Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: results of a meta-analysis of randomized controlled trials

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Authors' objectives
To compare granisetron with ondansetron in the prophylaxis of chemotherapy-induced nausea and vomiting.

Searching
MEDLINE and Cancerlit were searched from 1990 to 1999. Full publications and abstracts written in any language were eligible for inclusion. The references lists of the identified articles were searched for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with more than 25 patients per treatment arm were eligible for inclusion. Parallel group and crossover designs, and both blinded and open RCTs, were included.

Specific interventions included in the review
Comparisons of ondansetron with granisetron were eligible. Studies were included regardless of whether they included corticosteroids or not, and whether the drugs were administered by an oral (p.o.) or intravenous (i.v.) route. The granisetron regimes included: a single dose of 3 mg i.v., repeated after 1 day or on days 1 to 5; and a single dose of 1 to 2 mg p.o., given before and after 8 to 12 hours of chemotherapy. The ondansetron regimes included 8 to 32 mg i.v. followed by 8 mg p.o., with administration ranging from once only to daily for 5 days. Other cointerventions included metoclopramide (20 mg p.o.) and dexamethasone.

Participants included in the review
Patients undergoing chemotherapy (including those who had not previously had chemotherapy) were included. Patients undergoing radiation therapy or conditioning regimes during bone marrow transplantation were ineligible. Patients were excluded if they received prophylaxis for nausea and vomiting induced by radiation therapy or by the conditioning regimens administered during bone transplantation.

Outcomes assessed in the review
The anti-emetic effects of chemotherapy-induced nausea and vomiting were assessed. Studies had to contain information on the complete control of vomiting and/or nausea during the first 24 hours and/or after the first 24 hours of chemotherapy administration. Eight different scenarios of complete protection were assessed:

- acute vomiting induced by highly emetogenic chemotherapy;
- acute nausea induced by highly emetogenic chemotherapy;
- acute vomiting induced by moderately emetogenic chemotherapy;
- acute nausea induced by moderately emetogenic chemotherapy;
- delayed vomiting induced by highly emetogenic chemotherapy;
- delayed nausea induced by highly emetogenic chemotherapy;
- delayed vomiting induced by moderately emetogenic chemotherapy; and
- delayed nausea induced by moderately emetogenic chemotherapy.
Toxicities that were significantly more frequent in one treatment arm were also assessed.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The included studies were restricted to RCTs. No formal validity assessment was undertaken.

Data extraction
Three authors independently extracted the data according to a predefined protocol, and any disagreements were resolved by open discussion. For crossover studies, only the data on the anti-emetic efficacy of both anti-emetics during the first cycle were considered. The relative risk (RR) and 95% confidence interval (CI) were calculated for each of the outcomes for each study. The following data were extracted: author and year of publication; study design; the number of patients randomised and the number evaluated; chemotherapy regimen details; anti-emetic regimen; study focus; and the significance of toxicity between the treatment groups.

Methods of synthesis
How were the studies combined?
A pooled RR and chi-squared test of significance were calculated for each outcome using fixed-effect and random-effects models.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared test.

Results of the review
Fourteen RCTs (6,467 patients) were included.

Acute nausea and vomiting. No significant differences were found between granisetron and ondansetron for any of the outcomes. Significant heterogeneity was only found for those studies assessing acute vomiting induced by moderately emetogenic chemotherapy (p=0.03). After exclusion of the one RCT significantly favouring one drug, heterogeneity was no longer significant (p=0.11) and a similar, non significant pooled RR was found.

Acute vomiting induced by highly emetogenic chemotherapy: the RR was 1.06 (95% CI: 0.97, 1.14).
Acute nausea induced by highly emetogenic chemotherapy: the RR was 1.00 (95% CI: 0.93, 1.08).
Acute vomiting induced by moderately emetogenic chemotherapy: the RR was 0.99 (95% CI: 0.86, 1.14).
Acute nausea induced by moderately emetogenic chemotherapy: the RR was 0.97 (95% CI: 0.88, 1.07).

Delayed nausea and vomiting. No significant differences were found between granisetron and ondansetron for any of the outcomes. There was no evidence of significant statistical heterogeneity. Delayed vomiting induced by highly emetogenic chemotherapy: the RR was 1.00 (95% CI: 0.86, 1.14).
Delayed nausea induced by highly emetogenic chemotherapy: the RR was 1.08 (95% CI: 0.96, 1.22).
Delayed vomiting induced by moderately emetogenic chemotherapy: the RR was 1.02 (95% CI: 0.94, 1.12).
Delayed nausea induced by moderately emetogenic chemotherapy: the RR was 1.00 (95% CI: 0.93, 1.08).

Toxicity.
Only one study reported a significant difference in toxicity between the drugs: significantly more patients reported dizziness and blurred vision in the ondansetron arm than in the granisetron arm.

The authors reported that their review had several limitations: the number of studies and eligible patients were heterogeneous within the different outcomes; for some outcomes, the meta-analysis had a power of only 40% to detect a 5% difference in efficacy.

**Authors' conclusions**

Granisetron and ondansetron demonstrated similar anti-emetic efficacy for prophylaxis of chemotherapy-induced nausea and vomiting. Further RCTs are needed to confirm these results because of the low number of comparative studies that addressed delayed nausea and vomiting.

**CRD commentary**

The aims were stated and the inclusion criteria were defined in terms of the study design, interventions and outcomes. Two relevant databases were searched and no language restrictions were applied. The keywords used were not specified and the methods used to select the studies were not described. There was no attempt to locate unpublished material, thus raising the possibility of publication bias. The included studies were restricted to RCTs but no formal validity assessment was undertaken. With the exception of validity, relevant information on the primary studies was tabulated. The methods used to extract the data were described. Heterogeneity of the outcomes was statistically tested and illustrated graphically using forest plots. Where significant heterogeneity was found, some exploration of this was conducted.

The evidence presented supports the authors' conclusion. However, the conclusion should be view with caution given the limitations mentioned.

**Implications of the review for practice and research**

Practice: The authors state that the choice of one medication over another within each institution can be guided by cost considerations and/or physician preference. They also state that the results cannot be extrapolated to children.

Research: The authors state that research is required on the optimisation of delayed emesis management, and on the prevention of delayed nausea and vomiting induced by highly emetic chemotherapy regimes.

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