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REVIEW

Review of Palonosetron in the Prevention of Chemotherapy-Induced Nausea and Vomiting

Mitsue Saito

Department of Breast Oncology, Juntendo University Hospital, Tokyo, Japan. Email: mitsue@juntendo.ac.jp

Abstract: Palonosetron, the second generation 5-hydroxytryptamine-3 receptor antagonist (5-HT3RA), has shown superior efficacy in preventing the delayed phase of highly emetogenic chemotherapy induced nausea and vomiting (CINV) when administered in combination with dexamethasone in a randomized phase III trial, as compared with granisetron, a first generation drug in the same class. Since the 1990s, dramatic improvements have been achieved in anti-emetic therapy, including the development of neurokinin-1 receptor antagonists (NK-1RAs) such as aprepitant, as well as 5-HT3RAs. According to pharmacological research, palonosetron, compared to other 5-HT3RAs, not only has a prolonged half-life and high receptor affinity, but also shows other characteristics such as allosteric interactions and positive cooperativity with the receptor resulting in long-term alteration and internalization of this receptor. Although several other clinical trials have supported the favourable actions of palonosetron, more investigations are needed to confirm these advantages for highly emetogenic chemotherapy by using regimens recommended by international guidelines, including the advantages of combining Palonosetron dexamethasone and aprepitant. This review not only focuses on palonosetron, but also on the history and the future of antiemetics for CINV.

Keywords: CINV, MEC, HEC, 5-HT3RA, Palonosetron, anti-emetics.

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Introduction

Nausea and vomiting are still unpleasant side-effects of chemotherapy. Development of more effective anti-emetic agents and less toxic anticancer drugs is expected to improve quality of life for cancer patients. The National Comprehensive Cancer Network (NCCN) guideline(v.3 2009) listed palonosetron (Aloxi™) as a preferred serotonin receptor antagonist (5-HT3RA) for the prevention of CINV associated with highly emetogenic chemotherapy (HEC).[1] Moreover, palonosetron was also one of the main discussion topics for the Multinational Association of Supportive Care in Cancer MASCC in 2009.[2]

In this review, the recent results of clinical trials, mainly on palonosetron, and medical issues faced in anti-emetic field will be discussed.

Mechanism of Emetic Reaction

When a foreign substance enters the body, several mechanisms function to eliminate it and protect the organism against poisoning. A response like nausea or vomiting must originally have been triggered in response to a noxious oral ingestion or foul odour, so the sensors detecting foreign agents appear to be located not only in our digestive tracts but also in our brains, where the odour or ingested products and their metabolites, and even parenterally administered agents in the blood stream or cerebrospinal fluid, and neurotransmitters can stimulate vomiting. Therefore, most of the intravenously injected chemotherapeutic agents, which are potentially life-saving drugs, are reasonably, though ironically, recognized as toxic by those sensors which may thereby induce emesis.

Female gender and youth are risk factors[3] for emesis. Perhaps as the preservation of our species requires that women of reproductive age should be protected from toxic agents, these risk factors for emesis are reasonable. A history of alcoholism is a negative risk factor for emesis,[4] suggesting that alcohol might induce tolerance to chemotherapeutic agents.

The chemoreceptor trigger zone (CTZ) near the IVth ventricle and the vomiting centre (VC) located in the brain stem control the vomiting reflex via multiple neurotransmitters. Among them, dopamine, serotonin (5-HT), substance P and their corresponding receptors in various organs like the dorsal vagal complex, the CTZ and the VC in the brain and gastrointestinal tract reportedly play major roles in triggering the emetic reflex in patients receiving chemotherapy.[5,6]

5-hydroxytryptamine-3 (5-HT3) receptors are located on terminals of the vagus nerve in both the periphery and centrally. There must be at least two pathways for CINV: The first is that which runs from the peripheral organs to the central nervous system via serotonin released from enterochromaffin cells of the small intestine that activate 5-HT3 receptors located on vagal afferents. This might be the main mechanism by which orally ingested chemicals induce emesis, though enterochromaffin cells can be stimulated by blood-mediated free radicals produced by injected chemotherapeutic agents. The second pathway involves a direct stimulus to the 5-HT3 receptors located in the CTZ of the area postrema.[7] This could be the mechanism by which intravenously injected agents directly induce vomiting. From the CTZ, several neurotransmitters are released to stimulate the VC, which modulates the efferent vagal nerve, affecting not only the gastrointestinal tract but also various skeletal muscles resulting in emetic reactions, as well as the respiratory, vasomotor and salivary reactions specific to emesis.

Besides ordinary CINV as described above, emesis can be triggered by the five senses or even thoughts is called anticipatory CINV; this is observed in patients with memories of unsuccessful prevention of CINV.[8]

History of Anti-Emetics

Although the problem of side-effects related to each chemotherapeutic agent needs to be solved alongside progress in the development of cancer treatment, emesis is one of the oldest and most unpleasant side-effects of chemotherapy. However, there were few anti-emetics for preventing CINV until 5-hydroxytryptamine-3 receptor antagonists (5-HT3RAs) became available in 1990s.

Nausea and vomiting occurring within 24 hours has been defined as acute emesis, while that occurring between 24–120 hours is delayed emesis.[9] One of the highest emetogenic chemotherapies is cisplatin (CDDP), which became available in the late 1970s, and most anti-emetic studies before 2000 were done on CDDP. Originally, CDDP showed a unique pattern of emesis, with severe emetic reactions occurring within a few hours after receiving chemotherapy in almost all patients, with less severe emesis recurring,

in delayed form, after a wave of acute emesis.[10] In the 1980s, corticosteroids and dopamine receptor antagonists (dopamine RA), including metoclopramide, phenothiazines and antihistamines, were used.[11] However, these agents were less effective compared with the 5-HT3RAs, and had a higher potential for adverse events, e.g. extrapyramidal side-effects for dopamine RA, though a clinical trial of high-dose metoclopramide showed improved efficacy.[12] The development and clinical studies on ondansetron, granisetron, dolasetron and tropisetron in the 1990s indicated how serotonin plays a major role in acute emesis, as the control rate of nausea and vomiting in the acute phase was significantly improved by using 5-HT3RA.

As 5-HT3RAs have very favourable anti-emetic properties with acceptable side-effects,[13] such as headache, constipation and dizziness, they have now become the most widely used anti-emetic drugs.

Prospective randomized studies for CINV treatment demonstrated that 5-HT3RAs were all equivalent therapeutically for acute emesis, and this was supported by meta-analyses.[14,15] On the other hand, corticosteroids, the mechanism of which remains unknown, have been reported to be effective since the 1980s,[16] especially in combination with other anti-emetics, for both acute and delayed CINV.[17] Therefore, a combination of 5-HT3RA and corticosteroid was the best therapy to prevent both acute and delayed emesis until aprepitant became available.

In the 1990s, a classification of the acute emetogenicity of chemotherapy was proposed by Hesketh et al[18] and was revised by Grunberg et al in 2005[19] became the standard model for most of the guidelines. According to these classifications, highly emetogenic chemotherapy (HEC) is defined as an agent or regimen that causes acute emesis in 90% or more of patients. Moderately emetogenic chemotherapy (MEC) is an agent or regimen producing acute emesis in 30%–90% of patients, while low emetogenic chemotherapy (LEC) causes CINV in 10%–30% of patients. Minimal emetogenic chemotherapy induces nausea and vomiting in less than 10% of patients if no antiemetic treatment is applied.

The complete response (CR; no emetic episode and no rescue medication required) rate in the acute phase with HEC could be between 55% and 80% with prophylactic administration of a first generation 5-HT3RA and dexamethasone, while the CR rate for delayed emesis with HEC was mostly below 50% using the same two-drug regimen prophylactically and therapeutically (Table 1). No improvement in efficacy was obtained with additional administration of 5-HT3RA beyond 24 hours after chemotherapy.[20–22] Therefore, multiple day administration of a first generation 5-HT3RA is not recommended in current antiemetic guidelines.[1,2] Corticosteroids were the most frequently used drug to prevent delayed CINV; however, more than half of the patients receiving HEC in the 1990s suffered from delayed emesis.

Two major developments have improved the control of delayed emesis with HEC and MEC since early in this century: the developments of aprepitant (Emend™) and palonosetron (Aloxi™).

Development of aprepitant,[23,24] which was the first neurokinin-1 receptor antagonist (NK-1RA), and palonosetron, a second generation 5-HT3RA approved by the Food and Drug Administration (FDA) in 2003,[25,26] had a major influence on resolving the problem of delayed emesis. Moreover, the advent of aprepitant changed the guideline recommendation from two-drug regimens containing a 5-HT3RA and dexamethasone to triplet drug therapy containing a 5-HT3RA, dexamethasone and aprepitant for HEC. Introduction of aprepitant, with its good single administration safety profile, however, leads to reduction in the dose of dexamethasone in combination usage with aprepitant, considering its inhibitory effect on CYP3A4.[27]

Currently, a preference for palonosetron among the 5-HT3RAs for HEC or MEC was not recommended by the MASCC guideline committee in 2004, as none of the trials of palonosetron had been designed to evaluate either the efficacy for delayed emesis as a primary endpoint or the advantage of combining palonosetron with dexamethasone, as compared to the first generation 5-HR3RAs.

In 2006, the period when the last MASCC guideline was published,[28] a Japanese group started a phase III randomized trial comparing palonosetron with granisetron to prove the non-inferiority of palonosetron in acute emesis and its superiority in delayed emesis when used in combination with dexamethasone for HEC and anthracycline and cyclophosphamide combination (AC).[29] Although the regimen applied in this trial was not a triplet, which should have been recommended

Table 1. CR of palonosetron with or without other antiemetic(s) in prospective studies.

Antiemetics (comparator)	Phase	Total no. cases	Dose of palo (mg)	No. of cases	CR Rate(%)		
					Acute		
					HEC	AC	MEC
Palo	III	563	0.25	189		81.0	(>68.6)
(ond 32 mg)			0.75	189		73.5	(≧68.6)
(dol 100 mg)	III	569	0.25	189		63.0	(≧52.9)
			0.75	189		57.1	(≧52.9)
(ond 32 mg)	III	667	0.25	223	59.2(≧57.0)		
			0.75	223	65.5(≧57.0)		
Palo+dex	III	1114	0.75	555	75.3(≧73.3)		
(gr 40 μg/kg)			0.75	316	80.1(≧79.6)		
			0.75	239		69.0(≧64.8)	
	III	447	0.25	150	64.7(≧55.8)		
(ond 32 mg)			0.75	150	62.7(≧55.8)		
	II	231	0.25	77	81.8		
			0.75	78	79.5		
	II	204	0.25	68		82.4	
			0.75	69		92.8	
	II	32	0.25	32		84.4	
	II	85	0.25	85		99	
Palo+dex+apr	II	58	0.25	58		88	
	II	71	0.25	28	96.4		
	II	41	0.25	41		76	

for HEC because aprepitant was not then available in Japan, this study was the first to evaluate the superiority of palonosetron versus other 5-HT3RAs when administered with dexamethasone for delayed emesis. The NCCN recently updated its guidelines by listing palonosetron as the preferred 5-HT3RA for the prevention of CINV associated with HEC.[1]

Pharmacological Profile of Palonosetron and its Unique Mechanism of Action

Palonosetron is a potent single stereoisomeric 5-HT3RA (Fig. 1). The plasma half-life is approximately 40 hours,[13,30] which is much longer than the half-lives of other 5-HT3RAs, which are in the range of 5–12 hours.[31] Renal elimination is the main excretion route for the parent drug and its metabolites. The binding affinity of palonosetron for the 5-HT3 receptor is also at least 30-fold higher than those of the first generation 5-HT3RAs.[32]

The superiority of palonosetron compared with first generation 5-HT3RAs cannot be explained just by the differences in half-life and affinity because of the following reasons. If the advantage in efficacy of palonosetron was simply because of its longer half-life, the improved efficacy in delayed emesis could have been achieved with additional administration of a first generation 5-HT3RA beyond 24 hours. Moreover, if the improved clinical efficacy of palonosetron was just because of its high affinity to the receptor, the efficacy of other 5-HT3RAs should have improved with administration of higher doses saturating these receptors. Since the structure of palonosetron, which is based on a fused tricyclic ring system attached to a quinuclidine moiety, is unique and different from those of first generation 5-HT3RAs, which are based on a 3-substituted indole structure resembling serotonin, Rojas et al[33] postulated other mechanisms such as allosteric interactions and the positive cooperativity of palonosetron when binding to the 5HT3 receptor, which may lead to long-term alteration and internalization of receptors. These unique interactions between palonosetron and the 5-HT3 receptors were

Delayed			Overall	Author (period)	Ref
HEC	AC	MEC			
	74.1	(>55.1)	69.3(>50.3)	Gralla (03)	26
	64.6	(≧55.1)	58.7(≧50.3)		
	54.0	(>38.7)	46.0(>34.0)	Eisenberg (03)	25
	56.6	(>38.7)	47.1(>34.0)		
45.3(≧38.9)			40.8(≧33.0)	Aapro* (06)	38
48.0(≧38.9)			42.2(≧33.0)		
56.8(>44.5)			51.5(>40.4)	Saito (09)	29
53.5(>40.6)					
	61.1(>50.0)				
42.0(>28.6)			40.7(>25.2)	Aapro (06)	38
41.3(≧28.6)			35.3(≧25.2)		
53.2			49.4	Maemondo (09)	43
56.4			56.4		
	66.2		64.7	Segawa (09)	44
	71.0		69.6		
		59.4	59.4	Hajdenberg (06)	40
		89.5	96	Giuliani (08)	41
		78	78	Grote (06)	45
92.9			92.9	Herrington (08)	46
		66	51	Grunberg (09)	47

Abbreviations: HEC, highly emetogenic chemotherapy; AC, anthracycline and cyclophosphamice regimen; MEC, moderately emetogenic chemotherapy; palo, palonosetron; dex, dexamethasone; apr, aprepitant; ond, ondansetron; dol, dolasetron; gr, granisetron.
Notes: >, Superiority to the comparator in each study was indicated; ≧, non-inferiority to the comparator or numerically higher CR rates* than comparator in each study was indicated; ref, reference number.

demonstrated *in vitro*, whereas ondansetron and granisetron exhibited simple biomolecular binding.

Safety Profile of Palonosetron

Phase I studies showed a single dose of palonosetron has an acceptable tolerability profile. The most common treatment-related adverse events are headache, constipation and dizziness, similar to first generation 5-HT3RAs.[13] Palonosetron has a low potential for drug—drug interactions, because of the low rate of plasma binding and subsequent renal and hepatic elimination.[30] The incidence of QT interval prolongation, which was the adverse event associated with 5-HT3RAs of greatest concern, was reported to be very low,[34] and the cardiac safety of palonosetron was confirmed by the FDA[35] in 2008 and by the European Medicines Agency (EMEA)[36] in 2009.

Clinical Trials of Palonosetron

Prospective studies published as of July 2009 are described in Table 1.

Single drug administration of palonosetron

Five phase I and one phase II studies demonstrated favourable anti-emetic properties of palonosetron at doses of 3 μg/kg or 10 μg/kg (essentially equivalent to 0.25 mg or 0.75 mg) in preventing acute CINV.[37] Then the three phase III studies[25,26,38] led to FDA approval.

The primary endpoint of these three phase III trials was to prove the non-inferiority of palonosetron compared with a first generation 5-HT3RA in the CR rate during the acute phase of CINV. Among them, the two randomized double-blind phase III trials ($N = 570$ and $N = 592$, respectively) compared a single intravenous (iv) administration of palonosetron (0.25 mg and 0.75 mg) with a single iv dose of ondansetron (32 mg) or dolasetron (100 mg) in MEC patients treated prophylactically.[25,26] These studies confirmed the efficacy of palonosetron in preventing CINV as compared to both first generation 5-HT3RAs. Palonosetron (0.25 mg) showed a significantly higher CR rate than the comparator (81.0% vs. 68.6% for ondansetron) in the study by Gralla et al[26] and was

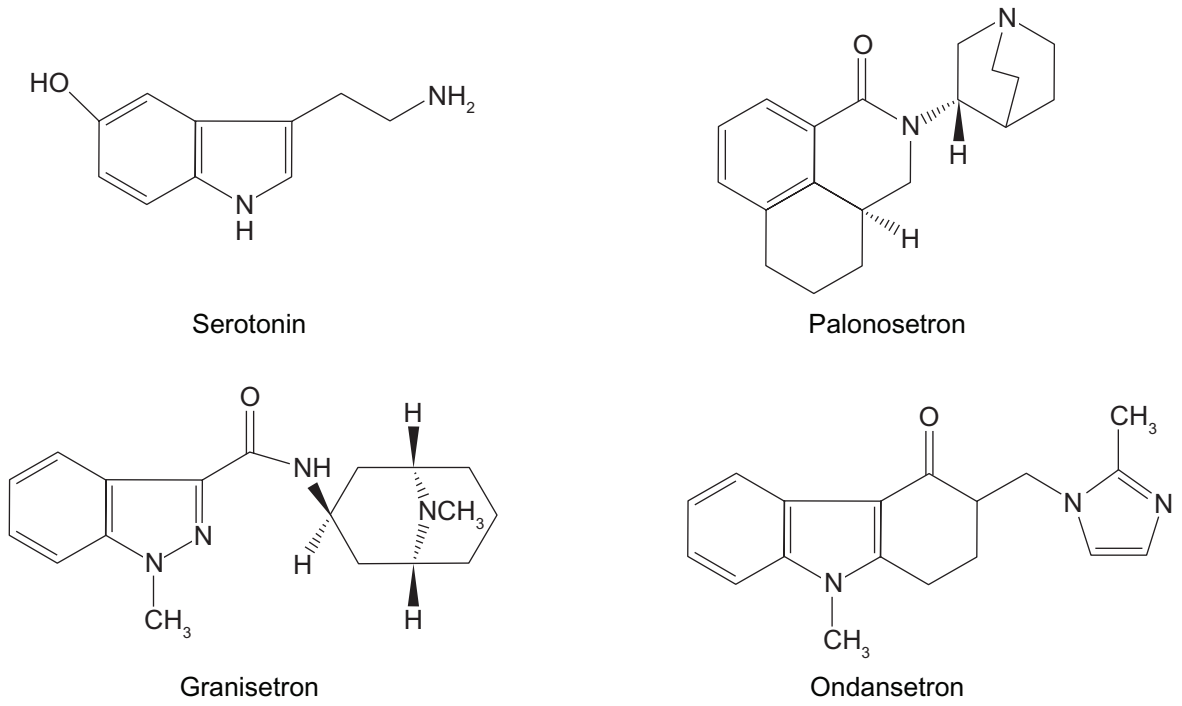

Figure 1. Structure of each molecule.

non-inferior to the comparator (63.0% vs. 52.9% for dolasetron) in the study by Eisenberg et al[25] in the acute phase of CINV.

One of the secondary endpoints of these trials was the CR rate for delayed emesis. palonosetron also exhibited a significantly higher CR rate than the other drugs: 74.1% vs. 55.1% (ondansetron) in Gralla et al's study and 54.0% vs. 38.7% (dolasetron) in Eisenberg et al's study in the delayed phase of CINV.

The other phase III trial performed by Aapro et al[38] also compared palonosetron (0.25 mg or 0.75 mg) with ondansetron (32 mg) in prophylactically treated patients receiving HEC including cisplatin ($\geq$60 mg/m^2), cyclophosphamide ($>$1500 mg/m^2) or dacarbazine. In this study, a single dose of palonosetron was not inferior to ondansetron in the prevention of CINV during the acute (59.2% vs. 57.0%) and delayed (45.3% vs. 38.9%) phases of CINV, or overall (40.8% vs. 33.0%).

Another secondary endpoint of the three phase III trials was an efficacy comparison between palonosetron (0.25 mg and 0.75 mg). The two proved to be equivalent in all aspects, including their safety profiles.

In conclusion, the hypothesis that the anti-emetic efficacy of palonosetron for acute CINV is not inferior to that of the first generation 5-HT3RAs was confirmed. Moreover, the possibility that palonosetron might have superior prophylactic effects in CINV for HEC and MEC has been raised.

Combination therapy with palonosetron and dexamethasone

Combination therapy of a 5-HT3RA and corticosteroids is recommended in the international guidelines such as MASCC and NCCN to prevent acute and delayed CINV associated with MEC and HEC. Therefore, randomized clinical trials using dexamethasone combined with palonosetron must be conducted to prove the superiority of palonosetron in anti-emetic efficacy compared to other 5-HT3RAs. In previous phase III trials, dexamethasone was given to only a few patients in MEC studies[25,26] and two-thirds of those in a HEC study.[38] According to those guidelines, aprepitant is also required in combination therapy for HEC and AC.[27,39]

In the phase III study done by Aapro et al,[38] two-thirds of patients received 20 mg of dexamethasone prophylactically. Among the HEC patients treated with dexamethasone, those in the palonosetron group showed a significantly higher CR rate for delayed CINV than those in the ondansetron group (42.0% vs. 28.6%, $P < 0.05$) in subgroup analysis. However, as the primary endpoint of this trial was to

prove non-inferiority in the prophylactic efficacy of palonosetron compared to ondansetron in the acute phase of CINV, further trials relevant to the new endpoint of investigating the efficay of palonosetron compared to other antiemetics, such as dexamethasone with or without aprepitant, are needed.

A phase II study ($N = 32$) done by Hajdenberg et al[40] evaluated the safety and efficacy of palonosetron (0.25 mg) plus dexamethasone (8 mg) for MEC. The CR rate was 84% in the acute phase and 59% in the delayed phase of CINV. The combination was well tolerated and no serious adverse events were reported.

In another phase II study performed by Giuliani et al[41] ($N = 85$), palonosetron (0.25 mg) and dexamethasone (8 mg) were administered to MEC patients receiving a FOLFOX-4 regimen for colorectal cancer. The CR rate was 99% and none of the patients experienced vomiting during the acute phase of CINV.

Recently, Yu et al[42] reported a phase II trial ($N = 208$) comparing palonosetron with granisetron administered with dexamethasone for HEC. The CR rate for acute emesis of patients in the palonosetron group was 83%, while that of the granisetron group was 72%.

Only one prospective randomized phase III trial[29] evaluated the efficacy of palonosetron combined with dexamethasone as compared with granisetron plus dexamethasone. Prior to this phase III study, two phase II trials in Japan[43,44] evaluated the optimal dosage of palonosetron for combined administration with corticosteroids.

In the Japanese trials ($N = 231$ for HEC and $N = 204$ for MEC), single doses of intravenous palonosetron (0.075 mg, 0.25 mg or 0.75 mg) were administered with dexamethasone. No dose-response relationships were detected among the 0.075 mg, 0.25 mg, and 0.75 mg doses of palonosetron in terms of CR in the acute phase of CINV, assessed as a primary endpoint. However, a clear dose–response relation ($P = 0.048$) was demonstrated in daily assessment over a 120-h study period when 0.075 mg, 0.25 mg, and 0.75 mg doses of palonosetron were administered with dexamethasone for HEC, indicating a significant difference in response between the 0.075 mg dose versus the two higher doses.[43] Moreover, a subgroup analysis of the patients receiving AC tended to show dose-dependent increases in the CR rate, with more than 10% difference in the highest CR rate being recorded in the 0.75 mg dose group as compared with the 0.25 mg and 0.075 mg dose groups, for both the delayed and overall CINV response rates.[44] Three doses of palonosetron were well-tolerated and no dose-dependent increase in adverse effects was noted. The tendency for better efficacy with the 0.75 mg dose compared to the other doses and the excellent safety profile of this dose were the reasons for selecting 0.75 mg as the fixed dose for use in the next trial.

A double-blind, double-dummy randomized comparative phase III trial ($N = 1114$) conducted by Saito et al[29] was the first to evaluate the superiority of combination therapy with Palonosetron (0.75 mg) plus dexamethasone as compared with granisetron (40 μg/kg) plus dexamethasone. Dexamethasone was administered at a dose of 16 mg iv on day 1 followed by either 8 mg iv (for CDDP) or 4 mg orally (for AC) on days 2 and 3. The primary endpoints were to prove the non-inferiority of palonosetron in acute phase of CINV and its superiority in the delayed phase of CINV associated with HEC and AC as compared with granisetron. The CR rate in the acute phase of CINV was 75.3% in the palonosetron group and 73.3% in the granisetron group. On the other hand, the CR rate in the delayed phase of CINV in the palonosetron group was significantly higher than that in the granisetron group (56.8% vs. 44.5%, $P < 0.0001$). A Kaplan–Meier plot of time to treatment failure is shown in Fig. 2. Both anti-emetic regimens were well tolerated and showed similar safety profiles.

Despite some controversies related to the design, this trial made a small but important step in the progress of anti-emetics. NK1RAs such as aprepitant are promising and are recommended in the guidelines to be included in further trials to answer the need for more potent regimens against CINV.

Triplet drug therapy including palonosetron

There have been three phase II trials, while no phase III trials using a three-drug regimen of anti-emetics had been reported as of the end of December, 2009.

A phase II trial conducted by Grote et al[45] ($N = 58$) was designed to evaluate the efficacy of triplet drug therapy including palonosetron (0.25 mg), dexamethasone (12 mg on day 1, and 8 mg on days 2

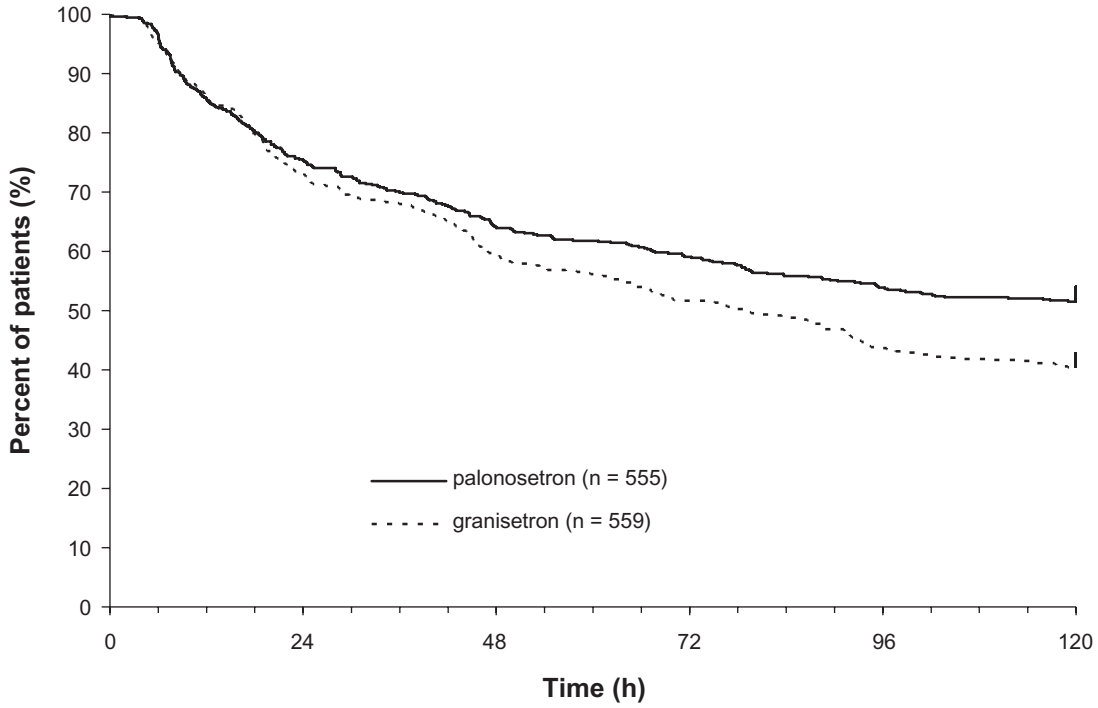

Figure 2. Kaplan–Meier plot of time to treatment failure.Kaplan–Meier curves for time to treatment failure. Hazard ratio: 1.299; 95% confidence interval: 1.106–1.526. Solid line: palonosetron (*N* = 555); dotted line: granisetron (*N* = 559) in phase III study in Japan (29).

and 3) and aprepitant (125 mg on day 1, and 80 mg on days 2 and 3) for MEC. The CR rate was 88% in the acute phase and 78% in the delayed phase of CINV.

Another phase II study (*N* = 41) for MEC conducted by Grunberg et al[46] showed a 76% CR rate for the acute phase and a 66% CR rate for the delayed phase of CINV. In this study, patients were prophylactically treated with palonosetron (0.25 mg), aprepitant (285 mg) and dexamethasone (20 mg).

A phase II study for HEC (*N* = 70) was performed by Herrington et al.[47] Patients were randomized into three arms. During the acute and delayed phases of CINV, the aprepitant group (*N* = 27) receiving prophylactic aprepitant with palonosetron plus dexamethasone showed favorable efficacy with triplet drug therapy (CR = 70.4% in acute, 59.3% in delayed), as compared to the control group (*N* = 16, CR = 56.2% and 31.2% respectively) receiving palonosetron plus dexamethasone. Patients in the other aprepitant group (*N* = 27) were administered additional aprepitant on days 2 and 3 showed similar CR rates (66.7% in acute, 63% in delayed).

In each of these studies, three-drug regimens were well tolerated and no unexpected severe side-effects were reported. These studies confirmed that combination therapy with palonosetron plus dexamethasone and aprepitant is safe and effectively prevents CINV associated with HEC and MEC.

Guidelines

There are several international guidelines regarding anti-emetics. Academic organizations such as MASCC,[21] NCCN[1] and the American Society of Clinical Oncology (ASCO)[39] have their own committees to develop anti-emetic recommendations.

Prevention is the mission of all oncologists giving anti-emetic therapy, and this has been a constant since the concept of "anticipatory emesis" was recognized, while the main target of CINV treatment has moved from the acute phase to CINV overall for the past two decades. The goal of anti-emetic therapy used to be the prevention of emesis, especially in the acute phase of CINV, as indicated in the ASCO guideline of 1999[48] and of MASCC in 1998[49] which are the oldest guideline reports.

After 5-HT3RAs became standardized for clinical use, most patients were free of acute emesis. Prevention or control of acute CINV is necessary but not sufficient for success in controlling delayed emesis. Control of delayed CINV in turn became the next

goal and is the future of research on improved combination therapy with multiple anti-emetics. With new treatments such as aprepitant and palonosetron, the current concern is to prevent overall CINV, especially nausea as well as vomiting.

The Perugia meeting included a consensus panel on anti-emetic guidelines for MASCC endorsed by eight other international oncology organizations. Those eight are ASCO, NCCN, Oncology Nursing Society (ONS), Cancer Care Ontario (CCO), the European Society of Medical Oncology (ESMO), the European Oncology Nursing Society (EONS), the South African Society of Medical Oncology (SASMO) and the Clinical Oncology Society of Australia (COCA). As the latest Perugia meeting was held in June of 2009 followed by MASCC; updated guidelines will be available on the website (www.mascc.org).[2] In general, evidence based medicine cannot always be implemented, because all the evidence required in the clinical setting is not available. If there is enough evidence, consensus is not necessary. As reaching a consensus for recommendations followed by the generation of guidelines is a very complicated process, trials should be well designed to consider future practice. Moreover, there are guidelines for generating guidelines.[50–54]

Some examples of the latest available anti-emetic guidelines are as follows; MASCC (in *Ann Oncol*) in 2006,[28] ASCO (in *J Clin Oncol*) in 2006,[39] ESMO (in *Ann Oncol*)[55] in 2008 and the NCCN website[1] in 2009. MASCC provides recommendations for prophylactic treatment of acute and delayed phases of CINV for every emetic risk category of chemotherapy (HEC, MEC, LEC and minimal). Other guidelines are basically similar to those of the MASCC, while some have been simplified to be more practical.

Discussion

Anti-emetic treatment has gradually been given enough attention to satisfy cancer patients receiving chemotherapy, along with the development of knowledge, assessment and new treatment tools. The difference in perceptions of the incidence of emesis-associated chemotherapy between physicians and patients reported by Grunberg et al[57] was instructive. What is needed for future is not only the development of more potent drugs but also identification of the best combinations, tailored to the characteristics of each chemotherapy regimen and individual patients.

Considering individual physical condition is a matter of course in medicine; however, we must also be conscious of the situation of each country and each individual. We should be aware of the fact that not all recommended drugs are available to everyone economically or politically. Good examples are the new anti-emetics described in this review. Aprepitant is "not available" in many countries and palonosetron is also unavailable even in several developed countries in the world. As the time-lags in drug approval by each government are inevitable and the difference in individual economical status or preference cannot be ignored, "international" guidelines might have a responsibility to provide treatment options. Otherwise, only privileged people will have access to not only novel therapies but also the standard therapy recommended in the updated guidelines. In this sense, the application of palonosetron plus dexamethasone to prevent delayed or all-over CINV induced by HEC or AC has to be considered as an recommended option if NK1RA is unavailable.

Rescue therapy, the strategy for failed CINV prevention, has yet to be clarified. We hoped to find an answer through anticipatory emesis trials. However, even in recent trials using anti-psychotics such as olanzapine interacting with various neurotransmitter receptors, the patients included were chemotherapy-naïve and the endpoint of these trials was not the investigation of rescue therapy for CINV.[58,59] Nonetheless, the data obtained in one of these trials included a high CR rate (97%) in the acute phase of CINV treated with olanzapine (10 mg), palonosetron (0.25 mg) and dexamethasone (20 mg for HEC or 8 mg for MEC), results which must be taken into consideration.[58]

The border between acute and delayed phases of CINV and anti-emetic therapy for multi-day chemotherapy has to be discussed. The phases of CINV were divided based on the emetic pattern associated only with CDDP.[10] There is neither a distinct border nor is the concept of an acute-delayed phase applicable especially during multi-day chemotherapy. MASCC,[21] NCCN[1] and ASCO[39] have recommended 5-HT3RA and dexamethasone administration daily for the prevention of nausea and vomiting induced by multi-day chemotherapy. However, treatment

with palonosetron or aprepitant, which is our focus in this paper, awaits future discussions, considering the data from several phase II trials already conducted.[56,59]

One of the controversial issues related to 5-HT3RAs is the dose difference of approval in each country. The recommended dose of palonosetron in the guideline is 0.25 mg, while a 0.75 mg dose was used in a phase III trial which was performed in a country where palonosetron was not approved by the government.[29] A meta-analysis demonstrated the equivalent efficacy and safety profiles of those two dosages.[60] In the guidelines, however, the lowest dose is recommended if efficacy is equivalent,[2] which is reasonable and universally supported. On the other hand, as with the administration of 0.75 mg of palonosetron in the aforementioned study, the data from dose-finding phase II studies showed more favourable CR rates in the 0.75 mg group than in the 0.25 mg group, as described above.[46] This phenomenon always depends on the sample size and/or background factors of the population. Biological and pharmacological truth is the endpoint of clinical trials; however, ambiguity is the common impression given by the results. Even though the possibility of a plateau between point A and point B has been strongly supported by pivotal trials, other possibilities include a slightly rising curve reflecting dose-dependence, or a bell-shaped dose-response curve, the top of which is somewhere between point A and B. These possibilities may have to be considered.

Palonosetron was granted FDA approval in March 2008 for the prevention of post-operative nausea and vomiting in the period up to 24 hours after surgery. Considering its pharmacological characteristics and clinical advantages not only in CINV but also in post-operative nausea and vomiting, palonosetron is expected to play a big role in the field of anti-emetic treatment.

Recent progress in anti-emetic research will help patients by freeing them from emesis and hopefully even nausea. The next goal is to assure that these treatments are available worldwide and able to provide tailored treatment options for every individual.

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Disclosure

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