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Palonosetron, second generation 5-HT₃ antagonist: a new perspective in CINV management

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It is well established that the majority of cancer patients who undergo moderately or highly emetogenic cytotoxic treatment without receiving prophylactic antiemetics will experience chemotherapy-induced nausea and vomiting (CINV). Although the exact mechanisms of CINV are not fully known, it is clear from preclinical experiments and more than 15 years of clinical investigations that serotonin plays a major role in initiating nausea and vomiting associated with emetogenic chemotherapy. Emetogenic chemotherapy damages the gastrointestinal mucosa, causing the release of serotonin (5-hydroxytryptamine [5-HT]) from enterochromaffin cells in the small intestine, which, in turn, activates 5-HT₃ receptors located on vagal afferents.¹ Activated vagal afferent fibres send signals to the brain stem vomiting centers, initiating emesis.¹ The introduction of 5-HT₃ receptor antagonists into clinical oncology in the 1990s led to significant improvements in control rates for acute nausea and vomiting associated with emetogenic chemotherapy, and 5-HT₃ receptor antagonists are now considered part of the standard of care. As single agents for antiemetic prophylaxis of acute CINV (occurring within 24 hours of chemotherapy) in patients receiving moderately emetogenic chemotherapy, 5-HT₃ receptor antagonists are reported to have complete response (CR) rates (i.e., no emesis, no use of rescue medication) of 50-70%.² Although they are commonly prescribed after the first day of chemotherapy, the effectiveness of 5-HT₃ receptor antagonists as single agents in preventing delayed CINV is less well established. Four 5-HT₃ receptor antagonists are currently approved for use in the United States and/or Europe: ondansetron, granisetron, tropisetron, and dolasetron. These agents have some pharmacologic differences in receptor binding affinity, selectivity, and metabolism. Despite these nuances, the minor pharmacologic differences of these agents have not translated into clinically meaningful differences among them. Therefore, according to cur-

rent evidence-based guidelines (American Society of Clinical Oncology, Multinational Association of Supportive Care in Cancer) and consensus guidelines (American Society of Health-System Pharmacists, National Comprehensive Cancer Network), these 5-HT₃ receptor antagonists are considered therapeutically equivalent and interchangeable when used at equipotent doses.³⁻⁷ Although 5-HT₃ receptor antagonists are part of the current standard of care for patients receiving chemotherapy, a substantial proportion of patients today continue to experience both acute and particularly delayed CINV after moderately or highly emetogenic chemotherapy.^{7,8} Therefore, there is still a need to develop new agents to improve control rates and patient care.

Palonosetron is a highly potent, second-generation, selective 5-HT₃ receptor antagonist. It has been shown to have a stronger binding affinity for the 5-HT₃ receptor compared with other agents in the class¹⁰ and an extended plasma elimination half-life of approximately 40 hours (Table 1).

Palonosetron is administered as a single fixed IV dose (0,25 mg) 30 minutes before chemotherapy. It is indicated for:

- the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy, and;
- the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy

As concerns metabolism and excretion, approximately equal contribution of renal and hepatic routes of elimination are described (~40% renally cleared unchanged; ~50% of administered dose metabolized). Furthermore, palonosetron is characterized by a low potential for drug interactions, and does not inhibit or induce cytochrome P450 isozymes at clinically relevant concentrations. The total body clearance is not significantly affected by gender, age, hepatic impairment, renal impairment, or co-medications.

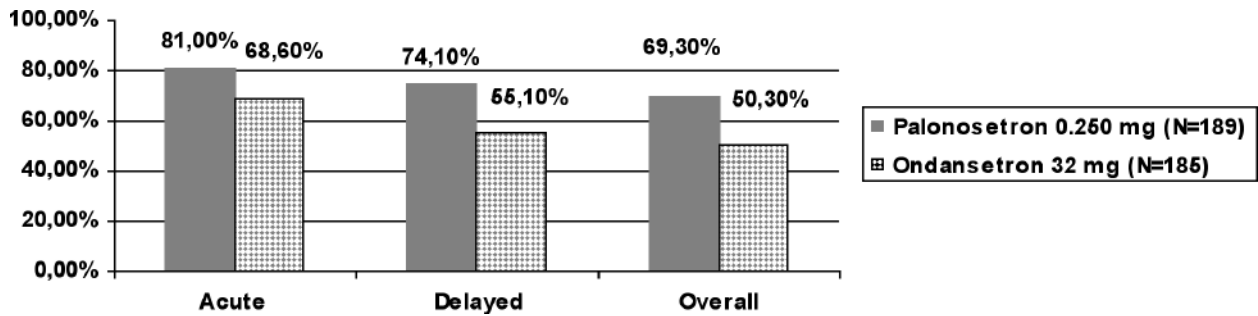


Figure 1. Gralla *et al.* Complete remission rate evaluated in an intention to treat analysis.

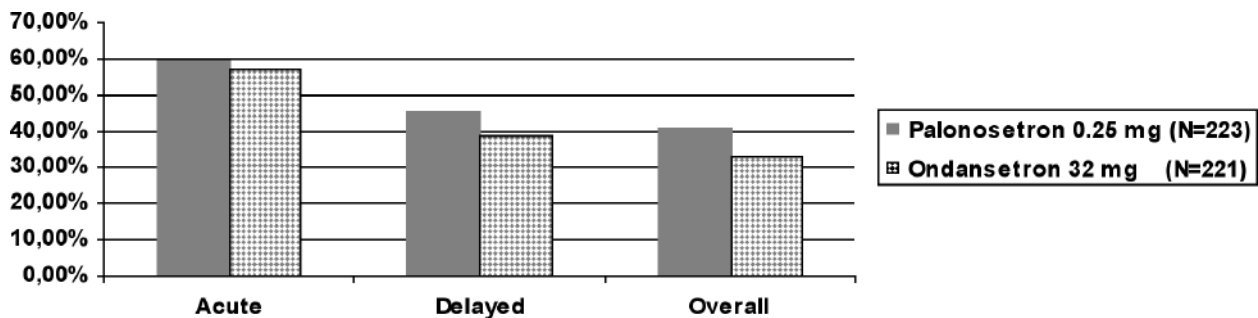


Figure 2. Apro *et al.* Complete remission rate evaluated in an intention to treat analysis.

Table 1. Binding affinity for 5-HT3 receptor.

5-HT3 antagonist (pKi, Log scale)	Half-life (hours)	Binding affinity
Aloxi	40.0	10,45
Granisetron	9.0	8,91
Tropisetron	8.0	8,81
Ondansetron	4.0	8,39
Dolasetron	7.3	7,60

Table 3. Apro *et al.* Complete remission rate evaluated in an intention to treat analysis.

Patients (N=667)	Acute (0-24 h)	Delayed (24-120 h)	Overall (0-120 h)
Palonosetron 0.25 mg (N=223)	59,2 %	45,3 %	40,8 %
Ondansetron 32 mg (N=221)	57 %	38,9 %	33%

Table 2. Gralla *et al.* Complete remission rate evaluated in an intention to treat analysis.

Patients (N=563)	Acute (0-24 h)	Delayed (24-120 h)	Overall (0-120 h)
Palonosetron 0.250 mg (N=189)	81,0 %	74,1 %	69,3 %
Ondansetron 32 mg (N=185)	68,6 % <i>p</i> =0.0085	55,1 % <i>p</i> <0.001	50,3 % <i>p</i> <0.001

Phase III randomized clinical trials demonstrated the efficacy of Palonosetron in comparison with first generation 5-HT3 antagonists.^{11,12}

1) Gralla *et al.* reported on a multicentric European study comparing Palonosetron (0.25 mg or 0.75, single IV administration) and ondansetron (32 mg, single IV administration) in 536 patients treated with moderately emetogenic chemotherapy. The Authors concluded that palonosetron (0.25 mg) was significantly superior to ondansetron (32 mg) in the prevention of acute and delayed CINV (Table 2 and Figure 1).

2) Eisemberg *et al.* reported on a multicentric study comparing Palonosetron (0.25 mg or 0.75, single IV administration) and dolasetron (100 mg, single IV administration) in 592 patients treated with moderately emetogenic chemotherapy. The Authors concluded that a single dose of palonosetron (0.25 mg) is effective as a single dose of dolasetron (100 mg) in preventing delayed CINV with a comparable safety profile.

In addition, Apro *et al.* conducted a randomized clinical trial comparing palonosetron and ondansetron in 667 patients treated with highly emetogenic chemotherapy, showing that palonosetron was not inferior to ondansetron (Table 3 and Figure 2).

Overall, the toxicity profile of single dose palonosetron was acceptable, headache, constipation and dizziness being the most common adverse events as for other 5-HT3 antagonists.

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