Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The three health technologies examined in the study were two orally administered 5-HT_3 antagonists used as antiemetics before chemotherapy, ondansetron, 8mg oral (PO) (Zofran, Glaxowellcome Research) every 8 hours; and granisetron 1mg (PO) (Kytril, SmithKline Beecham) every 12 hours on each day of the preparative regimen plus 1 additional day; and one high dose IV bolus ondansetron 32 mg (IV) every 24 hours. In addition all patients received 10 mg IV dexamethasone once daily whilst receiving a 5-HT_3 antagonist.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of all patients with malignant disease, scheduled to receive chemotherapy or chemoradiotherapy prior to BMT, who were over the age of 17 years and who had consumed less than 5 alcoholic drinks per day during the preceding year. Patients were required to have an estimated creatinine clearance of at least 50mL/min and normal liver function (defined as a total bilirubin less than 1.5 upper limit of normal (ULN) and aspartate aminotransferase (AST) less than 2 ULN).

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
Effectiveness evidence was from the period 1997-1998. No date for the cost evidence was given. The price year was 1998.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Costs were calculated for the same patient sample as that used in the effectiveness study. However, it was not clear if the costing was conducted retrospectively or prospectively.
Study sample
Power calculations were conducted and the sample size was estimated with the assumption that patients would have a mean score of 50% +/- 20%. A sample of 34 patients per group allowed for a power of 80% and a 2-sided alpha level of 0.025. In total 102 patients were randomised to three groups (34 in each group). Six patients (2 from each arm) withdrew early from the study, 1 due to an adverse drug reaction and 5 due to poor control of nausea and/or emesis.

Study design
This was a double-blind, randomised controlled trial carried out in a single centre. Patients were evaluated (followed-up) for 8 days of treatment. Patients were stratified by sex, total body irradiation containing preparative regimens and non-total body irradiation containing preparative regimens, such as: STAMP V; TBI/etoposide (VP)/cyclophosphamide (CY); etc. (Full details of all alternative preparative regimens are given in the paper). Patients were then assigned to an inpatient or outpatient setting primarily based on the conditioning regimen they were to receive. Randomisation was conducted by means of a permuted block design.

Analysis of effectiveness
Analysis was based on intention to treat. The health outcomes used to evaluate the treatment were:

- complete response, defined as no or mild nausea and no rescue emetics used;
- major response, defined as 1 episode of vomiting or moderate nausea (intake significantly decreased, but patient can eat) with rescue antiemetics allowed;
- minor response, defined as 2-4 episodes of vomiting, regardless of nausea or rescue emetic use;
- failure, defined as more than 4 episodes of vomiting regardless of nausea or rescue antiemetic use; and

major efficacy (ME), defined as complete responders plus major responders and recorded for each patient daily. The maximum possible score for a patient (ME on every day of treatment) was 100.

A separate analysis of nausea was conducted using a 100mm visual analogue scale (VAS), which was given to patients to analyse their subjective perceptions of nausea (0 = no nausea, 100 = severe nausea).

The authors examined patient scores at baseline in an attempt to highlight factors other than 5-HT_3 that may predict and/or influence a patient's composite score.

Groups were reported by authors to be balanced with respect to age, sex, weight, preparative regimen, and history of nausea and vomiting with prior chemotherapy.

Effectiveness results
Complete and major response rates for each day are presented graphically within the paper.

Complete response rates normalised over 8 days were: 48% for oral ondansetron, 47% for oral granisetron, and 49% for IV ondansetron.

The authors did not report any results for minor response rates.

Major efficacy rates normalised over 8 days were: 82% for oral ondansetron, 84% for oral granisetron and 81% for IV ondansetron. Major efficacy was defined as complete responders plus major responders. No statistically significant difference was found between the groups.

Failure rates normalised over 8 days were: 4% oral ondansetron, 3.3% oral granisetron and 2.6% for IV ondansetron.

Overall, 85% of all patients required rescue antiemetics on at least 1 day of their antiemetic regimen: 91% in the oral
ondansetron group, 85% in the oral granisetron group and 79% in the IV ondansetron group, (p=0.39).

The time path of the results was similar in all three groups; for the first three days patients did well but the response declined after this and most patients needed rescue antiemetics by day 4.

The results of the VAS questionnaires were presented as mean scores: (0 = no nausea, 100 = extreme nausea):
oral ondansetron = 32;
oral granisetron = 32; and
IV ondansetron = 27.

The differences were not statistically significant.

Overall, 81% of patients completed a VAS form every day, compliance within each group was recorded: 74% for IV ondansetron, 82% for oral ondansetron, and 88% for oral granisetron.

Early discharge without a VAS form was one reason for noncompliance, the other reason being that patients did not complete the form if they felt too sick.

The author's found that both history and severity of nausea (p<0.01) and vomiting (p<0.02) with previous chemotherapy and/or radiation were significantly associated with the patient's composite score. As a result patients who had previously experienced nausea and vomiting with treatment had lower composite scores for major efficacy.

Clinical conclusions
All three treatments in conjunction with IV dexamethasone produced similar results; prevention of acute nausea and vomiting but no prevention in delaying nausea and vomiting.

Measure of benefits used in the economic analysis
The authors did not use a summary measure of benefit in the economic analysis and, as such, they conducted a cost-consequences analysis. The reader is referred to the effectiveness results reported above.

Direct costs
No discounting was carried out which was appropriate as costs were incurred over a period of less than 2 years. The following costs were calculated: cost of scheduled 5-HT_3 antagonists, cost of rescue antiemetics. All costs were normalised over the treatment period. Resource quantities and cost were not reported separately. Costs were based on average wholesale prices for 1998. The authors did not report any sources for cost data.

Statistical analysis of costs
No statistical analysis of costs was carried out.

Indirect Costs
No indirect costs were included in the analysis.

Sensitivity analysis
No sensitivity analyses were conducted.

Estimated benefits used in the economic analysis
No summary benefits measure was calculated. The reader is therefore referred to the effectiveness results above.

**Cost results**
The total cost of scheduled 5-HT\_3 antagonists (normalised) was $539 for oral ondansetron, $684 for oral granisetron and $1,651 for IV ondansetron $174,7.

The mean cost of rescue medications (normalised) was $102 for oral ondansetron, $86 for oral granisetron and $96 for IV ondansetron. The differences were not statistically significant.

Total costs (scheduled plus rescue antiemetics) were:
oral ondansetron $641;
oral granisetron $770; and
IV ondansetron $1747, (p=0.0001, all comparisons)

Costs were calculated for 8 days. Costs of adverse effects were included within the costing analysis.

**Synthesis of costs and benefits**
Not relevant due to the cost-consequences approach.

**Authors' conclusions**
The authors concluded that there was no important difference between the three 5-HT\_3 antagonists in their effectiveness but that oral ondansetron plus dexamethasone offered the lowest cost treatment.

**CRD COMMENTARY - Selection of comparators**
The choice of comparators was justified as all three treatments are widely used as antiemetics for patients receiving chemotherapy. You, as the user of this database should decide if they are widely used treatments in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a single-centre randomised control trial, which was appropriate given the study question. The groups were shown to be comparable at baseline and confounding was dealt with in an appropriate statistical manner. The study sample was determined by means of a power calculation and appeared representative of the study population although it is not clear how the sample was derived. The analysis of effectiveness was handled credibly. This suggests that the effectiveness results should have high validity.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit in the economic analysis. The analysis was therefore classified as a cost-consequences analysis and the health benefits are associated with the effectiveness outcomes (see above comments). A cost-consequences approach was probably the most appropriate form of analysis for the intervention/patients examined.

**Validity of estimate of costs**
The perspective of the study was not reported. However, it appears to have been conducted from the perspective of the hospital, although it is not clear if all the necessary costs for this perspective have been included. Total costs were given and the drug regimen of the different patient groups was described, but separate quantities and prices for the different regimens were not reported. Resource use quantities were taken from the single study, but no statistical or sensitivity analysis of quantities was conducted. The average wholesale price of the drugs was used as the price source but no
further cost details were reported. The costs results may therefore need to be treated with caution.

**Other issues**
The authors did make appropriate comparisons of their results with the findings of other studies. The issue of generalisability was addressed in that the authors made it clear that the relative drug prices in the USA, where ondansetron is cheaper than granisetron, would have a big effect on the cost results. The authors appear to have reported the majority of the results obtained, although they did not report minor response rates and it is not clear why they did not do so. The authors' conclusions appear to reflect the study results. The authors did not report any limitations of their study.

**Implications of the study**
The findings of the study suggest that oral ondansetron plus dexamethasone is the most cost-effective choice (based on a non-significant cost difference and equal effectiveness). However, the authors suggest that there is an urgent need for more research on prevention of nausea and vomiting among the patients under study to find an improved treatment. They suggest the following avenue should be pursued: adding a dopamine antagonist; trying higher doses of ondansetron; and trials of neurokinin1.

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