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Serotonin type 3–receptor antagonists for chemotherapy-induced nausea and vomiting: Therapeutically equivalent or meaningfully different?

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Before the introduction of serotonin type 3–receptor (5-HT₃) antagonists, nausea and vomiting were the most frequently reported and most difficult to manage adverse effects experienced by oncology patients, as well as the most common reasons for non-compliance with cancer treatment regimens.¹

In a study published in 1990, Cubeddu and colleagues² demonstrated that serotonin is an important mediator of chemotherapy-induced nausea and vomiting (CINV) in patients treated with cisplatin, and they proved the efficacy of the first 5-HT₃ antagonist, ondansetron, in preventing chemotherapy-induced emesis. Cubeddu et al.³ subsequently demonstrated that levels of serotonin-breakdown products in the urine of patients receiving cisplatin peak approximately 6 hours after the chemotherapy dose and remain elevated after 24 hours. The logical interpretation of these data was that repeat dosing of a drug with a 6-hour half-life (ondansetron) is needed to achieve adequate control of CINV. This interpretation led to the 1991 U.S. marketing approval of ondansetron for the prevention of CINV administered before chemotherapy, with repeat doses recommended 4 and 8 hours after chemotherapy.

Additional 5-HT₃ antagonists—granisetron, dolasetron, and palonosetron—were subsequently approved in the United States, usually on the basis of noninferiority trials comparing each new agent with ondansetron, giving rise to the general acceptance of the notion that 5-HT₃ antagonists are therapeutically equivalent.⁴ The American Society of Clinical Oncology (ASCO) currently recommends a three-drug regimen entailing the

administration of a 5-HT₃ antagonist, dexamethasone, and a neurokinin 1 (NK1)–receptor antagonist on day 1, with continued use of dexamethasone on days 2–4 and the NK1 antagonist on days 2 and 3 for the prevention of CINV in patients receiving highly emetogenic chemotherapy (HEC).⁵ The recommended regimen for the prevention of CINV caused by moderately emetogenic chemotherapy (MEC) is a two-drug regimen, with a 5-HT₃ antagonist (given on day 1) along with dexamethasone⁵; an NK1 antagonist can be added on day 1 in patients at high risk for nausea and vomiting. ASCO recommends that if granisetron, ondansetron, or dolasetron is used on day 1, the 5-HT₃ antagonist and dexamethasone should be continued on days 2 and 3; if palonosetron is used on day 1, no additional doses of the drug are required, as its half-life is 40 hours, but dexamethasone is to be continued on days 2 and 3. Palonosetron was recently recommended as the preferred 5-HT₃ antagonist by ASCO,⁵ the National Comprehensive Cancer Network (NCCN),⁶ and the Multinational Association of Supportive Care in Cancer.⁷

Given that the acquisition cost of a dose of palonosetron is \$190, compared with a cost of less than \$5 for both granisetron and ondansetron, preferential use of palonosetron will have significant financial implications for the health care system.⁸ Yeh and colleagues,⁸ in an accompanying commentary (see page 500), conservatively estimate that if 5–10% of Medicare patients are switched to palonosetron from other treatments, the annual increase to the Medicare program will be \$74 million to \$147 million per year. In considering palonosetron's place in therapy, we must determine whether palonosetron is the most efficacious agent in its class, whether it is the safest agent in its class, and—if it is the most efficacious or safest—whether it is worth the extra cost.

Efficacy

Yeh and colleagues⁸ review the evidence that has been used by various organizations to support the designation of palonosetron as the preferred 5-HT₃ antagonist for the management of CINV in patients receiving MEC and HEC. They conclude that there is inadequate evidence to support granting palonosetron preferential status. This conclusion is based on the observation that the clinical trials and meta-analyses cited in support of the claim of palonosetron's superiority were not designed to compare palonosetron therapy with currently accepted best clinical practices.

Why, then, do the most widely followed clinical practice guidelines^{5–7} designate palonosetron as the preferred agent? The most recent version of the NCCN guidelines⁶ is based on four international, randomized, controlled, Phase III clinical trials (Table 1).^{9–12} Two trials focused on patients with HEC; one trial compared a single dose of palonosetron with a single dose of granisetron,⁹ while the other compared a single dose of palonosetron with a single dose of ondansetron.¹⁰ As discussed by Yeh et al., neither trial reflected the currently recommended use of 5-HT₃ antagonists for preventing HEC, as concurrent treatment with an NK1-receptor antagonist was not allowed and single (rather than multiple) doses of comparator agents were used. (For preventing CINV associated with HEC, the labeled dosage of ondansetron is 16 mg i.v. for three doses¹³ and that for granisetron is 1 mg i.v. twice a day.¹⁴) While complete-response rates for palonosetron in these studies were numerically higher—75.3% for palonosetron versus 73.3% for granisetron⁹ and 59.2% for

palonosetron versus 57% for ondansetron¹⁰—the differences were not significant. Although a single dose of palonosetron appears to prevent CINV just as well as grossly underdosed ondansetron or granisetron, we are left with no meaningful evidence to judge the efficacy of palonosetron compared with appropriately administered alternatives.

Two trials of palonosetron focused on patients with MEC, with one comparing a single dose of palonosetron and a single dose of dolasetron¹¹ and the other comparing a single dose of palonosetron and a single dose of ondansetron.¹² Again, neither trial compared palonosetron with adequately administered alternatives, and we are left with no meaningful evidence that would support palonosetron as a preferred agent over other, less expensive products.

Finally, a recent meta-analysis by Jin et al.¹⁵ concluded that a single dose of palonosetron was superior to a single dose of the other 5-HT₃ antagonists evaluated for the prevention of CINV (relative risk [RR], 1.11; 95% confidence interval [CI], 1.05–1.17) and that there was no differences in toxicity among the agents. Of note, the meta-analysis included three of the four trials described above,^{10–12} which compared palonosetron with underdosed alternative agents; these three trials accounted for 1198 (60%) of the 1997 patients included in the analysis. The Phase III randomized clinical trial conducted by Saito and colleagues,⁹ which enrolled more than 1000 patients and demonstrated that palonosetron was equivalent to granisetron, was not included.

We updated the meta-analysis by Jin et al.¹⁵ by including the trial by Saito et al.⁹ and calculated the number needed to treat with palonosetron in order to demonstrate improved antiemetic control relative to that achieved with other 5-HT₃ antagonists (Table 2). Our pooled estimates of the percentage of patients who had a complete response (no emesis or nausea in the first 24 hours) were 75% (95% CI, 73–77%) for palonosetron and 69% (95% CI, 67%–72%) for a single dose of the comparator drug (RR, 1.09; 95% CI, 1.04–1.14). This suggests that for 1 patient to experience a benefit from palonosetron (defined as a complete response), compared with an underdosed alternative agent, 17 patients (95% CI, 8–26 patients) must be treated with palonosetron. As previously discussed, the meta-analysis by Jin et al.¹⁵ and our update of it, both of which were based on trials comparing single doses of palonosetron and other 5-HT₃ antagonists, did not allow the use of NK1-receptor antagonists to help prevent CINV caused by HEC or the use of dexamethasone as an aid to the prevention of CINV in patients receiving MEC. Thus, the available literature does not support the preferred use of palonosetron in contemporary practice.

So, is palonosetron the most efficacious 5-HT₃ antagonist? Given what we know about the half-lives of these agents and the duration of serotonin elevation after chemotherapy administration, we should not be surprised to find that a single dose of palonosetron is more efficacious than a single dose of ondansetron, granisetron, or dolasetron for preventing CINV. What is surprising is that anyone would conduct, recruit patients for, and publish results of a trial in which the chosen comparator treatment is known a priori to be inferior to the agent under study (palonosetron). It is even more surprising that evidence from such trials would be used to designate that agent as preferred in treatment guidelines. To support the preferred use of palonosetron, a trial would need to be adequately powered to

demonstrate superiority, compare 5-HT₃ antagonists administered at standard dosages, and incorporate a standard regimen including an NK1-receptor antagonist or dexamethasone.

Safety

Since palonosetron has not been shown to be more efficacious than other 5-HT₃ antagonists, is it safer? While the meta-analysis by Jin et al.¹⁵ showed no difference in adverse effects among the agents, Q-T interval prolongation is a concern (this is a class effect with 5-HT₃ antagonists, including palonosetron²⁰). The risk of Q-T interval prolongation is dose dependent and more likely with i.v. bolus administration. These observations have led to the designation of the i.v. formulation of dolasetron as contraindicated in CINV and the withdrawal of the 32-mg i.v. dose of ondansetron from the market. Mason and Moon²⁰ calculated safety margins for the 5-HT₃ antagonists by dividing the in vitro drug concentrations needed for 50% inhibition of cardiac potassium channels by the expected maximum in vivo drug concentrations with the use of the standard dosage. Palonosetron had the best cardiac safety margin, with a safety ratio of 901, followed by granisetron at 605, ondansetron at 35, and dolasetron at 31. This essentially means that, with standard dosage and in the worst-case scenario, dolasetron concentrations would need to be increased 35-fold to produce a 50% inhibition of cardiac potassium channels. A practical interpretation of these data is that granisetron and palonosetron carry almost no risk of Q-T interval prolongation, while ondansetron and dolasetron carry a small risk. Avoiding ondansetron and dolasetron in patients taking other medications with the potential to prolong the Q-T interval or with underlying cardiac conduction abnormalities would be warranted.

Cost considerations

Finally, what are the cost implications of palonosetron's preferred status? An economic analysis showed that, when compared with ondansetron-containing regimens, palonosetron-based regimens have a cost per quality-adjusted life-year exceeding \$100,000 and were thus not considered acceptable.²¹ Of note, this analysis was based on prices for brand-name products because it was conducted before generic formulations of ondansetron and granisetron became available. For a cycle of chemotherapy, a single dose of palonosetron costs \$190, compared with six doses of granisetron (1 mg twice a day for three days) at a total cost of \$18 or six doses of ondansetron (8 mg twice a day for three days) at a total cost of \$6. The preferential use of palonosetron adds about \$184 to the cost per cycle of chemotherapy administered.

Which is the preferred agent?

Given the available data, is there a preferred 5-HT₃–receptor antagonist or are they therapeutically interchangeable? The three most important clinical criteria—efficacy, common toxicities, and Q-T interval prolongation—can be compared, as can cost. The evidence suggests that all four agents are equivalent in efficacy and common toxicities, although palonosetron and granisetron are least likely to result in Q-T prolongation. Our interpretation of these data is that all four agents are therapeutically interchangeable for most patients; the exceptions are patients treated with medications known to prolong the Q-T interval and patients with underlying cardiac conduction abnormalities, in whom

ondansetron and dolasetron should be avoided. Given therapeutic equivalence, cost considerations suggest that granisetron may actually be the preferred 5-HT₃ antagonist.

Summary and conclusion

Despite the number of randomized Phase III clinical trials, it seems there is no evidence demonstrating that palonosetron is more efficacious than other 5-HT₃ antagonists in contemporary practice. Reported trials are limited by the use of nonstandard antiemetic regimens and by suboptimal dosing of the 5-HT₃ antagonist comparators. A meta-analysis suggests no safety differences among agents, though ondansetron and dolasetron are associated with a small risk of Q-T prolongation and should be avoided in at-risk patients. Given the cost differences among agents, the preferred use of palonosetron is an irresponsible position.

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Table 1

Trials Cited in National Comprehensive Cancer Network Guidelines to Support Preferred Status of Palonosetron^{6, a}

Ref.	Dosage of Comparator	Emetogenicity of Chemotherapy	% Patients Receiving Dexamethasone	% Patients With Complete Response
9	Granisetron 40 µ/kg	High	100 (for 3 days)	Palonosetron, 75.3; granisetron, 73.3
10	Ondansetron 32 mg	High	79	Palonosetron, 59.2; ondansetron, 57.0
11	Dolasetron 100 mg	Moderate	5	Palonosetron, 63.0; dolasetron, 52.9
12	Ondansetron 32 mg	Moderate	0	Palonosetron, 81.0; ondansetron, 68.6 ^b

^a The primary endpoint in all studies was a complete response (no emetic episode and no use of rescue medication) during the 24 hours after chemotherapy. All studies used one dose of palonosetron 0.25 mg i.v. and one i.v. dose of the comparator drug. Unless otherwise indicated, the difference between drugs in complete-response rate was not significant.

^b $p = 0.025$.

Table 2

Updated Meta-analysis of Trials Comparing Single Dose of Palonosetron 0.25 mg I.V. With Other Serotonin Type 3-Receptor Antagonists^a

Ref	Fraction (%) Patients With Complete Response		Relative Risk (95% CI) ^b	Number Needed to Treat (95%CI) ^c
	Palonosetron	Comparator		
9	418/555 (75.3)	410/559 (73.3)	1.03 (0.96–1.10)	51 (0–183)
10	132/223 (59.2)	126/221 (57.0)	1.04 (0.89–1.22)	46 (0–240)
11	119/189 (63.0)	101/191 (52.9)	1.19 (1.00–1.42)	10 (0–20)
12	153/189 (81.0)	127/185 (68.6)	1.18 (1.05–1.33)	8 (2–14)
16	86/104 (82.7)	75/104 (72.1)	1.15 (0.99–1.33)	9 (0–20)
17	105/118 (89.0)	91/118 (77.1)	1.15 (1.03–1.30)	8 (2–15)
18	91/128 (71.1)	90/138 (65.2)	1.09 (0.92–1.28)	17 (0–50)
19	42/44 (95.5)	42/45 (93.3)	1.02 (0.92–1.13)	47 (0–262)
Overall ^d	(75.2)	(69.2)	1.09 (1.04–1.14)	17 (8–26)

^a CI = confidence interval.

^b Relative risk of development of chemotherapy-induced nausea and vomiting.

^c Number needed to treat to add one quality-adjusted life-year; calculated from fixed-effects (Mantel-Haenszel) meta-analysis model.

^d Pooled estimates from fixed-effects (Mantel-Haenszel) meta-analysis model with Woolf's test for heterogeneity; $p = 0.285$.