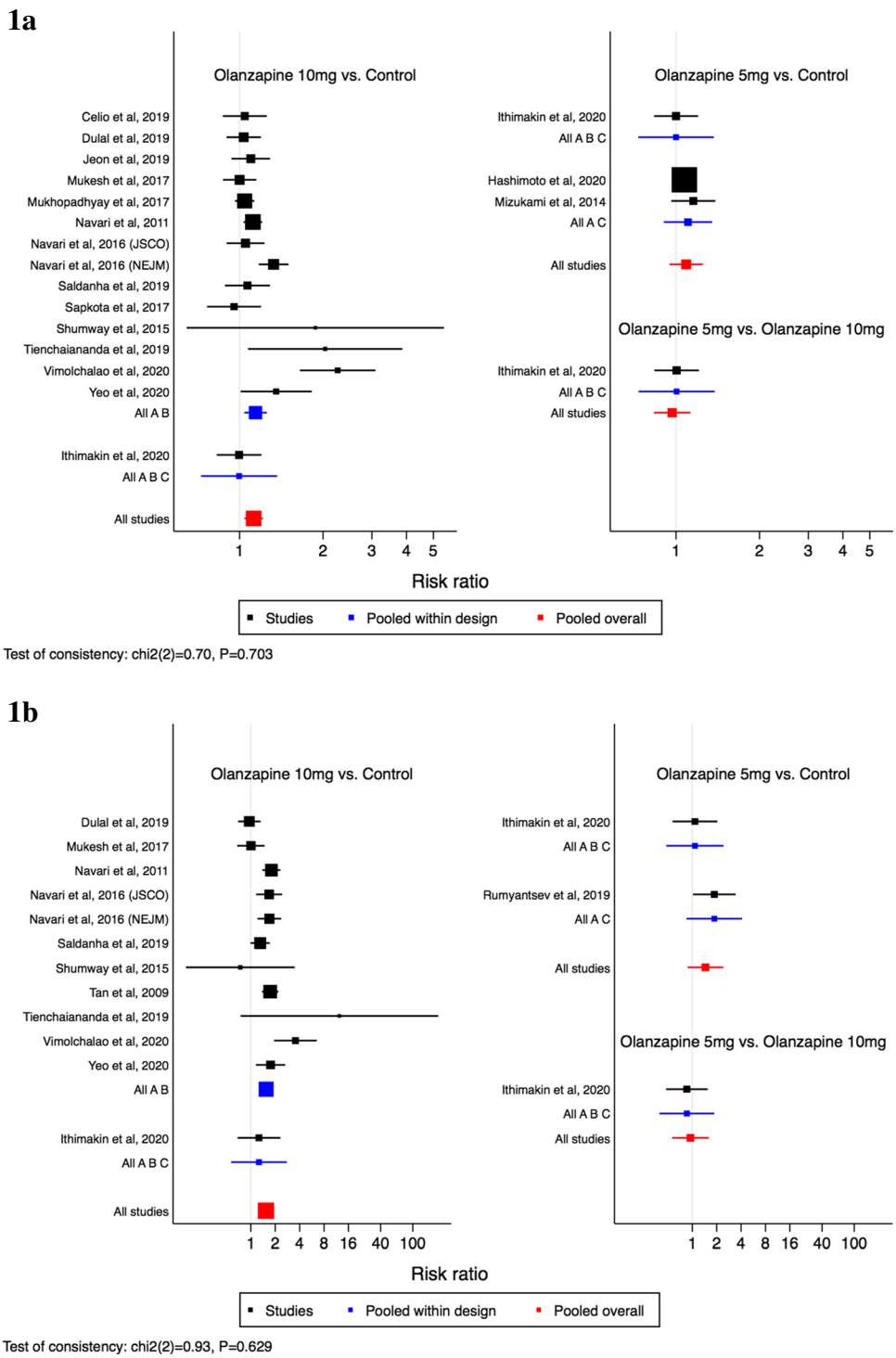

Fig. 1 Network meta-analysis. Complete response: **a** acute phase and **b** overall phase

There are limitations to this study. Due to the nature of systematic review and meta-analysis methodology that underlies the analyzed data, the validity of these conclusions is only as valid as the included studies; any risk of biases at the individual study level is not overcome by meta-analysis design. As well, as previously mentioned, there is a paucity of data. While a network meta-analysis may afford greater precision, it is ultimately limited to the number of published head-to-head trials.

In conclusion, 5 mg olanzapine prophylactic regimens may be as efficacious as 10 mg olanzapine regimens. Our analyses support individual published trials and supports rationale for future trials to compare 5 mg to 10 mg olanzapine regimens in head-to-head comparisons.

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Declarations

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Conflict of interest The authors declare no competing interests.

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