

A review of dolasetron as management of nausea and vomiting in cancer patients

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Objective. To systematically review the literature about the pharmacology, pharmacokinetics, efficacy, dosing, and adverse effects of dolasetron, and to define its role in the management of chemotherapy- and radiation-induced nausea and vomiting.

Data Synthesis. A MedLine search was conducted using 5-HT₃-receptor antagonists, antiemetics, chemotherapy toxicity, dolasetron, emesis, nausea, and vomiting as search terms. Reference lists and bibliographies of pertinent articles were also identified and reviewed. Both preclinical and clinical literature were reviewed and analyzed.

Data Synthesis. Dolasetron is a serotonin type 3 (5-HT₃)-receptor antagonist with potent antiemetic effects in the management of nausea and vomiting. Following administration, dolasetron is rapidly converted to hydrodolasetron, which is believed to be responsible for the drug's antiemetic activity. Results of multiple studies have demonstrated the efficacy of this agent in the prevention of chemotherapy-induced emesis, including that induced by cisplatin. As a single agent, dolasetron produces a complete response rate (RR) in 44% to 57% of patients treated with cisplatin (≥ 70 mg/m²) and in 59% to 80% of

patients treated with moderately emetogenic chemotherapy, such as cyclophosphamide, methotrexate, and fluorouracil (CMF) therapy. When combined with dexamethasone, the RRs are increased. Dolasetron is well tolerated, with headache (24%) and diarrhea (12%) the most commonly reported adverse effects. The efficacy and safety of dolasetron are comparable to those observed with other 5-HT₃-receptor antagonists. According to four recently published clinical practice guidelines for use of antiemetics, dolasetron is an appropriate first-line option for the prevention of nausea and vomiting due to moderately to highly emetogenic chemotherapy. Further clinical trials will determine the optimal dose and the role of this highly effective antiemetic agent for other purposes, such as treatment of delayed emesis and emesis resulting from radiation therapy and high-dose chemotherapy followed by bone marrow transplantation.

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Key Words: 5-HT₃-receptor antagonists; antiemetics; chemotherapy toxicity; dolasetron; emesis; nausea; vomiting.

INTRODUCTION

The past decade has brought numerous advances in the treatment of cancer, but few have revolutionized the delivery of cancer care as much as the serotonin-

receptor-antagonist class of antiemetics. These agents have significantly reduced the incidence of nausea and vomiting caused by chemotherapy, resulting in reduced complications of uncontrolled emesis and improved quality of life. Four serotonin type 3 (5-HT₃)-receptor antagonists are currently marketed worldwide, including dolasetron, granisetron, ondansetron, and tropisetron. Dolasetron (Anzemet[®], Aventis Pharmaceuticals, Frankfurt, Germany, or Parsippany, NJ, USA) is the most recently Food and Drug Administration (FDA)-approved agent with established efficacy in prevention of nausea and vomiting due to chemotherapy and surgical anesthesia. This review focuses on dolasetron's activity in

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treating emesis caused by chemotherapy and radiation therapy.

Clinical pharmacology

Dolasetron mesylate (MDL 73,147) is a pseudopelletierine derivative, with pharmacologic properties similar to those of other 5-HT₃ – receptor antagonists (Figure 1). It is a potent and highly selective antagonist of the 5-HT₃ receptor in the chemoreceptor trigger zone and gastrointestinal tract. Receptor blockade at these sites is the mechanism of dolasetron's protective effects against emesis due to chemotherapy and radiation therapy. The active metabolite of dolasetron, hydrodolasetron, is a 50-fold more potent antagonist of the 5-HT₃ receptor than the parent compound. Neither dolasetron nor any of its metabolites has demonstrated an affinity for dopamine, opioid, benzodiazepine, or any other type of serotonin receptors.

Clinical pharmacokinetics

The pharmacokinetics of dolasetron and hydrodolasetron have been studied in healthy volunteers and cancer patients.¹⁻¹² Table 1 summarizes the pharmacokinetic parameters of hydrodolasetron in both groups. Dolasetron is rapidly metabolized by carbonyl reductases to an active metabolite, known as either hydrodolasetron or reduced dolasetron. These reductases are ubiquitous and found in red blood cells and multiple other tissues. Interestingly, carbonyl reductases exhibit stereoselectiv-

Table 1. Pharmacokinetic Parameters of Dolasetron (Hydrodolasetron)^{1,7,10-12}

Pharmacokinetic parameter	Hydrodolasetron
Mean AUC _(0-∞) (ng _s h/mL)	200 mg iv: 3638
	100 mg iv: 1797
	50 mg iv: 910
	200 mg po: 2680
	100 mg po: 1181
Mean C _{max} (ng/mL)	200 mg iv: 647
	100 mg iv: 320
	50 mg iv: 161
	200 mg po: 520-601
T _{max} (h)	100 mg po: 225
	0.62-1.1 iv
t _{1/2} (h)	0.74-1.51 po
	6.6-10.3 iv
	7.0-8.8 po
Clearance (mL/min/kg)	6.9-10.8 iv
	12.9-15.5 po
	5.0-10.9
V _d (L/kg)	5.0-10.9

AUC=area under the curve; C_{max}=the maximum or peak concentration of a drug observed after its administration; T_{max}=time at which the C_{max} is achieved; V_d=volume of distribution.

ity in their reduction of dolasetron to hydrodolasetron, such that the R(+) enantiomer is favored. The R(+) enantiomer of hydrodolasetron accounts for more than 75% of the metabolite found in plasma and more than 86% of that in urine. Of note, the R(+) enantiomer is the most potent antagonist of 5-HT₃ receptors compared with the parent compound, the S(-) enantiomer, and other dolasetron metabolites. Thus, the R(+) enantiomer of hydrodolasetron is believed to be chiefly responsible for the antiemetic activity observed with dolasetron.^{1,2} Because the parent drug is only detected in plasma for less than 1 hour after a single 100-mg oral dose, hydrodolasetron is measured to assess its pharmacokinetic profile.

Following iv administration, dolasetron (50-200 mg) disappears rapidly from the blood stream, with a half-life of approximately 10 minutes. In contrast, dolasetron is rarely detected in the blood stream after oral administration of 200 mg.^{1,2} The pharmacokinetics of dolasetron are linear over a dose range of 50 to 200 mg. There is a dose-dependent increase in the area under the curve (AUC), but half-life, clearance, and volume of distribution are constant. Hydrodolasetron is formed rapidly, with a mean time to maximum concentration of less than 1 hour. Like its parent compound, hydrodolasetron's pharmacokinetics are linear over a dose range of 50 to 200 mg. The half-life of hydrodolasetron ranges from 6.6 to 8.8 hours. Hydrodolasetron is primarily eliminated in the urine, but is also further metabolized by the CYP2D6 and CYP3A4 cytochrome P-450 (CYP450) enzymes.³ *In vitro* study results also demonstrate that hydro-

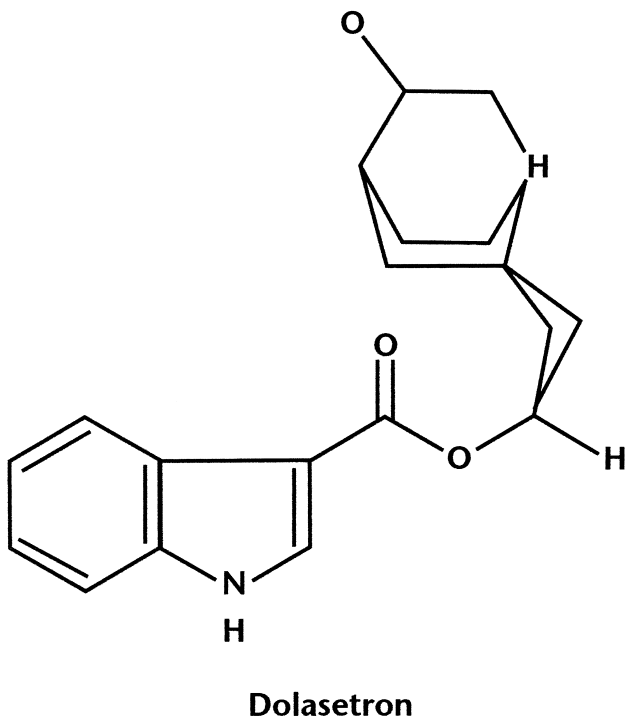


Figure 1. Chemical structure of dolasetron.

dolasetron is a competitive inhibitor of CYP2D6, although concentrations used in this study were two orders of magnitude above the maximum concentration achieved in human plasma. The clinical impact of the CYP2D6 inhibition with usual doses of dolasetron is not known, although recent study results demonstrate no significant effect of either cimetidine or rifampin, drugs known to inhibit or induce CYP2D6, respectively, on dolasetron metabolism.⁴

Because dolasetron is so rapidly cleared from the plasma, the “apparent” bioavailability of the drug must be estimated by comparing AUC values of hydrodolasetron following iv and oral administration. Using this method, the bioavailability of dolasetron is approximately 76%.¹ Coadministration of dolasetron with food delays the time to maximum plasma concentration, but the overall extent of absorption is not significantly affected.⁵

Results of additional dolasetron pharmacokinetic studies have demonstrated no clinically significant drug accumulation with multiple doses administered daily over 5 days.⁶ Furthermore, no differences in pharmacokinetics are observed between men and women nor between elderly and younger patients.^{7,8} The pharmacokinetic parameters of dolasetron in children with cancer are remarkably comparable to those in adults.⁹ Although liver dysfunction can impair the metabolism of dolasetron, dosage reductions are not required for patients with hepatic or renal impairment.^{10,11}

In comparing dolasetron’s pharmacokinetics with those of other 5-HT₃–receptor antagonists, dolasetron was observed to have a higher bioavailability (76%) and shorter time to maximum concentration (40 minutes) compared with ondansetron (56–71% and 1–2.1 hours, respectively) and granisetron (60% and 2 hours, respectively). In addition, dolasetron exhibits the longest half-life (7–8 hours) (ondansetron, 2.5–5 hours; granisetron, 4–6 hours). However, these pharmacokinetic advantages do not appear to translate into meaningful clinical benefit (i.e., improved efficacy or safety) in treating chemotherapy-induced emesis.¹

Clinical efficacy

The risk of developing chemotherapy-induced nausea and vomiting is determined by several factors, most importantly, the emetogenic potential of the specific chemotherapy agents used. The most emetogenic agent is cisplatin, especially when doses greater than or equal to 70 mg/m² are administered. Without coadministration of antiemetic agents, high-dose cisplatin produces emesis in virtually 100% of patients. This chemotherapy drug represents the standard by which antiemetic agents or strategies are compared. Many other commonly used chemotherapy agents such as the anthracyclines, cyclo-

phosphamide, and carboplatin, are classified as moderately emetogenic, commonly defined as producing emesis in approximately 30% to 90% of patients. Studies of dolasetron have evaluated this agent with both high-dose cisplatin and moderately emetogenic chemotherapy agents. Other factors that may increase the risk of emesis include female gender and prior exposure to chemotherapy, whereas a history of significant alcohol intake and advanced age are known to lower the risk.

Antiemetic studies have also examined both acute and delayed emesis. Acute emesis is arbitrarily defined as emesis that occurs within the first 24 hours after chemotherapy administration. This type of emesis responds well to prophylactic drugs, such as the 5-HT₃–receptor antagonists. Delayed emesis is arbitrarily defined as that which occurs more than 24 hours after chemotherapy administration and is generally difficult to manage.

In the dolasetron studies, complete response (CR) was consistently defined as no vomiting and no use of breakthrough antiemetic medications (i.e., antiemetics prescribed after a patient experiences symptoms, despite prophylactic therapy) during the evaluation period. A major response (MR) was defined as one to two episodes of vomiting during the evaluation time. Overall response rates (RRs) were defined as the sum of the CRs and MRs. The method of evaluating nausea varied among studies, although almost all studies employed a 100-mm visual analog scale (VAS), where 0 mm was defined as no nausea and 100 mm as the worst possible nausea.

Table 2 provides a summary of all clinical efficacy.^{13–26}

Acute emesis

High-dose cisplatin The efficacy of iv dolasetron for prevention of acute emesis due to high-dose cisplatin has been well documented. Initial studies sought to define the optimal dose of iv dolasetron. In an open-label, dose-escalation study, the safety and efficacy of iv dolasetron was evaluated in patients receiving cisplatin greater than or equal to 100 mg/m².¹³ Eighty-nine patients were treated at one of four dose levels: 1.8, 2.4, 3.0, and 5.0 mg/kg. CRs were observed in 24% to 52% of patients 24 hours after cisplatin administration, whereas the overall RR ranged from 48% to 82%. The 3.0- and 5.0-mg/kg doses did not result in an improvement compared with the 2.4-mg dose, and adverse effects were similar for all dose levels.

Yielding *et al.*¹⁵ performed a double-blind, multicenter, randomized study of two doses of dolasetron in patients scheduled to receive high-dose cisplatin (≥ 75 mg/m²). They randomized 62 chemotherapy-naïve patients to receive either 0.6 or 1.8 mg/kg of iv

dolasetron before chemotherapy administration. The higher dose produced better emetic outcomes, with 55% of patients receiving 1.8 mg/kg experiencing a CR compared with 31% in the 0.6 mg/kg group ($P=0.054$). Overall RRs (77% vs 55%; $P=0.039$) and time to first emesis (>24 vs 13.5 h; $P=0.004$) were significantly improved. Nausea VAS scores were better for the higher-dose group, although no statistical evaluation was provided. Dolasetron was well tolerated, with more than 80% of patients reporting satisfaction with treatment. This study formed the basis of further study of the 1.8-mg/kg dose.

Dolasetron proved to be superior to metoclopramide, the previous gold-standard antiemetic for cisplatin-induced emesis, in a double-blind study conducted by Chevallier *et al.*¹⁸ These investigators randomized 226 patients receiving high-dose cisplatin (≥ 80 mg/m²) to either dolasetron 1.2 or 1.8 mg/kg or metoclopramide (7 mg/kg). Patients who had received prior chemotherapy were included in the study. CRs were achieved in significantly more patients treated with dolasetron (48% at 1.2 mg/kg, $P=0.0058$; 57% at 1.8 mg/kg, $P=0.0009$) than metoclopramide (35%). CR rates between the two dolasetron groups were not significantly different ($P=0.4733$). Both the dolasetron 1.2 and 1.8 mg/kg doses were superior to metoclopramide in time to first emetic episode (>24 , 22.5, and 5.5 h, respectively; $P<0.0003$), control of nausea, and patient satisfaction. Subset analyses revealed that male gender, history of alcohol intake, and no prior exposure to chemotherapy were all factors independently associated with improved antiemetic outcomes; these factors were evenly distributed among the treatment groups. Extrapyramidal side effects occurred in 12% of patients treated with metoclopramide and in none of the patients who received dolasetron. The most common adverse effect associated with dolasetron was mild headache. The authors recommended 1.8 mg/kg as the most effective dose of dolasetron.

The comparable efficacy of iv dolasetron and ondansetron, another 5-HT₃-receptor antagonist, was demonstrated in a study of 609 cancer patients receiving their first course of high-dose cisplatin (≥ 70 mg/m²).¹⁹ The patients were randomly assigned to receive dolasetron 1.8 or 2.4 mg/kg or ondansetron 32 mg before chemotherapy. Patients were stratified by cisplatin dose: (a) those receiving lower-dose cisplatin (70 to 90 mg/m²), or (b) those receiving higher-dose cisplatin (≥ 91 mg/m²). The CRs for the three groups were 49.2%, 45.6%, and 50.4% for the lower-dose cisplatin group (mean dose, 74.7 mg/m²), respectively; for the higher-dose group (mean 100.6 mg/m²), 36.8%, 31.3%, 31.8%, respectively. The severity of nausea between the dolasetron groups

and the ondansetron group was not significantly different, although the 1.8-mg/kg dolasetron group had less nausea than did the 2.4-mg/kg group ($P=0.044$). In addition to confirming that men and patients with a history of alcohol use had better control of nausea and vomiting, these study results also showed that the use of narcotic analgesics was associated with lower CR rates. This novel finding must be confirmed in future clinical trials.

Audhuy *et al.*²⁰ compared two different doses of dolasetron with granisetron in patients receiving high-dose cisplatin (≥ 80 mg/m²). Patients were randomized in the double-blind study to receive either single iv doses of dolasetron 1.8 or 2.4 mg/kg, or granisetron 3 mg. Of the 474 assessable patients, 54%, 47%, and 48% of patients, respectively, achieved CRs. These differences were not statistically significant. Results for overall RRs, time to first emesis, use of rescue antiemetics, nausea scores, adverse effects, and patient satisfaction were comparable between the two groups. Chemotherapy-naïve patients had higher CR rates than did patients who had received prior chemotherapy (51–63% vs 40–43%; $P=0.0008$). The authors concluded that the three treatment arms were equally effective and well tolerated. Interestingly, there was a trend toward superior results with the lower dolasetron dose of 1.8 mg/kg as compared with 2.4 mg/kg, and this dose was recommended as the optimal dose by the authors.

Kris *et al.*²¹ administered oral dolasetron 200 mg and oral dexamethasone 20 mg to 75 patients receiving high-dose cisplatin (≥ 70 mg/m²). Dexamethasone is a corticosteroid that, when combined with a 5-HT₃-receptor antagonist, increases emetic RRs. Patients were randomized to receive a second dose of the regimen at 16 hours or no further antiemetics. CRs for emesis were achieved in 76% of all patients, including an RR of 74% in the 35 patients receiving more than 100 mg/m² of cisplatin. RRs between the two-dose group and the single-dose group did not differ (76% for both groups), nor did the number of patients who experienced no nausea during the study (54%, single-dose group; 61%, two-dose group). These results confirm the efficacy of oral dolasetron and dexamethasone in the management of emesis due to high-dose cisplatin chemotherapy.

Moderately emetogenic chemotherapy Multiple clinical trials each demonstrate the efficacy of dolasetron in controlling acute emesis due to moderately emetogenic chemotherapy. An open-label, dose-escalation study, conducted by Hesketh *et al.*²² administered iv dolasetron to 69 patients receiving doxorubicin (25–75 mg/m²) and/or cyclophosphamide (400–1200 mg/m²), both of which were categorized as moderately emetogenic. These patients were sequentially assigned to receive

Table 2. Summary of Published Dolasetron Studies

Author (yr)	No. of assessable patients	Study design and treatment arms	CR rate (%)	Overall RR (%)	Nausea control	Comments
<i>Acute emesis: high-dose cisplatin</i>						
Kris <i>et al.</i> ¹³ (1994)	89	Open-label, dose escalation			Mean VAS score*	
		• DOL 1.8 mg/kg iv	• 5/21 (24%)	• 10/21 (48%)	• 43 mm	
		• DOL 2.4 mg/kg iv	• 12/25 (48%)	• 14/25 (56%)	• 43 mm	
		• DOL 3.0 mg/kg iv	• 11/21 (52%)	• 16/21 (76%)	• 25 mm	
		• DOL 5.0 mg/kg iv	• 11/22 (50%) (<i>P</i> =0.207)	• 18/22 (82%) (<i>P</i> =0.055)	• 20 mm (<i>P</i> =NR)	
Conroy <i>et al.</i> ¹⁴ (1994)	164	Open-label, dose escalation			None or mild nausea	Study included non-chemotherapy-native patients
		• DOL 10 mg iv	• 5/30 (17%)	• 10/30 (33%)	• 11/30 (36%)	
		• DOL 20 mg iv	• 18/39 (46%)	• 25/39 (64%)	• 23/39 (58%)	
		• DOL 30 mg iv	• 14/36 (39%)	• 21/36 (58%)	• 20/36 (56%)	
		• DOL 40 mg iv	• 16/34 (47%)	• 26/34 (76%)	• 23/34 (68%)	
		• DOL 50 mg iv	• 16/25 (64%) (<i>P</i> =0.01)	• 18/25 (72%) (<i>P</i> =0.01)	• 18/25 (71%) (<i>P</i> =0.07)	
		Double-blind, randomized			Mean change in VAS from baseline	
		• DOL 0.6 mg/kg iv	• 9/29 (31%)	• 16/29 (55%)	• 33 mm	
		• DOL 1.8 mg/kg iv	• 17/31 (55%) (<i>P</i> =0.054)	• 24/31 (77%) (<i>P</i> =0.039)	• 15 mm (<i>P</i> =NR)	
		• DOL 3.0 mg/kg iv			Median VAS change from baseline	
Harmen <i>et al.</i> ¹⁶ (1996)	55	Double-blind, randomized			• 8 mm	
		• DOL 1.8 mg/kg iv	• 12/25 (48%)	• 16/25 (64%)	• 43.5 mm (<i>P</i> =NR)	
		• DOL 0.6 mg/kg iv × 3 (total, 1.8 mg/kg)	• 7/30 (23%) (<i>P</i> =0.065)	• 13/30 (43%) (<i>P</i> =NR)		

*100-mm scale, with 0=no nausea and 100 mm=worst possible nausea.

CR=complete response; DEX=dexamethasone; DOL=dolasetron; GRA=granisetron; MCP=metoclopramide; MR=major response; NR=not reported; NS=not significant; OND=ondansetron; VAS=visual analog scale.

Author (Year)	Study Design	Patients	Intervention	Control	Primary Endpoints	Secondary Endpoints	Notes
Kasimis <i>et al.</i> ¹⁷ (1997)	Double-blind, randomized	30	DOL 0.6 mg/kg iv × 1	DOL 0.6 mg/kg iv × 3 (total, 1.8 mg/kg)	• 6/14 (43%)	• 10/14 (71%)	Mostly male patients (77%); differences not statistically significant because of small sample size
			DOL 0.6 mg/kg iv × 3	(total, 1.8 mg/kg)	• 4/16 (25%) (P=NR)	• 8/16 (50%) (P=NR)	
Chevallier <i>et al.</i> ¹⁸ (1997)	Double-blind, randomized	225	DOL 1.2 mg/kg iv	MCP 7 mg/kg iv	• 40/84 (48%) [†]	NR	Study included chemotherapy non-naïve patients and closed early because of slow accrual.
			DOL 1.8 mg/kg iv	MCP 7 mg/kg iv	• 41/72 (57%) [‡]		
			MCP 7 mg/kg iv	MCP 7 mg/kg iv	• 24/69 (35%) (P=0.0058 vs MCP) [†]		
			MCP 7 mg/kg iv	MCP 7 mg/kg iv	• 33% (P=0.019 vs MCP) [§]		
Hesketh <i>et al.</i> ¹⁹ (1996)	Double-blind, randomized	609	DOL 1.8 mg/kg iv	OND 32 mg iv	• 88/198 (44%)	• 125/198 (63%)	Platinum, but all not chemotherapy naïve (7.6–9.3%)
			DOL 2.4 mg/kg iv	OND 32 mg iv	• 82/205 (40%)	• 111/205 (54%)	
			OND 32 mg iv	OND 32 mg iv	• 88/206 (43%) (P=NS)	• 122/206 (59%) (P=NS)	
			OND 32 mg iv	OND 32 mg iv			
Auhuy <i>et al.</i> ²⁰ (1996)	Double-blind, randomized	474	DOL 1.8 mg/kg iv	GRA 3 mg iv	• 88/163 (54%)	• 101/163 (62%)	Study included non-chemotherapy naïve patients
			DOL 2.4 mg/kg iv	GRA 3 mg iv	• 75/161 (47%)	• 100/161 (62%)	
			GRA 3 mg iv	GRA 3 mg iv	• 72/150 (48%) (P=NS)	• 95/150 (63%) (P=NS)	
			GRA 3 mg iv	GRA 3 mg iv			
Kris <i>et al.</i> ²¹ (1997)	Randomized	75	DOL 1.8 mg/kg iv	OND 32 mg iv	• 88/163 (54%)	• 101/163 (62%)	Patients with no nausea
			DOL 2.4 mg/kg iv	OND 32 mg iv	• 75/161 (47%)	• 100/161 (62%)	

*100-mm scale, with 0 = no nausea and 100 mm = worst possible nausea.

CR = complete response; DEX = dexamethasone; DOL = dolasetron; GRA = granisetron; MCP = metoclopramide; MR = major response; NR = not reported; NS = not significant; OND = ondansetron; VAS = visual analog scale.

Table 2. (Continued)

Author (yr)	No. of assessable patients	Study design and treatment arms	CR rate (%)	Overall RR (%)	Nausea control	Comments
Hesketh et al. ²² (1996)	69	Acute emesis: moderately emetogenic chemotherapy Open-label, dose escalation	<ul style="list-style-type: none"> • 29/38 (76%) 	<ul style="list-style-type: none"> • 34/38 (90%) 	<ul style="list-style-type: none"> • 23/38 (61%) 	Only 6% of patients received prior chemotherapy
			<ul style="list-style-type: none"> • 28/37 (76%) (P=NR) 	<ul style="list-style-type: none"> • 37/37 (100%) (P=NR) 	<ul style="list-style-type: none"> • 20/37 (54%) (P=NR) 	
			<ul style="list-style-type: none"> • 1/4 (25%) 	<ul style="list-style-type: none"> • 1/4 (25%) 	<ul style="list-style-type: none"> • 38 mm 	
			<ul style="list-style-type: none"> • 14/21 (67%) 	<ul style="list-style-type: none"> • 15/21 (71%) 	<ul style="list-style-type: none"> • 0 mm 	
			<ul style="list-style-type: none"> • 9/20 (45%) 	<ul style="list-style-type: none"> • 9/20 (45%) 	<ul style="list-style-type: none"> • 37 mm 	
			<ul style="list-style-type: none"> • 12/15 (80%) 	<ul style="list-style-type: none"> • 13/15 (87%) 	<ul style="list-style-type: none"> • 0 mm 	
			<ul style="list-style-type: none"> • 6/9 (67%) (P=NS) 	<ul style="list-style-type: none"> • 7/9 (78%) (P=NR) 	<ul style="list-style-type: none"> • 0 mm (P=NS) 	
			<ul style="list-style-type: none"> • DOL 0.3 mg/kg iv • DOL 0.6 mg/kg iv • DOL 1.2 mg/kg iv • DOL 1.8 mg/kg iv • DOL 2.4 mg/kg iv 	<ul style="list-style-type: none"> • DOL: 13 mm 		
			<ul style="list-style-type: none"> • DOL: 236/353 (67%) (P=0.013) 	NR	<ul style="list-style-type: none"> • DOL: 10 mm (P=0.051) 	
			<ul style="list-style-type: none"> • DEX: 271/402 (67%) • No DEX 162/294 (55%) (P=0.001) 	<ul style="list-style-type: none"> • DEX: 8 mm • No Dex: 16 mm (P<0.001) 	<ul style="list-style-type: none"> • Median VAS change from baseline 	
Lofters et al. ²³ (1997)	696	Double-blind, randomized	<ul style="list-style-type: none"> • DOL: 197/343 (57%) 	NR	<ul style="list-style-type: none"> • Mean nausea VAS score 	<ul style="list-style-type: none"> • RRs for each treatment arm not reported
Fausser et al. ²⁴ (1996)	398	Double-blind, randomized	<ul style="list-style-type: none"> • DOL 2.4 mg/kg iv ± DEX 8 mg iv 	<ul style="list-style-type: none"> • DEX: 271/402 (67%) 	<ul style="list-style-type: none"> • DEX: 8 mm 	Study included non-chemotherapy-naïve patients; 75% of OND patients received 32 mg
			<ul style="list-style-type: none"> • OND 32 mg iv ± DEX 8 mg iv 	<ul style="list-style-type: none"> • No DEX 162/294 (55%) (P=0.001) 	<ul style="list-style-type: none"> • No Dex: 16 mm (P<0.001) 	

*100-mm scale, with 0 = no nausea and 100 mm = worst possible nausea.

CR = complete response; DEX = dexmethasone; DOL = dolasetron; GRA = granisetron; MCP = metoclopramide; MR = major response; NR = not reported; NS = not significant; OND = ondansetron; VAS = visual analog scale.



Rubinstein et al. ²⁵ (1997)	319	Double-blind, randomized • DOL 25 mg po • DOL 50 mg po • DOL 100 mg po • DOL 200 mg po • OND 24-32 mg po	<ul style="list-style-type: none"> • 36/80 (45%) • 39/79 (49%) • 46/76 (61%) • 61/80 (76%)[†] • 60/83 (72%) ($P \leq 0.0001$, [linear dose-response trend]) • 65/83 (78%) ($P = 0.0001$, [linear dose-response trend]) • 68/80 (85%)[‡] • 65/83 (78%) ($P = 0.0001$, [linear dose-response trend]) • 65/83 (78%) ($P < 0.0019$ vs lower doses)* 	<ul style="list-style-type: none"> • 46/80 (58%) • 47/79 (60%) • 55/76 (72%) • 68/80 (85%)[‡] • 65/83 (78%) ($P = 0.0001$, [linear dose-response trend]) • 65/83 (78%) ($P < 0.0019$ vs lower doses)* 	<ul style="list-style-type: none"> • 29 mm • 31 mm • 3.5 mm • 0 mm* • 3 mm ($P = 0.0001$, [linear dose-response trend]) • 3 mm ($P < 0.0019$ vs lower doses)* 	<p>Median VAS change from baseline</p> <ul style="list-style-type: none"> • 49 mm • 10 mm • 11 mm • 7 mm ($P = 0.0006$ [linear dose-response trend]) 	<p>Study included non-chemotherapy- and radiation therapy-naïve patients</p>
Grote et al. ²⁶ (1997)	307	Double-blind, randomized • DOL 25 mg po • DOL 50 mg po • DOL 100 mg po • DOL 200 mg po	<ul style="list-style-type: none"> • 24/78 (36%) • 34/83 (41%) • 49/80 (61%)[†] • 46/78 (59%)[†] • 46/78 (59%)[†] ($P < 0.0001$ [linear dose-response trend]) • 46/78 (59%)[†] ($P < 0.01$ vs lower doses)[‡] 	<ul style="list-style-type: none"> • 28/78 (36%) • 43/83 (52%) • 52/80 (65%)[‡] • 56/78 (72%)[‡] • 56/78 (72%)[‡] ($P < 0.0001$ [linear dose-response trend]) • 56/78 (72%)[‡] ($P < 0.01$ vs lower doses)[‡] 	<ul style="list-style-type: none"> • 42/76 (55%) • 62/80 (78%) • 55/71 (78%) • 70/80 (88%) • 70/80 (88%) ($P < 0.001$ [linear dose-response trend]) 	<ul style="list-style-type: none"> • 12.5 • 1.0 • 0 • 0 ($P = 0.003$ [linear dose-response trend]) 	<p>Study included non-chemotherapy-naïve patients</p>

*100-mm scale, with 0 = no nausea and 100 mm = worst possible nausea.
 CR = complete response; DEX = dexamethasone; DOL = dolasetron; GRA = granisetron; MCP = metoclopramide; MR = major response; NR = not reported; NS = not significant; OND = ondansetron; VAS = visual analog scale.

dolasetron 0.3, 0.6, 1.2, 1.8, and 2.4 mg/kg. The majority of patients were women (71%), had breast cancer (55%), received both cyclophosphamide and doxorubicin (59%), and were chemotherapy naïve (94%). The overall RR for acute emesis for all dose levels was 65%. No dose-response relationship was defined in this trial; however, the statistical power was compromised by low numbers of patients in the 0.3- and 2.4-mg/kg dose groups. More than 70% of patients reported being very satisfied or satisfied with treatment.

Lofters *et al.*²³ compared the efficacy of dolasetron with that of ondansetron for prevention of acute emesis associated with moderately emetogenic chemotherapy, randomizing 703 chemotherapy-naïve patients to receive either iv dolasetron 2.4 mg/kg or ondansetron 32 mg with or without iv dexamethasone 8 mg. Most patients were women (71%), and breast cancer was the most common tumor type. Of the 696 assessable patients, 57% (197 of 343) of dolasetron-treated patients had CRs for emesis compared with 67% (236 of 353) of ondansetron-treated patients ($P=0.013$). The addition of dexamethasone to either 5-HT₃-receptor antagonist improved the CR rates (67% vs 55%; $P=0.001$) and reduced mean VAS scores for nausea ($P<0.001$). No significant differences in quality of life (QOL) between the ondansetron and dolasetron groups occurred, although dexamethasone-treated patients had significant improvements in two QOL domains, physical functioning ($P=0.017$) and role functioning ($P=0.010$). This is the only study demonstrating a superior outcome with another 5-HT₃-receptor antagonist over dolasetron. The reasons for these disparate results are unclear, although one possible reason is that the optimal dose of dolasetron was not used. As discussed previously, several study results suggest that the 1.8-mg/kg dose is more efficacious than is the 2.4-mg/kg dose used in this study, although these differences were not statistically significant. Otherwise, the treatment arms were evenly balanced, except the dolasetron arm included more doxorubicin-treated patients. History of alcohol use was not reported for the participants.

In a multicenter, randomized, double-blind study, Fauser *et al.*²⁴ compared four different dose levels of oral dolasetron with oral ondansetron in the management of acute emesis due to moderately emetogenic chemotherapy. Three hundred ninety-nine patients were randomized to receive single doses of dolasetron 25, 50, 100, or 200 mg or ondansetron 8 mg for three to four doses (total, 24–32 mg). Both chemotherapy-naïve and non-chemotherapy-naïve patients were included. Again, most patients were women (61%) and had breast cancer (40%). After 24 hours, a statistically significant linear dose-response relation-

ship was noted with CR rates, overall RRs, time to first emetic episode, and severity of nausea for dolasetron. CR rates were 45%, 49.4%, 60.5%, and 76.3% for the four dolasetron doses, respectively, versus 72.3% for ondansetron. Adverse effects were comparable between the groups. The authors concluded that oral dolasetron 200 mg was as effective as multiple-daily dose regimens of oral ondansetron.

Four different doses of oral dolasetron were evaluated in a multicenter study of 319 chemotherapy-naïve and non-chemotherapy-naïve cancer patients.²⁵ Patients were randomized to receive oral dolasetron 25, 50, 100 or 200 mg before administration of iv doxorubicin and/or cyclophosphamide. The majority of patients were women (81%) with breast cancer (69%). At 24 hours, the CR and overall RRs generally correlated strongly with increased dose (31%, 36%; 41%, 52%; 61%, 65%; 59%, 72%, respectively). The two higher dose levels proved significantly more effective than the two lower dose levels ($P<0.05$). Similar statistically significant trends were reported for control of nausea, time to first emetic episode, and patient satisfaction measured by VAS. No differences in the incidence of adverse effects among the four doses were noted.

A similar study of the same four oral dolasetron doses discussed above was conducted in 307 patients receiving chemotherapy including either carboplatin (275–400 mg/m²) or cisplatin (20–50 mg/m²).²⁶ A total of 184 patients (59.9%) received carboplatin, and 123 patients (40.1%) received cisplatin. The CR rates were 44.7%, 71.3%, 73.2%, and 82.5%, respectively ($P<0.001$ for linear dose-response trend). A statistically significant linear trend was noted for overall RRs, control of nausea, and patient satisfaction as doses increased. No differences in adverse effects were noted among the dose levels.

Delayed emesis

In the Lofters²³ study of dolasetron versus ondansetron, the investigators also examined the effect of both drugs on delayed emesis. Patients randomized to receive dolasetron for acute emesis then received oral dolasetron 200 mg/d, oral dexamethasone 8 mg/d, or a combination of oral dexamethasone and dolasetron. Similarly, patients randomized to iv ondansetron for acute emesis then received oral ondansetron 8 mg twice a day, oral dexamethasone alone (8 mg), or a combination of the two. These regimens were administered from day 2 to day 7 after chemotherapy. CR rates did not differ significantly between the ondansetron (39%, 110 of 285) and dolasetron (36%; 96 of 270) groups ($P=0.459$), but the dexamethasone-treated patients fared much better than patients not receiving dexamethasone (48%, 124 of

261 vs 28%, 82 of 294) ($P < 0.001$). Dexamethasone also improved nausea control. These results demonstrating a lack of additive benefit of 5-HT₃-receptor antagonists compared with the benefits of corticosteroids alone in prevention of delayed emesis have been shown for other 5-HT₃-receptor antagonists as well. Whether the use of 5-HT₃-receptor antagonists for delayed emesis is at all beneficial, based on the lack of proven benefit and high cost of therapy, is highly controversial.

Few clinical trials have examined the efficacy of 5-HT₃-receptor antagonists in fractionated or multiple-day cisplatin regimens, in which delayed emesis and acute emesis coexist beginning on day 2 of therapy. Fauser *et al.*²⁷ recently reported the results of their double-blind trial of dolasetron alone or combined with dexamethasone in 210 patients receiving cisplatin 15 to 50 mg/m²/d for 2 to 5 days. Patients were randomized to receive either iv dolasetron 100 mg alone or in combination with iv dexamethasone 20 mg. Approximately 60% of patients had received prior chemotherapy, and the majority of patients were men ($\approx 80\%$) with testicular cancer ($\approx 50\%$). Of the 198 assessable patients, the CR rates were higher with the combination regimen (72.9%) than with dolasetron alone (40.8%) ($P < 0.0001$); RRs for both groups attenuated with each day of treatment, reflecting a decreased RR to dolasetron in patients experiencing delayed emesis. By day 5, less than 20% of all patients had maintained a CR. Nausea control was improved in the dolasetron-and-dexamethasone group. Ninety-four percent of patients receiving the combination did not require antiemetic medications for symptoms compared with 78% of patients receiving dolasetron ($P < 0.001$).

Dolasetron use in special populations

Pediatric population An open-label dose-escalation study by Coppes *et al.*²⁸ evaluated four doses of iv dolasetron (0.6, 1.2, 1.8, 2.4 mg/kg) in 46 pediatric patients (3–18 years of age) receiving moderately to highly emetogenic chemotherapy and experiencing acute emesis. The CR rates were 10% (1 of 10), 25% (3 of 12), 67% (8 of 12), and 33% (4 of 12), respectively. The authors concluded that 1.8 mg/kg was the optimal iv dolasetron dose for pediatric patients.

Coppes *et al.*⁹ performed a similar open-label, dose-escalation study of three oral dolasetron doses (0.6, 1.2, and 1.8 mg/kg) in 32 children receiving moderately to highly emetogenic chemotherapy. Patients with prior chemotherapy exposure were permitted in the study. At 24 hours, the CR rates were higher with dolasetron 1.8 mg/kg (50%; 5 of 10) as compared with 0.6 mg/kg (33%; 3 of 9) and 1.2 mg/kg doses (31%; 4 of 13). The drug was well tolerated, with mild adverse effects similar to those reported in adult studies.

Bone marrow transplantation Only 1 published study of dolasetron use during bone marrow transplantation (BMT) has been published. Twenty patients undergoing 3 days of total body irradiation followed by 2 days of high-dose cyclophosphamide administration in preparation for BMT were given oral dolasetron 50 to 200 mg before each radiation treatment or chemotherapy infusion.²⁹ During irradiation, 13 of the 20 patients (65%) had fewer than two emetic episodes, and 15 of 20 patients (75%) had none or only mild nausea. On days 1 and 2 of cyclophosphamide administration, 11 of 20 (55%) and 6 of 20 (30%) patients, respectively, had fewer than two emetic episodes, whereas 8 of 20 (40%) and 7 of 20 (35%) patients, respectively, had none or only mild nausea. These results are comparable to results observed in other studies of 5-HT₃-receptor antagonists, but additional studies with dolasetron in BMT are needed.

Radiation therapy Data evaluating the efficacy of dolasetron in radiation-induced nausea and vomiting are limited. Bey *et al.*³⁰ conducted a trial of iv dolasetron in patients receiving upper abdominal radiation therapy, which produces nausea and vomiting in approximately 50% of patients. Fifty of the planned 200 patients were randomized to receive placebo or dolasetron 0.3, 0.6, or 1.2 mg/kg before radiation therapy and were monitored for 24 hours. Only 50 patients completed the study, because of changing medical practice (i.e., the use of fractionated radiation therapy, which is less toxic than single, high-dose radiation therapy, was becoming more popular; therefore, patient recruitment slowed significantly). Of the 50 patients, 66% had received prior chemotherapy or radiation therapy, and more than half of these had a history of prior nausea and vomiting with their treatment. The CR and overall RRs were statistically superior for the dolasetron groups (91%, 100%; 71%, 93%; 58%, 83%, respectively) compared with the placebo group (54%, 54%). Use of rescue antiemetics and degree of nausea were also reduced in the dolasetron-treated group. The low RRs in the highest dolasetron group were attributed to the lower number of chemotherapy-naïve patients in that group. Given the high incidence of nausea and vomiting in patients receiving radiation therapy of the upper abdomen, the use of a placebo arm is no longer considered appropriate in this setting. Including a placebo group may have affected accrual to the study and ultimately resulted in inadequate power to compare differences among dose levels. Thus, the optimal dose of dolasetron before radiation therapy remains to be determined.

Determining the optimal dolasetron dose

Most of the clinical trials evaluating iv dolasetron in the management of chemotherapy-induced emesis have employed weight-based doses, although standardized

doses have been used for oral dolasetron and for iv dolasetron in postoperative nausea and vomiting. Whitmore *et al.*³¹ reviewed the data regarding 1598 patients enrolled in 14 clinical trials of iv dolasetron administered according to body weight. The doses were converted to fixed doses based on weight. Results of this pooled analysis showed that a fixed iv dose of 100 mg produced the highest CR rate (53%).

Single doses of dolasetron are as effective as multiple-dose regimens for cisplatin-induced emesis. Harman *et al.*¹⁶ compared iv dolasetron 1.8 mg/kg with the same total amount of dolasetron divided into three separate doses (0.6 mg/kg each) in patients receiving high-dose cisplatin (≥ 80 mg/m²). Results showed that the single dose was superior to the multiple dose in both CR (48% vs 23%) and overall RRs (64% vs 43%) for emesis, although these differences were not statistically significant.

Limited evidence reveals that lower doses of dolasetron may be effective. In a small multicenter study of 30 patients receiving greater than or equal to 80 mg/m² of cisplatin,¹⁷ a single iv dose of dolasetron 0.6 mg/kg produced an overall RR of 71% and a 43% CR rate for acute emesis. These RRs were clinically superior to a multiple-dose regimen of 0.6 mg/kg iv for three doses (total, 1.8 mg/kg) (overall RR, 50%; CR rate, 25%). Conversely, VAS scores for nausea showed lower scores for the multiple-dose group. Although the results of this trial did not reach statistical significance, most likely because of small sample size, further investigation into the use of low-dose dolasetron for chemotherapy-related nausea and vomiting is warranted.

Conroy and colleagues¹⁴ conducted a multicenter, open-label, dose-escalation study of lower doses of iv dolasetron in patients receiving high-dose cisplatin (≥ 50 mg/m²). In this study, chemotherapy-naïve and non-chemotherapy-naïve patients were sequentially assigned to receive doses of dolasetron 10, 20, 30, 40, and 50 mg before cisplatin administration and were monitored for 24 hours for efficacy and safety. The median dose of cisplatin was 100 mg/m². A dose-dependent increase in CR rate (17–64%) and CR plus MR rates (33–76%) for emesis was noted ($P = 0.01$). This increase may be partially due to more female patients and more non-chemotherapy-naïve patients being treated at the lowest dose level; in many antiemetic trials, women and patients who had previously received chemotherapy had lower response rates than did men and chemotherapy-naïve patients. The differences in control of nausea were not significantly different ($P = 0.07$), although time to first nausea episode ($P = 0.04$) and time to first emetic episode ($P = 0.003$) were significantly improved at higher doses.

Although both 100 mg and 1.8 mg/kg are generally accepted as the lowest, most effective dose of iv dolasetron, the optimal dose of oral dolasetron still elicits controversy. Determining this dose is important because the use of oral antiemetics is encouraged whenever possible. Oral antiemetics are as effective as their iv counterparts, but are generally less expensive. Results of one study showed that oral dolasetron 200 mg was effective in the prevention of cisplatin-induced emesis.²¹ Results of two large clinical trials demonstrated that for moderately emetogenic chemotherapy, dolasetron 100 mg has produced results equivalent to those produced by 200 mg.^{25,26}

Adverse effects

Like all 5-HT₃-receptor antagonists, dolasetron is generally well-tolerated, with headache (24%) and diarrhea (12%) the most commonly experienced adverse effects. Less commonly reported adverse effects include fever (4%), fatigue (4%), abdominal pain (3%), hypertension (3%), pain (2%), dizziness (2%), and chills (2%).³²

The 5-HT₃-receptor antagonists are known to produce electrocardiographic changes, specifically prolongation of the QTc interval. The cardiac effects of iv dolasetron (1.2, 1.8, 2.4 mg/kg) and iv ondansetron 32 mg were compared with that of placebo in 30 healthy male volunteers.³³ Both drugs produced transient, asymptomatic prolongations in the QTc interval in the 4 hours following drug administration. The mechanism of cardiac effects may differ for the two drugs; dolasetron appeared to have more effect on ventricular depolarization (prolonged QRS interval), whereas ondansetron had more of an effect on ventricular repolarization (prolonged JT interval). Hesketh *et al.*¹⁹ compared the cardiac effects of ondansetron and dolasetron and observed that both agents increased PR, QRS, and QTc intervals, although dolasetron had more of an effect than did ondansetron. Still, the effects were minor and were judged to be clinically insignificant.¹⁹ Additionally, Audhuy *et al.*²⁰ concluded that granisetron and dolasetron produced comparable but clinically irrelevant electrophysiologic changes in cardiac function.

Antiemetic guideline recommendations

Four published clinical practice guidelines (National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], American Society of Health-System Pharmacists [ASHP], Multinational Association for the Supportive Care of Cancer [MASCC]) for the appropriate use of antiemetics with chemotherapy and radiation therapy conclude that the 5-HT₃-receptor antagonists are clinically equivalent, although some recommended doses differ.^{34–37} The four agree that either 1.8 mg/kg or 100 mg is the optimal iv dose, but

the oral-dose recommendations vary from 100 to 200 mg. Both the NCCN and ASCO recommend 100-mg oral doses, whereas ASHP recommends 100 to 200 mg and MASCC recommends 200 mg. Interestingly, the oral dolasetron dosage published in the ASHP and MASCC guidelines were selected before the FDA approved the 100-mg oral dose. The guidelines agree that selection of a 5-HT₃ – receptor antagonist should be based on institutional cost of the drug. In addition, all four guidelines advocate use of 5-HT₃ – receptor antagonists in combination with corticosteroids, and the use of oral agents when possible. Finally, the ASCO guidelines recommend use of single doses rather than multiple doses. For radiation therapy, the guidelines are more varied, reflecting the relative lack of data supporting the use of 5-HT₃ – receptor antagonists in this setting. The guidelines do agree that a 5-HT₃ – receptor antagonist is appropriate for radiation therapy of intermediate (e.g., upper hemibody) to high (e.g., total body or hemibody) emetogenic risk.

Thus, dolasetron is an appropriate first-line choice for prevention of emesis related to chemotherapy and radiation therapy. Dolasetron should be combined with dexamethasone and given before moderately to highly emetogenic chemotherapy. Single oral doses are preferable. Oral dolasetron is also an acceptable option for prevention of radiation-induced emesis in intermediate- to high-risk patients.

CONCLUSIONS

Dolasetron is a highly effective 5-HT₃ – receptor antagonist for the prevention of chemotherapy-induced emesis. Results of several clinical trials have demonstrated the efficacy of dolasetron in managing emesis due to highly and moderately emetogenic chemotherapy. Intravenous dolasetron is as effective as granisetron and ondansetron with cisplatin (≥ 70 mg) regimens. Fewer data exist to support the use of oral dolasetron in this setting, but this route of administration appears to produce efficacy comparable to that of iv dolasetron. Likewise, oral and iv dolasetron have proved to be as effective as ondansetron and granisetron when used with moderately emetogenic chemotherapy regimens. Limited but positive data verify the activity of dolasetron for radiation therapy-induced emesis. Future studies of dolasetron will focus on its optimal dose and its role in delayed emesis, and emesis caused by radiation therapy and BMT preparative regimens.

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