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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BACKGROUND. The introduction of serotonin antagonists as antiemetics for prophylaxis of chemotherapy-induced nausea and vomiting represented a major step toward better patient tolerance and adherence to this type of treatment. Several published trials compared different serotonin antagonists without demonstrating clear superiority of any one of them. Because most of these trials compared ondansetron with granisetron, the authors conducted a meta-analysis to determine if the current data available show any therapeutic difference between them.

METHODS. MEDLINE and CANCERLIT databases were searched from 1990 to May 1999, and pertinent article references also were surveyed, without restriction to English language. The authors included all randomized controlled trials (RCTs) that had more than 25 patients per arm and compared ondansetron to granisetron for prophylaxis of acute (A) (< 24 hours) and delayed (D) (> 24 hours) nausea (N) and vomiting (V) induced by highly (H) or moderately (M) emetogenic chemotherapy. Only the first chemotherapy cycle was considered for studies that involved a crossover design.

RESULTS. Fourteen studies with 6467 evaluable patients among the 21 studies retrieved were selected for this meta-analysis. In none of the eight scenarios studied (AHV, AHN, AMV, AMN, DHV, DHN, DMV, and DMN) could the authors detect any significant differences in the antiemetic efficacy of any of these medications.

CONCLUSIONS. The authors conclude that both granisetron and ondansetron have similar antiemetic efficacy for prophylaxis of chemotherapy-induced nausea and vomiting. Because the number of comparative studies that addressed the delayed nausea and vomiting scenarios is low, further RCTs are still needed to confirm these results. ***Cancer* 2000;89:2301–8.** *© 2000 American Cancer Society.*

KEYWORDS: chemotherapy, nausea, vomiting, ondansetron, granisetron, meta-analysis, randomized clinical trials.

The introduction of serotonin antagonists as antiemetics for prophylaxis of chemotherapy-induced nausea and vomiting represented a major step toward better patient tolerance and adherence to this type of treatment.

Ondansetron was the most approved medication for this group followed by granisetron and tropisetron. Several studies compared the antiemetic efficacy of these medications for the prophylaxis of nausea and vomiting induced by chemotherapy as well as radiation therapy. In fact, two other meta-analysis exist in the literature. One of

them compared the efficacy of serotonin antagonists with that of older conventional antiemetics,[1] and the other addressed the antiemetic effects of different serotonin antagonists for the prevention of radiation therapy–induced nausea and vomiting.[2] Whereas these new medications are better than the older conventional antiemetics[1] in the prevention of radiation-induced nausea and vomiting, there was no evidence of any of these new antiemetic medications being superior to one another.[2]

Regarding the prevention of chemotherapy-induced nausea and vomiting, conclusions of nonsystematic reviews[3–5] as well as those of a recently conveyed expert panel by the American Society of Clinical Oncology coincide regarding the lack of superiority of one serotonin antagonist antiemetic drug over another. However, to our knowledge, no systematic review of all randomized trials that address this question has been conducted yet. We decided to undertake such an effort to clarify if, with an increased number of patients afforded by the combination of these trials in the context of a meta-analysis, we could identify one of these medications as a superior antiemetic agent.

METHODS

We did a systematic search in MEDLINE and CANCERLIT databases, and we also searched for the reference lists of identified articles for additional relevant articles. Reviewing the literature, we found that most of the randomized trials retrieved compared granisetron with ondansetron whereas we only found three randomized studies containing more than 25 patients per arm that compared tropisetron with ondansetron.[6–8] Therefore, we elected to restrict this meta-analysis only to studies that compared ondansetron with granisetron. Studies also were included whether they utilized corticosteroids or not and regardless of the route of administration (intravenous or orally).

We considered studies eligible for this meta-analysis if they: 1) were randomized controlled; 2) compared the antiemetic efficacy of ondansetron with that of granisetron for the prophylaxis of chemotherapy-induced nausea and vomiting; 3) included more than 25 patients per arm; and 4) contained information regarding the complete control of vomiting and/or nausea during the first 24 hours and/or after the first 24 hours after chemotherapy administration. We included trials published between 1990 and May 1999, written in English or in other languages. We analyzed both published articles and abstracts, if the information reported was not yet published as a full article. When we found both abstracts and published articles on the same patient population, we analyzed only the latter. Studies that included a crossover design were considered only regarding their data on the antiemetic efficacy of both antiemetics during the first cycle, before patients were crossed over to the other arm of the study. Only the data regarding the efficacy of ondansetron and granisetron were extracted from the two trials that compared the antiemetic efficacy of three drugs (granisetron, ondansetron, and tropisetron).[7,8] Trials were excluded if they compared these medications in other settings such as for prophylaxis of nausea and vomiting induced by radiation therapy or by the conditioning regimens administered during bone marrow transplantation. No attempt was made to check for additional data with the authors of the studies that were retrieved.

When we study the prophylaxis of chemotherapy-induced nausea and vomiting, we need to consider whether we were dealing with acute (<24 hours) (A) or delayed (>24 hours (D) nausea (N) and vomiting (V) induced by both moderately (M) and highly (H) emetogenic cancer chemotherapy. Therefore, we grouped and analyzed the data of all eligible trials in eight different scenarios of complete protection from acute vomiting induced by highly emetogenic chemotherapy (AHV); acute nausea induced by highly emetogenic chemotherapy (AHN); acute vomiting induced by moderately emetogenic chemotherapy (AMV); acute nausea induced by moderately emetogenic chemotherapy (AMN); delayed vomiting induced by highly emetogenic chemotherapy (DHV); delayed nausea induced by highly emetogenic chemotherapy (DHN); delayed vomiting induced by moderately emetogenic chemotherapy (DMV); and delayed nausea induced by moderately emetogenic chemotherapy (DMN). We also surveyed all eligible studies for reported toxicities that were significantly more frequent with either ondansetron or granisetron treated patients.

The data from each study were abstracted according to a predefined protocol independently by three of the authors, and disagreements were solved by an open discussion. For each eligible study, we extracted the number of patients who achieved complete control of nausea and/or vomiting in each of the above mentioned scenarios. We then calculated for each study the relative risk (RR) and its 95% confidence interval (CI) followed by the overall combined RR and the chi-square test of significance for all studies within each scenario. The chi-square test of heterogeneity also was calculated to assess if the studies analyzed within each of the scenarios were similar enough to be combined. We did not assign different weights based on the assessment of the quality of the studies selected

TABLE 1
Excluded Trials and the Reasons for Exclusion

Trial	Reason for exclusion
Massida and Ionta[14]	< 25 patients per arm
Yalcin et al.[15]	< 25 patients per arm
Kalaycio et al.[16]	< 25 patients per arm and bone marrow transplant patients
Pellier et al.[17]	Not enough information to exclude for complete control of emesis in the first 24 hours or after 24 hours of chemotherapy administration
Poon and Chow[18]	< 25 patients per arm
Perez et al.[13]	No data regarding antiemetics for the first cycle before the crossover to the other antiemetic
Zeidman et al.[19]	Although the study included 60 patients, it included both highly and moderately emetogenic regimens having < 25 patients for each of these groups

for this meta-analysis. We performed all calculations with the True Epistat (Epistat Services, Richardson, TX) and with the Epimeta (Centers of Disease Control, Atlanta, GA) softwares. We used for all scenarios both random and fixed effects models.

RESULTS

We identified 14 eligible studies with 6467 evaluable patients of a total of 21 studies found in our initial literature search. Table 1 shows the studies that were not considered for this meta-analysis and the reasons for exclusion. Table 2 shows the characteristics of the studies that were deemed eligible for this meta-analysis. The number of patients in each of the studied scenarios ranged from 1119 to 3962.

For the acute control of nausea and vomiting for both highly and moderately emetogenic chemotherapy, doses of granisetron given before chemotherapy ranged from 10 μg/kg to 3 mg and of ondansetron, from 8 mg to 40 mg with or without steroids according to the protocol used by each trial (Table 2). As shown in Figures 1 and 2, in none of the scenarios of acute nausea and vomiting prophylaxis could we identify a significant difference favoring either granisetron or ondansetron. Similar results also were obtained for delayed nausea and vomiting induced by highly and moderately emetogenic chemotherapy.

Except for the control of acute vomiting induced by moderately emetogenic chemotherapy (AMV), the chi-squares for heterogeneity were not significant. When we excluded the trial by Bonneterre et al.[9] in this scenario, the overall chi-square was 0.6656 (two-tailed, $P = 0.41$), and the overall chi-square for heterogeneity became 8.9149 ($P = 0.11$). In this study, the percentage of patients without emesis on Day 1 was 84% for the ondansetron arm and 69% for the granisetron arm (RR, 1.9; 95% CI, 1.03–3.51; $P = 0.054$). Therefore, because this was the only trial to our knowledge that significantly favored one of the medications within this scenario, it probably is responsible for most of the observed heterogeneity. Nevertheless, even when we excluded this trial, the overall conclusions within the AMV scenario did not change. All calculations were performed with both random and fixed effect models yielding similar results.

Regarding differences in toxicity, as shown in Table 2, there was only one study[10] that reported significant differences in toxicities between ondansetron and granisetron. Perez et al.[10] noted that significantly more patients treated with ondansetron experienced dizziness and blurred vision.

DISCUSSION

Despite an expert panel[5] and nonsystematic reviews of the literature[3,4] indicating that there seems to be no superior serotonin antagonist for the prevention of chemotherapy-induced nausea and vomiting, to our knowledge, no formal meta-analysis has ever been conducted to corroborate this position. Therefore, we attempted to systematically review all the data from randomized controlled trials that addressed whether granisetron was superior to ondansetron for the prophylaxis of chemotherapy-induced nausea and vomiting.

We elected to consider only the rate of complete control of nausea and/or vomiting for this meta-analysis because these are the most reliable efficacy indicators of antiemetic medications.[11] Likewise, to reduce the possible confusion that could be imparted by the inclusion of very small studies, we elected to consider only those with more than 25 patients per arm.[12]

We could not detect with this meta-analysis any superiority of ondansetron over granisetron within all the scenarios studied. However, the number of studies and eligible patients are heterogeneous within the different scenarios. Therefore, more studies may be necessary to firmly establish this issue, especially regarding the DHV and DHN settings that were ad-

TABLE 2
Randomized Controlled Trials Company GRA versus OND

Study (year)	Design of the study	No. of patients randomized/ evaluated for the first cycle of chemotherapy	Chemotherapy given	Antiemetic regimen utilized	Study focus	Significant toxicity differences between the groups
Bonneterre et al. (1995)[9]	Randomized, crossover, open, chemo-naive	150/150	Moderately emetogenic	GRA 3 mg i.v. OND 8 mg i.v. and then p.o. q 8 × 9 Steroids not specified	AMV, DMV, AMN, DMN	NS
Gebbia et al. (1995)[20]	Randomized, open, chemo-naive	182/166	Highly emetogenic	GRA 3 mg i.v. and 3 mg i.v. q day repeated after Day 1 OND 24 mg i.v. and 8 mg p.o. b.i.d. after Day 1 Steroids not allowed	AHV, DHV, AHN, DHN	NS
Gebbia et al. (1995)[20]	Randomized, open, chemo-naive	164/158	Moderately emetogenic	GRA 3 mg i.v. OND 16 mg i.v. Steroids not allowed	AMV, DMV, AMV, DMV	NS
Gralla et al. (1998)[21]	Randomized blinded, chemo-naive	1054/1053	Highly emetogenic	GRA 2 mg p.o. OND 32 mg i.v. Steroids permitted	AHV, AHN	NS
Huc et al. (1998)[22]	Randomized, crossover, blinded open, chemo-naive	188/188	Moderately emetogenic	GRA 1 mg p.o. before and repeated once after 8–12 hrs of chemotherapy OND 8 mg p.o. and repeated once after 8–12 hrs of chemotherapy Steroids only allowed if part of the chemotherapy regimen	AMV, AMH, DMV	NS
Italian Group (1995)[23]	Randomized double-blind, chemo-naive or not	973/966	Highly emetogenic	GRA 3 mg i.v. OND 8 mg i.v. Dexamethasone 20 mg i.v. added to both arms Delayed nausea controlled with 8 mg of dexamethasone b.i.d. Days 2 and 3 and 4 mg b.i.d. on Day 4 with metoclopramide 20 mg p.o. q 6 Days 2–4	AHV, AHN, DHV, DHN	NS
Jantunen et al. (1993)[7]	Randomized, crossover, open, chemo-naive or not	166/92[a]	Moderately emetogenic	GRA 3 mg i.v. OND 8 mg i.v. Steroids only allowed if part of the chemotherapy regimen	AMV	NS
Mantovani et al. (1995)[8]	Randomized, open, chemo-naive	117/77[a]	Highly emetogenic	GRA 3 mg i.v. OND 24 mg i.v. Steroids not allowed	AHV	NS
Martoni et al. (1996)[24]	Randomized, open, cross-over, chemo-naive	124/124	Highly emetogenic	GRA 3 mg i.v. Day 1 OND 8 mg i.v. × 3 on Day 1 and 8 mg p.o. × 2 on Day 2 Steroids not allowed	AHV, AHN	NS

(*continued*)

TABLE 2
(*continued*)

Study (year)	Design of the study	No. of patients randomized/ evaluated for the first cycle of chemotherapy	Chemotherapy given	Antiemetic regimen utilized	Study focus	Significant toxicity differences between the groups
Navari et al. (1995)[25]	Randomized, blinded, chemo-naive	994/987	Highly emetogenic	GRA before chemotherapy: 10 μg/kg i.v. or 40 μg/kg i.v.[b] OND 0.15 mg/kg before and q 4 × 2 after chemotherapy Steroids not allowed	AHV, AHN	NS
Noble et al. (1994)[26]	Randomized, blinded, chemo-naive	359/359	Moderately emetogenic	GRA 3 mg i.v. q day Days 1–5 OND 24 mg i.v. (8 mg t.i.d. on Days 1–5) Steroids not allowed	AMV, DMV	NS
Park (1997)[27]	Randomized, open, chemo-naive or not	97/95	Highly emetogenic	GRA 3 mg i.v. ON 8 mg i.v. before and q 8 × 2 on Day 1 then 8 mg p.o. q 12 Days 2–6 Steroids allowed	AHV, DHV	NS
Perez et al. (1998)[10]	Randomized, blinded, chemo-naive	1085/1068	Moderately emetogenic	GRA 2 mg p.o. OND 32 mg i.v. Steroids allowed (80% of patients received steroids)	AMV, AMN, DMV, DMN	Dizziness abnormal vision significantly more common with OND
Ruff et al. (1994)[28]	Randomized, blinded, chemo-naive or not	497/496	Highly emetogenic	GRA 3 mg i.v. OND 8 mg i.v.[b] OND 32 mg i.v. Steroids not allowed	AHV, AHN	NS
Stewart et al. (1995)[29]	Randomized, blinded, chemo-naive or not	514/488	Moderately emetogenic	GRA 3 mg i.v. OND 8 mg i.v. + 8 mg p.o. b.i.d. Days 1–5[b] OND 8 mg p.o. + 8 mg p.o. b.i.d. Days 1–5	AMV, AMN, DMV, DMN	NS

GRA: granisetron; AMV: acute vomiting induced by moderately emetogenic chemotherapy; OND: ondansetron; DMV: delayed vomiting induced by moderately emetogenic chemotherapy; AMN: acute nausea induced by moderately emetogenic chemotherapy; DMN: delayed nausea induced by moderately emetogenic chemotherapy; NS: not significant; AHV: acute vomiting induced by highly emetogenic chemotherapy; DHV: delayed vomiting induced by highly emetogenic chemotherapy; AHN: acute nausea induced by highly emetogenic chemotherapy; DHN: delayed nausea induced by highly emetogenic chemotherapy.

[a] Tropisetron arm included in the study.

[b] Because both arms of granisetron and of ondansetron had equivalent antiemetic efficacy in these three studies they were combined for the meta-analysis calculations.

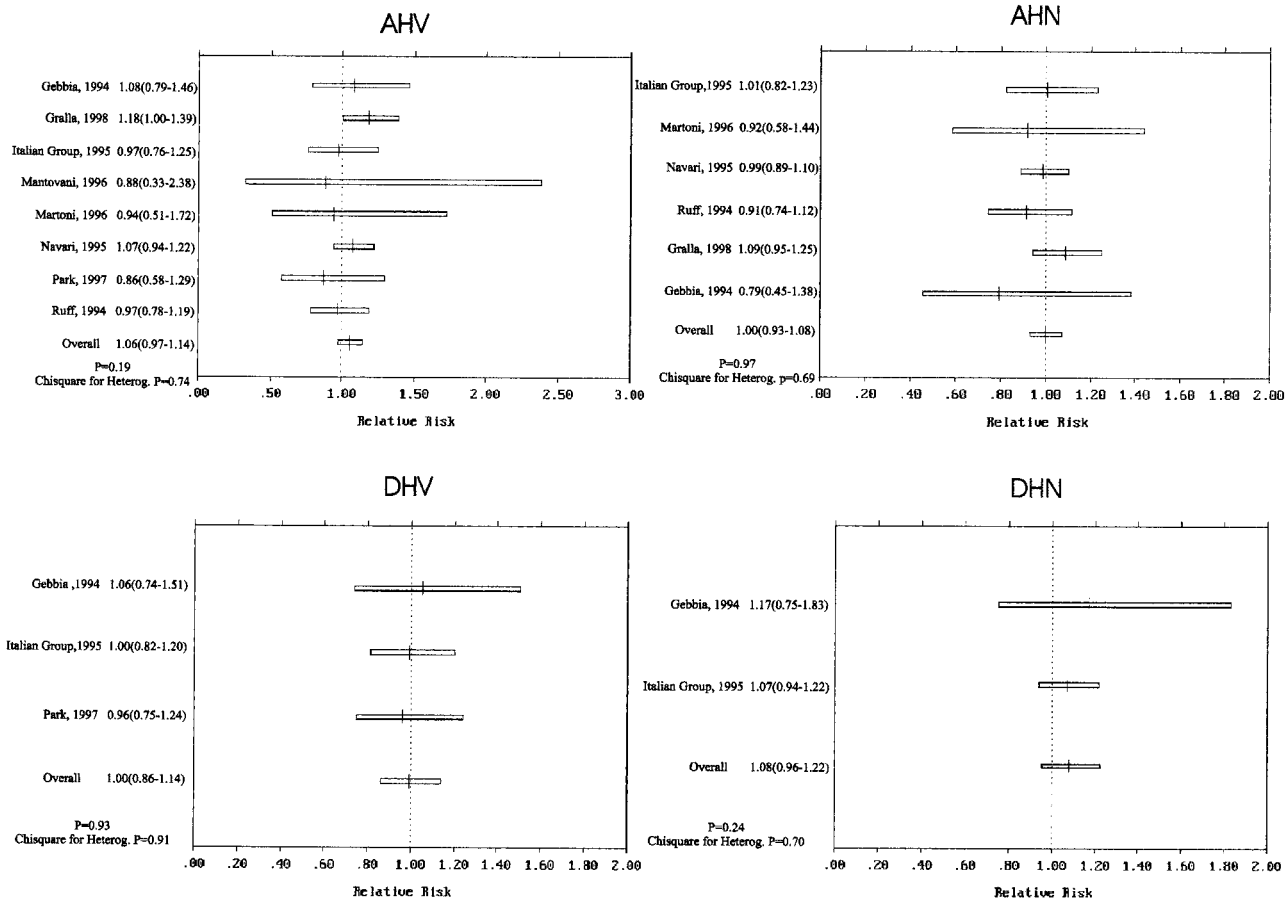

FIGURE 1. Meta-analysis of granisetron versus ondansetron for highly emetogenic chemotherapy. For each article, the first author, relative risk, and its 95% confidence intervals are represented. Relative risk above 1 favor ondansetron. AHV: acute vomiting induced by highly emetogenic chemotherapy; AHN: acute nausea induced by highly emetogenic chemotherapy; DHV: delayed vomiting induced by highly emetogenic chemotherapy; DHN: delayed nausea induced by highly emetogenic chemotherapy.

dressed by fewer studies. For these particular scenarios, we had in this meta-analysis a power of only approximately 40% to detect a 5% difference of antiemetic efficacy between these medications.

Regarding toxicity, both ondansetron and granisetron were considered safe throughout the studies reviewed. Most of these studies reported the well known toxicities of serotonin antagonist medications such as headache, constipation and diarrhea, and, less frequently, sedation. In most studies, these toxicities occurred at similar rates with both antiemetic drugs. Only Perez et al.[10] described a significant difference in toxicity, reporting a higher frequency of dizziness and blurred vision in the group of patients treated with ondansetron. These findings may be due to the fact that in this study patients treated with ondansetron received 32 mg i.v. right before chemotherapy, which represents the highest dose of this medication used in this setting. A similar toxicity profile was obtained by Perez et al. in another study,[13] not included in the meta-analysis (Table 1), in which the same dose of ondansetron was utilized.

This meta-analysis also can indicate new avenues of research such as the need of optimizing delayed emesis management as well as further research on preventing delayed nausea and vomiting induced by highly emetogenic chemotherapy. Furthermore, because the studies analyzed did not include children, the results of this meta-analysis cannot be extrapolated to the pediatric population.

The dose range for both antiemetics and the use of corticosteroids among the studies included in this meta-analysis varied considerably. However, no significant differences in efficacy or toxicity emerged when all studies were grouped together in the different scenarios described. Therefore, the choice of one

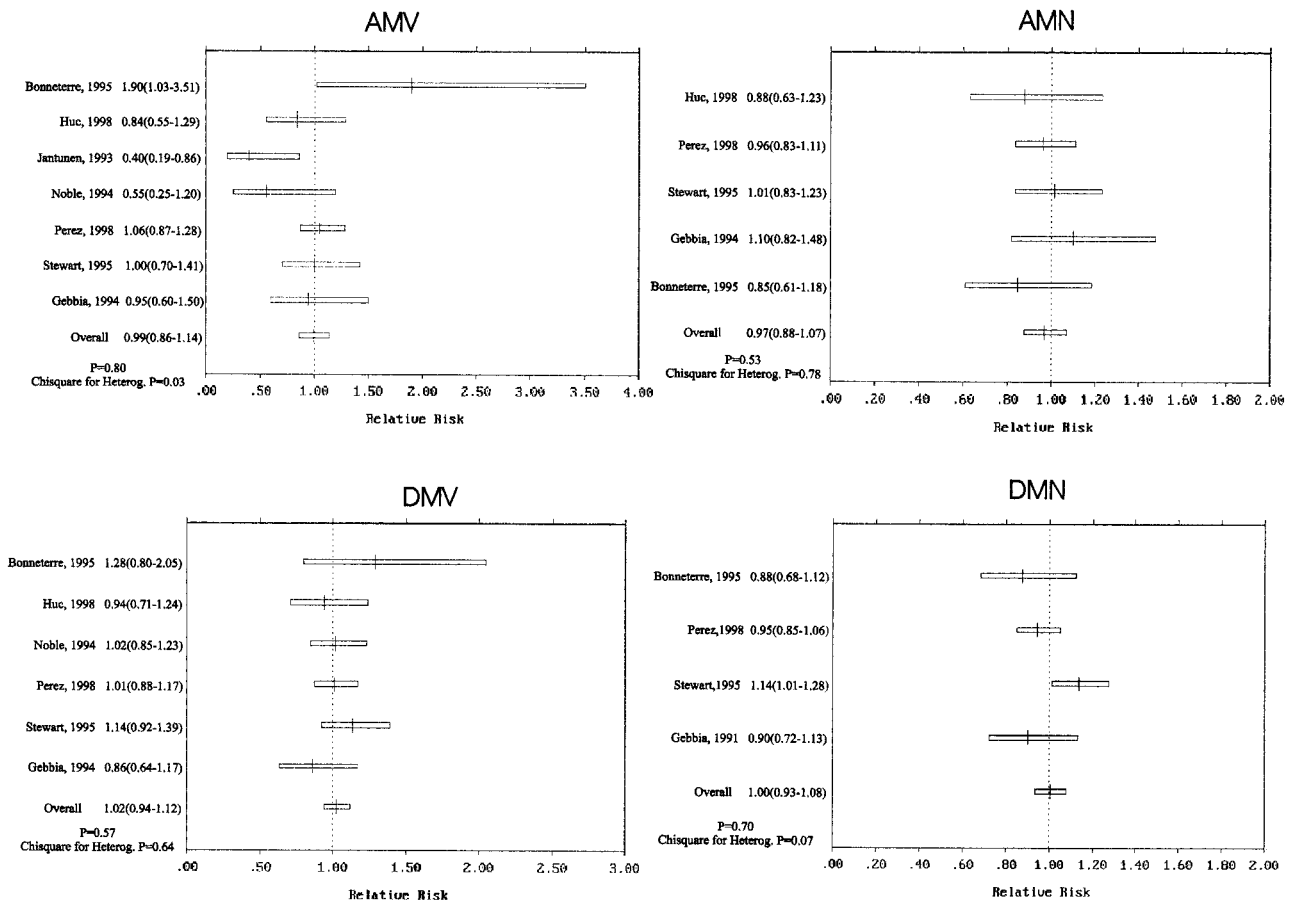

FIGURE 2. Meta-analysis of granisetron versus ondansetron for moderately emetogenic chemotherapy. For each article, the first author, relative risk, and its 95% confidence intervals are represented. Relative risk above 1 favor ondansetron. AMV: acute vomiting induced by moderately emetogenic chemotherapy; AMN: acute nausea induced by moderately emetogenic chemotherapy; DMV: delayed vomiting induced by moderately emetogenic chemotherapy; DMN: delayed nausea induced by moderately emetogenic chemotherapy.

medication over another within each institution can be guided by cost considerations and/or physician preferences.

REFERENCES

1. Jantunen IT, Kataja VV, Muhonen TT. An overview of randomized studies comparing 5-HT3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. *Eur J Cancer* 1997;33:66–74.
2. Tramer MR, Reynolds DJM, Stoner NS, Moore RA, McQuay HJ. Efficacy of 5-HT3 receptor antagonists in radiotherapy-induced nausea and vomiting: a quantitative systematic review. *Eur J Cancer* 1998;34:1836–44.
3. Herrstedt J. Are there differences between 5-HT3 receptor antagonists?. In: Dicato MA, editor. Medical management of cancer treatment induced emesis. London: Martin Dunitz Ltd, 1998:167–82
4. Gandara DR, Roila F, Warr D, Edelmn MJ, Perez EA, Gralla RJ. Consensus proposal for 5HT3 antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy. Dose, schedule, and route of administration. *Support Care Cancer* 1998;6:237–43.
5. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of anti-emetics: evidence-based, clinical practice guidelines. *J Clin Oncol* 1999;17:2971–94.
6. Marty M, Kleisbauer JP, Fournel P, Vergnenegre, Carles P, Loria Kanza Y, et al. Is navoban (tropisetron) as effective as Zofran (ondansetron) in cisplatin-induced emesis? The French navoban study group. *Anticancer Drugs* 1995; 6(Suppl 1):15–21.
7. Jantunen IT, Muhonen TT, Kataja V, Flander MK, Teerenhovi L. 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy: a randomized study. *Eur J Cancer* 1993;29A:1669–72.
8. Mantovani G, Maccio A, Bianchi A, Curreli L, Ghiani M, Proto E, et al. Comparison of granisetron, ondansetron, and tropisetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer: a randomized controlled trial. *Cancer* 1996;77:941–8.

9. Bonneterre J, Hecquet B. Granisetron (IV) compared with ondansetron (IV plus oral) in the prevention of nausea and vomiting induced by moderately-emetogenic chemotherapy: a crossover study. *Bull Cancer* 1995;82:1038–43.
10. Perez EA, Hesketh P, Sandbach J, Reeves J, Chawla S, Markman M, et al. Comparison of single-dose oral granisetron versus intravenous ondansetron in prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: a multicenter, double-blind, randomized parallel study. *J Clin Oncol* 1998;16:754–60.
11. Petitti DB. Meta-analysis decision analysis and cost-effectiveness analysis. New York: Oxford University Press, 1994: 70–89.
12. Petitti DB. Meta-analysis decision analysis and cost-effectiveness analysis. New York: Oxford University Press, 1994: 90–114.
13. Perez EA, Lembersky B, Kaywin P, Kalman L, Yocom K, Friedman C. Comparable safety and anti-emetic efficacy of a brief (30-second bolus) intravenous granisetron infusion and a standard (15-minute) intravenous ondansetron infusion in breast cancer patients receiving moderately emetogenic chemotherapy. *Cancer J Sci Am* 1998;4:52–8.
14. Massida B, Ionta MT. Prevention of delayed emesis by a single intravenous bolus dose of 5-HT3-receptor-antagonist in moderately emetogenic chemotherapy. *J Chemother* 1996;8:237–42.
15. Yalçin S, Tekuzman G, Baltali E, Ozisiky Y, Barista I. Serotonin receptor antagonists in prophylaxis of acute and delayed emesis induced by moderately emetogenic, single-day chemotherapy. A randomized study. *Am J Clin Oncol* 1999; 22:94–6.
16. Kalaycio M, Mendez Z, Pohlman B, Overmoyer B, Boparai N, Jones E, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of nausea and vomiting after high-dose chemotherapy. *J Cancer Res Clin Oncol* 1998; 124:265–9.
17. Pellier P, Dilly SG, Friedman C, Yocom K. Crossover analysis of efficacy and side effects of granisetron and ondansetron. *Proc ASCO* 1994;13:441.
18. Poon RTP, Chow LWC. Comparison of anti-emetic efficacy of granisetron and ondansetron in Oriental patients: a randomized crossover study. *Br J Cancer* 1998;77:1683–5.
19. Zeidman A, Daynan BD, Bem Zion T, Kaufman O, Cohen AM, Mittelman M . Granisetron and ondansetron for chemotherapy-related nausea and vomiting. *Haematologia (Budap)* 1998;29:25–31.
20. Gebbia V, Cannata G, Testa A, Curto G, Valenza R, Cipolla C, et al. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 1994; 74:1945–52.
21. Gralla R, Navari RM, Hesketh PJ, Popovic W, Strupp J, Nay J, et al. Single-dose granisetron has equivalent anti-emetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. *J Clin Oncol* 1998;16:1568–73.
22. Huc P, Block S, Carlier D, Darloy F, Bonneterre ME, Bleuse JP, et al. Granisétron (per os) comparé à ondansétron (per os) dans la prévention des nausées et vomissements inducts par prévention des chemothérapies moyennement émétisantis. *Bull Cancer* 1998;85:562–8.
23. The Italian Group for Anti-emetic Research. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. *Ann Oncol* 1995; 6:805–10.
24. Martoni A, Angelelli B, Guaraldi M, Strocchi E, Pannuti F. An open randomized cross-over on granisetron versus ondansetron in the prevention of acute emesis induced by moderate dose cisplatin-containing regimens. *Eur J Cancer* 1996; 32A:82–5.
25. Navari R, Guandara D, Hesketh P, Hall S, Mailliard J, Ritter H, et al. Comparative clinical trial of granisetron and ondansetron in prophylaxis of cisplatin-induced emesis. *J Clin Oncol* 1995;13:1242–8.
26. Noble A, Bremer K, Goedhals L, Cupissol D, Dilly SG on behalf of the Granisetron Study Group. A double-blind, randomized, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. *Eur J Cancer* 1994; 30A:1083–8.
27. Park JO, Rha SY, Yoo NC, Kim JH, Roh JK, Min JS, et al. A comparative study of intravenous granisetron versus intravenous and oral ondansetron in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. *Am J Clin Oncol* 1997;20:569–72.
28. Ruff P, Paska W, Goedhals L, Pouillart P, Rivière A, Vorobiof D, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multi-centre double-blind, randomized, parallel-group study. *Oncology* 1994;51:113–8.
29. Stewart A, McQuade B, Cronje JD, Goedhals L, Gudgeon A, Corette L, et al. Ondansetron compared with granisetron in the prophylaxis of cyclophosphamide-induced emesis in outpatients: a multicentre, double-blind, double-dummy, randomized, parallel group study. *Oncology* 1995;52:202–10.