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A Risk-Benefit Assessment of Serotonin 5-HT$_3$ Receptor Antagonists in Antineoplastic Therapy–Induced Emesis

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Summary

Insight into the pathophysiology of antineoplastic therapy–induced nausea and vomiting led to the development of the serotonin 5-HT$_3$ receptor antagonists as the most potent class of antiemetic agents. Among those which have been investigated are ondansetron, granisetron, tropisetron and dolasetron. A risk-benefit analysis of these drugs must not only account for the modest clinical differences in efficacy and tolerability, but also should include such issues as ease of use, route of administration, dosage considerations and patient preference.

Pharmacokinetic and preclinical studies reveal distinctions among these antiemetics, but, overall, these distinctions do not translate in to clinically significant differences. In clinical trials, the most widely studied members of the 5-HT$_3$ receptor antagonists are granisetron and ondansetron, which have been found to possess equivalent antiemetic efficacy. Dolasetron and tropisetron are also available, and some randomised trials have also documented their similar antiemetic activity, depending on the doses and schedules used. The equivalent efficacy of oral granisetron 2mg versus intravenous ondansetron 32mg has recently been demonstrated in prospective randomised clinical trials in patients receiving either highly emetogenic or moderately emetogenic antineoplastic therapy. The utilisa-

tion and efficacy of oral ondansetron and dolasetron in patients receiving moderately emetogenic antineoplastic therapy has also been documented.

This review offers a brief overview of the pharmacokinetic and preclinical research on the 5-HT_3 antagonists, a review of the comparative clinical trials of the major members of this class and a summary risk-benefit assessment that considers clinical applicability and cost, as well as efficacy and safety.

Preventing the nausea and vomiting associated with antineoplastic agents has been a major challenge to clinicians seeking to improve quality of life for patients undergoing cancer treatment. Arguably, this is also an issue of treatment efficacy, since the capacity to tolerate optimal antineoplastic intervention with highly emetogenic agents is often a key factor in patient compliance and the ability to complete drug regimens that offer optimal prospects for antitumour response and improved indices of survival.

In the past decade, selective serotonin 5-HT_3 receptor antagonists have emerged as the mainstay of antiemetic therapy for patients undergoing anticancer therapy.[1] Granisetron, ondansetron, tropisetron and dolasetron are the most well tested and clinically applied therapies, although other 5-HT_3 antagonists have been evaluated and used in oncology settings.[2] Pharmacokinetic and preclinical studies reveal distinctions among the primary 5-HT_3 antiemetics, but overall, these distinctions do not translate into clinically significant differences.

As a result, decisions regarding antiemetic treatment with 5-HT_3 antagonists require a nuanced risk-benefit analysis that not only accounts for modest clinical differences in efficacy and tolerability, but also includes such issues as ease of use, route of administration, dosage considerations and patient preference. The following review offers a brief overview of pharmacokinetic and preclinical research on 5-HT_3 antagonists; a review of comparative clinical trials of the major 5-HT_3 antiemetics (granisetron, ondansetron, tropisetron, and dolasetron); and a summary risk-benefit assessment that considers clinical applicability and cost as well as efficacy and safety.

1. The Emergence of Serotonin 5-HT_3 Receptor Antagonists

Over the past 15 years, considerable advances have been made in the prevention of antineoplastic therapy–induced emesis. Research on antiemetic treatments for cancer patients expanded in the 1980s, in part because of the wider use of highly emetogenic antineoplastic therapy agents such as cisplatin.[2] Corticosteroids, antipsychotics, benzodiazepines, phenothiazines, and metoclopramide, the previous mainstay of antiemetic therapy, were the principle antiemetics used in the early 1980s. These agents were often used in combinations that increased efficacy and/or reduced adverse effects, but adverse effects – most notably the extrapyramidal effects associated with metoclopramide – prompted investigators to continue to seek better antiemetics for anticancer therapy.[3] Metoclopramide only provided relief from acute emesis associated with highly emetogenic antineoplastic agents in 30% to 40% of patients, even when combined with corticosteroids such as dexamethasone and benzodiazepines such as lorazepam.[2]

One clue leading to significant improvements in antiemetic therapy was the observation that dopamine receptor antagonism was not the exclusive antiemetic mechanism of metoclopramide. It was shown that only high-dose metoclopramide could reduce cisplatin-induced emesis successfully,[4] and that the resulting concentrations were greater than those required to antagonise dopamine receptors. In studies with ferrets, Miner and colleagues[5,6] demonstrated that high doses of metoclopramide antagonised the 5-HT_3 class of serotonin receptors, and that this action was its primary antiemetic mechanism of action in cisplatin therapy. Although dopamine receptor antagonism appeared to play a role in antiemetic treatment for

mildly or moderately emetogenic drugs, its role in highly emetogenic drug therapy was insignificant or nonexistent.[6]

Because increasing doses of metoclopramide carry correspondingly higher risks of extrapyramidal adverse effects, the recognition of the role of 5-HT_3 receptors in emesis fuelled the search for more selective 5-HT_3 antagonists. In research with ferrets, Miner and colleagues[5,7] evaluated 2 such agents, renzapride (BRL 24924) and bemesetron (MDL-72222), which were found to prevent or reduce emesis induced by cisplatin. A variety of 5-HT_3 antagonists were then studied in human phase I and II trials that confirmed their relative safety and efficacy in highly emetogenic cisplatin therapy.[8] Over the past decade, granisetron, ondansetron, tropisetron and, most recently, dolasetron have emerged as the most effective and applicable 5-HT_3 receptor antagonists for antiemetic therapy, although others have been tested with variable results.

Research into the role of 5-HT_3 receptors in antineoplastic therapy–induced emesis has provided new insights into the pathophysiology of nausea and vomiting. It has been hypothesised that the primary site of emetogenesis following antineoplastic therapy administration is the gut wall, leading to activation of vagal afferents, which in turn trigger central emetic pathways. The apparent mediation of serotonin (5-HT) led to the theory that cytotoxins stimulate the release of 5-HT and other neurotransmitters from enterochromaffin cells in the small intestinal mucosa.[9] Excessive release of 5-HT from enterochromaffin cells occurs in response to cytotoxic drugs.[10] A critical advance in our understanding of emetogenesis has been the finding that 5-HT specifically stimulates vagal afferent 5-HT_3 receptors; hence, the rationale for 5-HT_3 antagonists as antiemetics.

In addition to the 5-HT_3 receptors present on vagal afferent nerves, recent studies have demonstrated the presence of 5-HT autoreceptors on the enterochromaffin cells in guinea pigs.[11] The enterochromaffin cell 5-HT_3 receptor is a low affinity site that responds to high levels of 5-HT, such as those which occur following highly emetogenic antineoplastic therapy. This then results in increasing surges of 5-HT, in what amounts to a positive feedback loop that further contributes to the pathophysiology of emesis.[9] 5-HT_3 receptor activation also may occur at the nucleus tractus solitarius or the area postrema in the brain stem, but these sites probably play a secondary role in emetogenesis.[12]

Given these pathways, the differential effects of 5-HT_3 antagonists depend upon a number of factors, including receptor binding affinity; receptor selectivity; whether receptor block is surmountable; and whether 5-HT_3 antagonism occurs on vagal afferent nerves, enterochromaffin cells or both.

2. Pharmacokinetic and Preclinical Findings of 5-HT_3 Antagonists

2.1 Pharmacokinetics

Granisetron, ondansetron, tropisetron and dolasetron are well absorbed and widely distributed throughout the body. Among healthy volunteers, the terminal phase plasma half-life of granisetron is approximately 5 hours in younger patients (21 to 42 years old) and 8 hours in elderly patients (65 to 81 years old) receiving a single 40 μg/kg dose.[13] Among adult cancer patients, the plasma half-life is 9 hours. In healthy volunteers receiving a single 0.15 mg/kg dose of ondansetron, the mean elimination half-life for the age groups 19 to 40, 61 to 74, and ≥75 was 3.5, 4.7, and 5.5. hours, respectively.[14] In adult cancer patients, the mean elimination half-life was 4 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period. In one study of tropisetron, the terminal half life ranged from approximately 7 hours in 'fast metabolisers' to 30 hours in 'poor metabolisers'.[15]

Dolasetron is rapidly metabolised to a more potent and selective metabolite, hydrodolasetron, which possesses a longer half-life.[16,17] The plasma half-life of hydrodolasetron varies from 4.6 to 11.7 hours in studies, with a mean of 7 to 9 hours in adults.[18] Metabolite profiles of oral and intravenous formulations are virtually identical.[18]

Table I. Receptor binding affinity (pK) of serotonin 5-HT_3 receptor antagonists (adapted from van Wijngaarden et al.,[20] with permission)

	5-HT receptors				Other receptors
	1B	1C	3	4	α_1
Tropisetron	–	–	8.81	6.16	–
Granisetron	–	–	8.42	–	–
Ondansetron	5.43	5.31	8.07	–	5.44

2.2 Preclinical Research

Clinical data do not suggest any clear-cut relationship between the plasma kinetics of these 5-HT_3 antagonists and their efficacy as antiemetics. However, in preclinical research, control of antineoplastic therapy–induced emesis is obtained with doses of granisetron that are 2- to 3-fold lower than those required for tropisetron and 8- to 10-fold lower than those required for ondansetron.[19]

The other primary preclinical differences among 5-HT_3 antagonists involve selectivity, dose-response curves and antiemetic predictability. The issue of selectivity is chiefly associated with receptor binding affinities, which have been determined in comparative animal studies using radioligand binding techniques.[20] Granisetron, ondansetron, tropisetron[20] and dolasetron[16] all showed high affinity for the 5-HT_3 receptor. Ondansetron also showed weak activity at 5-HT_{1B}, 5-HT_{1C}, α_1- and opioid μ-receptors. Tropisetron was weakly active at the 5-HT re-uptake sites. Dolasetron also demonstrated weak affinity [50% inhibitory concentration (IC_{50}) >10 μmol/L] for 5-HT_{1A}, 5-HT_{1B}, and 5-HT_2 receptors, as well as α_1-, α_2-, and β-adrenoceptors, dopamine D_2, and muscarinic M_1, M_2, M_3, M_4, and M_5 receptors.[16] In contrast, granisetron did not demonstrate activity at any receptor site other than 5-HT_3. See table I for receptor binding affinity of 5-HT_3 antagonists.)

Normal depolarisation of the vagus nerve by 5-HT is counteracted by 5-HT receptor antagonists.[9] In one study in rats, 5-HT_3 antagonists were compared with regard to their capacity to antagonise serotonin-induced depolarisation with either surmountable or insurmountable block of the 5-HT_3 receptor.[21] Concentration response curves revealed that ondansetron and tubocurarine (which blocks 5-HT_3 receptors on the rat vagus nerve) antagonised 5-HT-induced depolarisation with a surmountable block of the 5-HT_3 receptor, while the action of granisetron and tropisetron involved an insurmountable block. It is theorised that excessive 5-HT release will be unable to overcome the action of agents that insurmountably block 5-HT_3 receptors.

Preclinical dose-response studies of the antiemetic effects of 5-HT_3 antagonists have also revealed important differences. A key study in ferrets evaluated the antiemetic efficacy of varying doses of granisetron and ondansetron to prevent emesis induced by 10 mg/kg intravenous cisplatin.[19] Increasing intravenous doses of granisetron resulted in a predictable decrease in the number of vomits, with a linear dose-response relationship. Ondansetron demonstrated a nonlinear dose-response relationship, with an initial decline followed by a sharp increase in the number of vomits at about 75 μg/kg, until further dose elevation reestablished control of emesis (fig. 1).[19] This study also evaluated dose-response curves for granisetron, ondansetron and tropisetron for radiation-induced emesis. Granisetron and tropisetron had linear dose-response relationships, whereas ondansetron again showed a nonlinear relationship.

These differences may be related to the fact that agents with nonlinear dose-response curves also possess 5-HT_4 receptor agonist activity, which heralds gastric prokinetic activity.[9] Agents such as metoclopramide, renzapride, and ondansetron have prokinetic activity and exhibit nonlinear dose-response curves, while granisetron and tropisetron, which do not evidence prokinetic activity, exhibit the predictable linear dose-response relationships.

In a single-dose study against emesis induced by intravenous cisplatin 10 mg/kg in ferrets,[16] intravenous dolasetron 0.5 mg/kg given 30 minutes before and 45 minutes after cisplatin, abolished emesis. Single oral doses of dolasetron 0.5 and 2.0 mg/kg, given 30 minutes before cisplatin, also significantly inhibited emesis. Clinical studies of in-

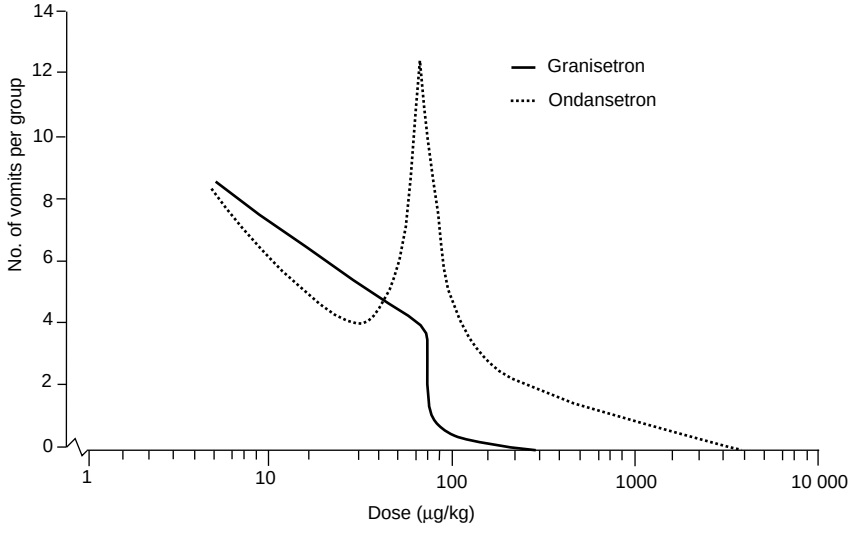

Fig.1. The antiemetic effect of intravenous (IV) ondansetron or granisteron (0.005 to 5.0 mg/kg) against emesis induced by cisplatin (10 mg/kg) in ferrets. Figures drawn from a minimum of 36 animals for each compound (reproduced from Andrews et al.,[19] with permission).

travenous dolasetron have revealed a statistically significant dose response, with efficacy increasing with dose.[22,23] Doses lower than 0.6 mg/kg were suboptimal; efficacy plateaued at 1.8 to 2.4 mg/kg.[17,22,24-27]

The 5-HT_3 receptor antagonists also exhibit different relative effects on afferent neuronal 5-HT_3 receptors and enterochromaffin cell 5-HT_3 receptors. Granisetron, ondansetron, tropisetron and dolasetron block vagal afferent receptors, whereas the enterochromaffin cells 5-HT_3 receptor is blocked by granisetron and tropisetron but not by ondansetron.[11] Whether observed clinical differences among these agents are associated with these differential effects is uncertain, although both afferent neuronal and enterochromaffin cells 5-HT_3 receptor sites appear to play key roles in the pathophysiology of emesis, and antagonism at both sites is presumed to contribute to antiemetic effects.

It has yet to be shown whether the varying pharmacokinetic profiles and preclinical findings among 5-HT_3 receptor antagonists translate into important distinctions in terms of overall clinical efficacy and safety. However, issues of selectivity of action, potency, and dose-responsitivity translate into clinical differences in dosage, oral *vs* intravenous administration in some clinical settings and predictability of response.

3. Establishment of 5-HT_3 Antagonists as Antiemetics of Choice

A large number of dose-ranging and phase II studies have helped to establish optimal dose, route of administration, and schedule of 5-HT_3 antagonists for patients receiving both moderately and highly emetogenic antineoplastic regimens.[2,8] In addition, many studies have established the superiority in both efficacy and safety of the major 5-HT_3 antagonists (granisetron and ondansetron and, to a lesser extent, tropisetron and dolasetron) when compared with previous standard regimens, including, most notably, metoclopramide, which carries increased risk of extrapyramidal adverse effects.[3,8,28-30] For purposes of this risk-benefit assessment, only comparative clinical trials of the 5-HT_3 antagonists will be reviewed.

TABLE II TO GO HERE (LANDSCAPE)

4. Comparative Clinical Trials of 5-HT_3 Antagonists

Given that ondansetron and granisetron were the first available 5-HT_3 antagonists and are the most clinically tested and used of the new antiemetic treatments, most comparative clinical trials of 5-HT_3 receptor antagonists have involved these 2 agents. Only 2 trials have included tropisetron in a comparator group. Two studies have compared dolasetron and ondansetron;[23,26] one compared dolasetron and granisetron.[17] The trials thus far published employ differing designs, patient populations, and antineoplastic therapy regimens, thus it is difficult to readily compare results. However, all trials were randomised with clear-cut assessment criteria and defined patient populations,[12] offering insight and tentative conclusions regarding relative efficacy and tolerability. Table II summarises results of 13 comparative clinical trials of 5-HT_3 antagonists tested for antiemetic efficacy.

4.1 Moderately Emetogenic Antineoplastic Therapy

An open-label, randomised, crossover study conducted by the French Northern Oncology Group compared granisetron 3mg (a single intravenous infusion on first day of antineoplastic therapy) with intravenous ondansetron 8mg given before antineoplastic therapy followed by an 8mg tablet every 8 hours for 3 days in cancer patients receiving non cisplatin based antineoplastic therapy.[31] Among 150 evaluable patients, a day 1 efficacy analysis revealed that 52% of patients receiving granisetron achieved total control of nausea and vomiting, compared with 45% of ondansetron patients. The difference was not statistically significant and there were no observed differences in complete response rates, overall control of either acute or delayed emesis or adverse effects. Patient preferences were similar (39% preferred granisetron, 34% ondansetron, and 27% expressed no preference).

An open, randomised, crossover comparison of single doses of intravenous granisetron (3mg),

Table II. Results of comparative trials of serotonin 5-HT_3 receptor antagonists

Antineoplastic therapy	Antiemetic agent [complete control of vomiting (%)]												Reference
	Granisetron				Ondansetron				Tropisetron		Dolasetron		
	PO 2mg	IV 3mg	IV 10 μg/kg	IV 40 μg/kg	IV 8mg	IV 24mg	IV 32mg	IV 0.15 mg/kg × 3	IV 5mg	IV 25-200mg	IV 1.8 mg/kg	IV 2.4 mg/kg	
Non cisplatin													
		52.0				45.0							31
	80.0[a]				68.5				74.6[a]				32
						72.3[a]				57.7[b]			23
	59.4[a]						58.0[a]						34
Cisplatin (mg/m^2)													
≥15		91.5				89.1							35
≥50		56.0			59.0		51.0						36
≥50		73.0				71.0							38
≥60	54.7						58.3						40
≥80		72.1				73.3			67.6				37
≥80		48.0									54.0	47.0	17
≥70-<91							50.4				49.2	45.6	26
≥91							31.8				36.8	31.3	26
≥60			38.0	41.0				39.0					39
≥100			28.0	33.0				25.0					39

a $p < 0.05$.

b Dolasetron 25mg = 45%; 50mg = 49.4%; 100mg = 60.5%; 200mg = 76.3%.

Abbreviation: IV = intravenous; PO = oral.

tropisetron (5mg) and ondansetron 8mg was conducted in 160 patients receiving moderately emetogenic antineoplastic therapy.[32] Among 130 evaluable patients, response data for the first cycle showed complete emetic control in 84%, 74.5% and 60.7% of granisetron, tropisetron and ondansetron recipients, respectively. The difference between granisetron and ondansetron rates were statistically significant ($p < 0.01$). Complete control of emesis over all 3 cycles was achieved in 80% of granisetron recipients, as compared with 75% in the tropisetron group and 69% in the ondansetron group (granisetron *vs* ondansetron, $p < 0.05$). Patients in all 3 arms of the study experienced similar adverse effects, with approximately one-third reporting headache. After 3 antineoplastic therapy cycles, more patients expressed preference for granisetron (41.5%) as opposed to ondansetron (16.9%) or tropisetron (15.4%), and 26.2% expressed no preference.

A double-blind crossover trial compared intravenous granisetron and ondansetron in 623 antineoplastic therapy–naive patients with breast cancer administered therapy with cyclophosphamide-doxorubicin.[33] Ondansetron 32mg was given as a 15-minute infusion 30 minutes before antineoplastic therapy, while granisetron 10 μg/kg was administered as a 30-second infusion within 5 minutes of antineoplastic therapy, using a double-dummy technique. Efficacy and tolerability were evaluated for 48 hours after 2 treatment cycles. A preliminary analysis of intent-to-treat data from the first cycle showed comparable prevention of emesis for the 2 treatment groups. More ondansetron recipients had no nausea at 24 hours compared with granisetron recipients ($p = 0.035$), although control of nausea was comparable in the 2 groups at 48 hours. Crossover data revealed that 49% of patients preferred granisetron and 51% preferred ondansetron; this was not significant. Although overall incidence of adverse effects was also comparable for the 2 groups, dizziness (14% *vs* 5%) and visual disturbance (6% *vs* 0.3%) were more common with ondansetron.[33] The data suggest that intravenous granisetron and ondansetron at the dose levels administered in this trial were similarly effective in preventing emesis in antineoplastic therapy–naive cancer patients receiving moderately emetogenic antineoplastic therapy. The bolus infusion of granisetron was well tolerated and not associated with increased risk of adverse effects.

Perez and colleagues recently completed a multicentre, double-blind, parallel group trial comparing the prophylactic efficacy of oral granisetron 2mg with intravenous ondansetron 32mg in 1085 antineoplastic therapy–naive patients undergoing treatment with moderately emetogenic antineoplastic therapy (cyclophosphamide or carboplatin-based regimens).[34] Half of the patients ($n = 542$) received two 1mg granisetron tablets or placebo 1 hour before antineoplastic therapy; the other half ($n = 543$) received a 15-minute infusion of ondansetron or placebo 30 minutes before antineoplastic therapy. Among those patients who received oral granisetron, total control of nausea and vomiting at 24 hours was obtained in 59.4%, compared with 58% of those receiving intravenous ondansetron. At 48 hours, 46.7% of granisetron-treated patients obtained total emetic control, compared with 43.8% of ondansetron recipients. Adverse events, measured for 11 days post treatment, were similar in both groups, although dizziness (9.6% in the ondansetron group *vs* 5.4% in the granisetron group) and abnormal vision (4.2% in the ondansetron group *vs* 0.6% in the granisetron group) were significantly more common in patients treated with ondansetron. It was concluded that oral granisetron and intravenous ondansetron were comparably efficacious in controlling nausea and vomiting in antineoplastic therapy–naive patients receiving moderately emetogenic antineoplastic therapy.[34]

A multicenter, randomised, double-blind study compared single oral doses of dolasetron (25, 50, 100 or 200mg) with oral, multiple-dose ondansetron (8mg x 3 or 8mg x 4) in 399 cancer patients receiving various types of moderately emetogenic antineoplastic therapy.[23] Dolasetron was given 1 hour before antineoplastic therapy to 316 patients; ondansetron was administered 1.5 hours before

and 6.5, 14.5, and 22.5 hours after the start of antineoplastic therapy to 83 patients (total ondansetron dose 32mg); 21 patients did not receive the final dose at 22.5h.[23] A single oral dose of 200mg dolasetron was therapeutically equivalent to multiple-dose ondansetron.[23] Complete response rates were equivalent for dolasetron 200mg and ondansetron (76.3% and 72.3%, respectively); both of those rates were significantly higher than complete response rates for dolasetron 25mg and 50mg.[23] Complete response rate with dolasetron 200mg was significantly higher than that with dolasetron 100mg.[23] Median patient satisfaction rating was 99mm on a 100mm visual analogue scale (where 100mm = completely satisfied) for 200mg dolasetron, and 98mm for ondansetron.[23]

4.2 Highly Emetogenic Antineoplastic Therapy

The first double-blind, randomised crossover trial comparing a single 3mg dose of intravenous granisetron and intravenous ondansetron 8mg 3 times daily included 309 patients on 5-day fractionated antineoplastic therapy, 260 of whom were receiving cisplatin and 49 of whom were receiving ifosfamide.[35] Antiemetic treatment was given on each day of antineoplastic therapy, and the 5-day complete response rates were 44% in granisetron recipients and 39.8% in ondansetron recipients. Over the first 24 hours at cycle 1, approximately 90% of patients in both groups were complete responders. Complete response rates were similar for patients receiving cisplatin or ifosfamide. The investigators noted a statistically significant difference in patient preference in favour of granisetron: 34% preferred granisetron, 25.6% preferred ondansetron, and 39.2% expressed no preference (granisetron *vs* ondansetron, $p < 0.05$). Both regimens were well tolerated.

Ruff and colleagues[36] conducted a study comparing intravenous ondansetron 8mg or 32 mg with intravenous granisetron 3 mg administered as a single dose before cisplatin-based antineoplastic therapy. Among 496 patients randomly assigned in this double-blind trial, no significant differences were observed in the 24-hour response rates of the 3 patient groups in terms of complete control of vomiting (mean 56%) and nausea (mean 70%). Adverse events, mainly headache, were minor and comparable, and the investigators concluded that all 3 antiemetic protocols were similarly well tolerated and effective.

Single intravenous doses of ondansetron 24mg, granisetron 3mg and tropisetron 5mg were compared in an open, randomised trial in 86 head-and-neck cancer patients receiving cisplatin-based antineoplastic therapy.[37] Both granisetron (74% complete control) and ondansetron (65.3%) were found to more effectively control emesis than tropisetron (44.3%; $p < 0.004$) during the first 24 hours after treatment. There were no significant differences in the tolerability profiles of these 3 regimens. Methodological limitations of the trial include the small number of patients, the fact that it was not blinded, and the lack of published detail about methods of randomisation and indices of efficacy and tolerability.

A crossover study by Martoni and colleagues[38] evaluated 5-HT_3 antiemetics in 62 patients receiving cisplatin-based antineoplastic therapy. Ondansetron was administered primarily as an 8mg infusion 3 times on day 1 (though some patients received two such infusions) and 8mg orally twice daily on day 2. Granisetron 3mg was administered intravenously on day 1. No significant differences were observed with respect to either complete control of vomiting or nausea between the 2 groups, although 49% of patients receiving granisetron expressed a preference for it, compared with 21% of patients receiving ondansetron and 30% who expressed no preference (granisetron *vs* ondansetron, $p = 0.008$).[38] No reasons were given for the patient preference data in light of the similar tolerability and efficacy profiles; it is therefore not clear whether the single versus repeat dose schedule accounted for preference for granisetron.

A double-blind, parallel-group, randomised study of 987 antineoplastic therapy–naive patients administered cisplatin therapy found approximately equivalent antiemetic control for these 3

regimens: intravenous granisetron 10 μg/kg; intravenous granisetron 40 μg/kg; and intravenous ondansetron 0.15 mg/kg 3 times a day, all administered on the day of antineoplastic therapy.[39] Efficacy was analysed by time to first nausea and vomiting, rate of complete control and lack of nausea or vomiting. Total control was attained by 38%, 41%, and 39% of all patients who received granisetron 10 μg/kg, granisetron 40 μg/kg and ondansetron, respectively. The results indicated that single-dose intravenous granisetron at 2 dose levels was as effective as 3 doses of intravenous ondansetron in the prevention of emesis induced by cisplatin therapy.

A double-blind, randomised, parallel study of 609 patients receiving first-course cisplatin therapy found comparable efficacy and tolerability with a single dose of intravenous dolasetron mesylate salt (1.8 mg/kg or 2.4 mg/kg) and a single intravenous dose of ondansetron 32mg.[26] Complete response rates for dolasetron 1.8 mg/kg and 2.4 mg/kg and for ondansetron, were 49.2%, 45.6% and 50.4% for patients receiving the lower of the 2 cisplatin dose ranges (70 mg/m^2 to <91 mg/m^2), respectively. Complete response rates for patients in the higher cisplatin dose stratum (91 mg/m^2) were 36.8%, 31.3%, and 31.8%, for dolasetron 1.8 mg/kg, dolasetron 2.4 mg/kg and ondansetron, respectively.[26] The lower dolasetron dose was tolerated slightly better than the higher one.[26] Headache and diarrhoea were the most common adverse events reported, though all regimens were well tolerated.[26]

In a multicenter, double-blind, double-dummy, randomised trial in which data from 474 patients were evaluable, the European Dolasetron Comparative Study Group found comparable safety and efficacy when patients received either a single dose of intravenous dolasetron 1.8 mg/kg or 2.4 mg/kg or intravenous granisetron 3mg.[17] All 3 regimens were given 30 minutes prior to administration of cisplatin-containing antineoplastic therapy.[17] Complete responses were achieved by 54%, 47%, and 48% of patients receiving dolasetron 1.8 mg/kg, dolasetron 2.4 mg/kg or granisetron 3mg, respectively.[17] Again, headache and diarrhoea were the most common adverse effects; the incidence of adverse events was comparable among treatment groups.[17]

4.3 Comparative Risk/Benefit Analysis of 5-HT$_3$ Antagonists

The two most commonly used 5-HT$_3$ antagonists – granisetron and ondansetron – have largely been found comparable in the head-to-head trials conducted to date. Tropisetron and dolasetron have favourable safety and efficacy profiles that are also comparable to granisetron and ondansetron, although too few clinical trials have been conducted to place these 5-HT$_3$ antagonists in the same rank as the 2 current mainstays of antiemetic treatment for cancer patients.

Thus, in conducting a useful risk-benefit assessment of 5-HT$_3$ antiemetics, issues of dose, schedule, route of administration, patient preference and cost become paramount. Five comparative trials of patients receiving moderately emetogenic antineoplastic therapy and 8 trials of patients receiving cisplatin-based antineoplastic therapy have revealed a number of trends that provide a basis for clinical distinctions and rational decision-making.

4.4 Safety

In the 5 trials comparing antiemetic regimens for moderately emetogenic antineoplastic therapy, results from 3 suggest similar efficacy for ondansetron and granisetron. In the one crossover trial, granisetron was found to be more effective than ondansetron and patients preferred the regimen.[32] However, certain methodological drawbacks limit interpretation: for example, the study was not blinded, nausea was not assessed and carry-over effects may have affected analysis of crossover results. In the large study of 1085 antineoplastic therapy–naive patients, equivalent efficacy was found for oral granisetron and intravenous ondansetron,[34] suggesting that a less costly and more easily administered antiemetic regimen can yield similar results in preventing nausea and vomiting. In addition, there was a statistically

higher incidence of visual disturbances and dizziness among ondansetron-treated patients, as opposed to granisetron-treated patients, in two of these trials.[33,34] Although these were relatively infrequent adverse effects in ondansetron recipients, they almost never occurred in granisetron-treated patients.

A trial comparing single oral doses of dolasetron and multiple oral doses of ondansetron in patients receiving moderately emetogenic antineoplastic therapy found comparable safety profiles for both agents, with mild to moderate headache the most common adverse effect associated with both agents.[23] Efficacy was comparable in patients receiving a single, 200mg dose of dolasetron and those given multiple doses of ondansetron (total dose 32mg).[23]

Among the 8 trials in cisplatin-treated patients, there was no evidence of significantly better efficacy for granisetron or ondansetron, although one trial demonstrated that both agents were superior to tropisetron.[37] However, patients were found to prefer granisetron to ondansetron in 2 crossover trials.[35,38] In the first, granisetron was administered as a single intravenous dose, while ondansetron was administered as 3 daily intravenous doses,[35] although the use of the double-dummy technique essentially precluded the possibility that preference was related to dose schedule. In the second trial, one intravenous dose of granisetron was preferred to the 3-dose ondansetron regimen followed by an oral dose the next day,[38] although the investigators did not explore whether dosing differences accounted for patient preferences. Indeed, neither study investigated the reasons for patient preference, so no firm conclusions regarding these distinctions can currently be drawn.

In two of the randomised comparative trials demonstrating equivalent antiemetic efficacy for granisetron and ondansetron, the relative ease of the schedules and routes of administration could be said to favour granisetron. In the first trial, which included 260 cisplatin-treated patients, oral granisetron was shown to be as effective as intravenous ondansetron.[38] The second, a large, double-blind, randomised, parallel group study of 987 patients receiving cisplatin, had no crossover design and could not evaluate patient preference. It did, however, establish equivalent safety and efficacy for single dose intravenous granisetron and the 3-dose regimen of ondansetron.[39]

A 30-second infusion of granisetron has also been found to be well tolerated and efficacious. In a double-blind crossover study of 623 breast cancer patients receiving cyclophosphamide and doxorubicin, a 30-second infusion of granisetron 10 μg/kg administered within 5 minutes of antineoplastic therapy was found to be as effective in preventing emesis as a 15-minute infusion of ondansetron 32mg given 30 minutes prior to antineoplastic therapy.[33] Both regimens were associated with similarly good safety and tolerability profiles.

Intravenous dolasetron (1.8 mg/kg and 2.4 mg/kg) has been compared in separate trials to intravenous ondansetron 32mg[26] and intravenous granisetron 3mg.[17] Efficacy and safety of both dolasetron doses were comparable to those of the other agents. Single doses of each agent were used in both trials.[17,26] Patient satisfaction ratings were similar for both dolasetron doses and granisetron or ondansetron in these trials.[17,26]

Another group of investigators recently compared the safety and efficacy of oral granisetron and intravenous ondansetron in patients receiving cisplatin therapy.[40] In this multicenter, double-blind trial, 1054 patients were randomised to receive either oral granisetron (2mg given 1 hour before cisplatin therapy) or ondansetron (32mg infused 30 minutes before cisplatin therapy). Alternate treatment groups received placebo to facilitate blinding; dexamethasone was administered to all patients as needed. The total control rate for both groups was similar: 54.7% for oral granisetron and 58.3% for intravenous ondansetron. With dexamethasone, the total control rate was 58.8% for oral granisetron and 61.5% for intravenous ondansetron. Adverse effects, including headache (15%); constipation (14%) and diarrhoea (10%) occurred with similar frequency in both groups. The inves-

tigators concluded that the comparable efficacy and safety, when considered *vís-a-vís* issues of convenience and lower cost, favoured the use of oral granisetron in this clinical setting.[40] This suggests that oral administration of an antiemetic is an acceptable alternative, even in cisplatin-treated patients. This recommendation carries 3 qualifiers: that the antiemetic agent used has good bioavailability, that the patient has an intact gastrointestinal tract to ensure absorption and that the patient is likely to comply with therapy. Efficacy of oral 5-HT_3 antagonist therapy is already proven for use with moderately emetogenic antineoplastic therapy.

The safety profiles of the 5-HT_3 antagonists are more favourable than that of the former standard, metoclopramide, which was associated with the risk of extrapyramidal reactions. However, a few reports have shown associations of 5-HT_3 antagonists with electrocardiographic (ECG) abnormalities. Preclinical studies in anaesthetised dogs showed that ondansetron and another 5-HT_3 antagonist, zatosetron, could prolong the QTc interval.[41] In a small study of patients receiving cisplatin, 85% of patients receiving intravenous ondansetron 32mg or dolasetron 1.8 to 3.0 mg/m^2 showed statistically significant prolongation of the QTc interval.[42] In a study of 12 patients receiving intravenous granisetron 50 μg/kg (5 × the standard dose), 4 experienced significant ECG changes.[43] In general, these ECG alterations have not been considered life-threatening or the basis for contraindication in the vast majority of patients.[2] One report, however, has linked treatment with ondansetron to the development of angina.[44]

Clinical trials of dolasetron have revealed clinically asymptomatic, insignificant increases in QTc, QT, PR, QRS and JT intervals.[17,26,27] At 1 to 2 hours post-treatment, dolasetron recipients had significantly greater QTc and PR prolongation compared to baseline levels than did those given granisetron[17] or ondansetron.[26] Dolasetron also was associated with significantly greater QRS prolongation at 1 to 2 hours post-treatment compared to ondansetron.[26]

It should be noted that oral ondansetron, which has a mixed record of antiemetic efficacy in cisplatin-based antineoplastic therapy, has not been approved for use in patients receiving cisplatin. Thus, when cisplatin dose and other patient

Table III. Cost comparison ($US) of intravenous serotonin 5-HT_3 receptor anatgonists for prevention of antineoplastic therapy–induced emesis. Costs were calculated based on December 1997 wholesale manufacturer prices (40mg vial ondansetron $US244.30; 1mg vial granisetron $US177.40; 100mg vial dolasetron $US149.88)

Agent	Patient weight (kg)			
	50	60	70	80
Noncisplatin antineoplastic therapy				
Ondansetron 32mg × 1[a]	195.54	195.54	195.54	195.54
Granisetron 10 μg/kg[a]	88.70	106.44	124.18	141.92
Dolasetron 1.8 mg/kg[a]	134.89	161.87	188.85	215.83
Dolasetron 100mg[a]	149.88	149.88	149.88	149.88
Cisplatin antineoplastic therapy				
Ondansetron 0.15 mg/kg × 3[a]	137.42	164.90	192.39	219.87
Ondansetron 32 mg × 1[a]	195.54	195.54	195.54	195.54
Granisetron 10 μg/kg[a]	88.70	106.44	124.18	141.92
Non-FDA approved doses sometimes used				
Ondansetron 8mg × 1	48.86	48.86	48.86	48.86
Ondansetron 16mg × 1	97.72	97.72	97.72	97.72
Ondansetron 24mg × 1	146.58	146.58	146.58	146.58
Granisetron 1mg × 1	177.40	177.40	177.40	177.40

a US Food and Drug Administration (FDA) approved doses

variables indicate that oral granisetron is a viable option, it may be considered a treatment of choice, given its ease of administration and reduced cost.

4.5 Cost Considerations

Owing to the similar efficacy profiles of 5-HT_3 antagonists, issues of cost should be included in any calculation of risks and relative benefits. Table III includes a breakdown of costs for intravenous ondansetron *vs* intravenous granisetron for non cisplatin, cisplatin-based at US FDA approved doses and also costs for non FDA approved doses that are sometimes used. Note that the US FDA-approved doses of granisetron are considerably less expensive than the FDA-approved dose levels of ondansetron for both non cisplatin and cisplatin-based antineoplastic therapy.[30] This may not be true for the doses approved in Europe. The approved dose of ondansetron is 4-fold higher in the US than in Europe (32mg in the US *vs* 8mg in Europe), while for granisetron the opposite is true (10 mg/kg in the US *vs* 40 mg/kg in Europe). Most data suggest that the lower and higher recommended doses of each drug are equivalent in efficacy,[36,39,45-50] suggesting that the lower dose should be used. Because dolasetron has only recently been approved at the time of writing, cost comparisons involving this agent cannot be made.

For our recent multicentre trial comparing oral granisetron 2mg and intravenous ondansetron 32mg among 1054 cancer patients receiving cisplatin, these equally efficacious regimens were associated with markedly different costs.[40] The cost of the oral granisetron regimen was $US62, as compared to $US129 for intravenous ondansetron at the time that this study was performed. Table IV provides data about the relative efficacy and cost of the 2 regimens.

This risk-benefit analysis yields sufficient data to make the following tentative conclusions: granisetron and ondansetron are the most well studied, predictable, and consistently efficacious 5-HT_3 antiemetics. Both have similar safety and tolerability profiles, with headache, constipation and diarrhoea being the most common (though mild) adverse effects seen with both agents, although visual disturbances and dizziness, while relatively rare, are more common with intravenous ondansetron. Some concerns have been raised about cardiac events with ondansetron, though clinicians should be aware of this possibility in all 5-HT_3 treated patients who may experience ECG changes. When possible, oral granisetron is a treatment of choice for patients receiving cisplatin. Patients may prefer granisetron because it affords either the possibility of oral treatment, or the possibility of fewer additional infusions, during antineoplastic therapy. Several cost analyses suggest that both intravenous and oral granisetron are less expensive than intravenous ondansetron based on doses approved for use in the US. As mentioned previously, cost comparisons including dolasetron have not been made.

5. Conclusion

In an era when ease of administration, patient preference and cost-effectiveness are critical issues in the delivery of healthcare, these factors must be considered in any risk-benefit analysis. Because the 5-HT_3 inhibitors evidence similar efficacy, these factors become evermore relevant. Although more head-to-head trials of 5-HT_3 antagonists are needed, it appears that ondansetron and granisetron are the most well established 5-HT_3 antiemetics, demonstrating high levels of complete control of emesis and favourable safety and tolerability pro-

Table IV. Emetic control and cost regimen: comparison of results in 1054 cisplatin-treated patients randomised to receive either oral granisetron or intravenous ondansetron (reproduced from Gralla et al.,[40] with permission)

Antiemetic regimen	Number of patients	Total emetic control (%)		Cost of regimen ($US)
		all patients	with corticosteroids	
Oral granisetron 2mg	534	54.7	58.8	62
Intravenous ondansetron 32mg	520	53.8	61.5	129

files. Ondansetron may be associated with more visual disturbances or dizziness, though the incidence of these adverse effects is low.[33,34] Cost analyses using doses approved in the US tend to favour granisetron over ondansetron in both intravenous and oral preparations. In addition, granisetron can more readily be given as a single intravenous dose for patients receiving non cisplatin or cisplatin-based regimens, and unlike ondansetron, it is approved as an oral agent for cisplatin-based (highly emetogenic) antineoplastic therapy. Finally, 3 clinical trials indicate patient preference for granisetron, although several of these trials have methodological limitations.[12] Although the documented pharmacokinetic and preclinical differences among 5-HT_3 antagonists have not translated into clear-cut clinical differences, they influence issues such as dose and schedule, which in turn influence ease of administration and patient preferences.

Thus, in a risk-benefit assessment, ease of administration and schedule (oral *vs* intravenous; multiple intravenous doses *vs* single IV dose) appear to argue well for patient acceptance and preference, which may have further beneficial effects on compliance and quality-of-life. Cost analyses also favour granisetron in its intravenous and oral preparations at the FDA-approved doses. Comparative trials to date offer a rationale for utilisation of the most cost-effective 5-HT_3 antiemetic, as all have a good overall record of safety and efficacy. Oral therapy potentially offers advantages such as reduced cost and improved convenience.

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