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Clinical update on palonosetron in the management of chemotherapy-induced nausea and vomiting

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ABSTRACT

The need to control chemotherapy-induced nausea and vomiting is continuously stimulating research to find better options for the optimal antiemetic care. Palonosetron is different from conventional serotonin receptor antagonists not only by the fact of having a longer half-life but also by higher binding affinity for serotonin receptors. It is the first agent in the class which is approved for preventing both delayed and acute emesis induced by moderately emetogenic chemotherapy. Recent studies using palonosetron-based antiemetic regimens, as well as in the clinical setting of multiple-day chemotherapy, have been reported. Palonosetron plus dexamethasone given as a pre-treatment infusion was effective for preventing acute and delayed emesis after moderately emetogenic chemotherapy. Palonosetron in combination with dexamethasone and aprepitant was highly effective in preventing emesis in the days following administration of moderately emetogenic chemotherapy. Treatment was well tolerated, with no unexpected adverse events. Multiple-day dosing of palonosetron plus dexamethasone was safe and effective for prevention of emesis induced by 5-day cisplatin-based chemotherapy. There was no evidence of cumulative toxicity when palonosetron was given three times over 5 days. Further evidence from ongoing clinical trials with palonosetron with or without dexamethasone will be available soon. Palonosetron represents an useful addition to the therapeutic armamentarium for the management of chemotherapy-induced nausea and vomiting. Further studies are needed to assess the effectiveness of palonosetron in combination with dexamethasone compared with that of older serotonin receptor antagonists combined with dexamethasone. However, palonosetron may offer advantages of convenience over the short-acting older antagonists due to its ability to be given as a single intravenous dose prior to chemotherapy.

Introduction

Nausea and vomiting (emesis) remains among the most distressing side effects of cancer chemotherapy, often limiting the ability to deliver the cytotoxic therapy itself[1]. Chemotherapy-induced nausea and vomiting (CINV) occur within a few hours of treatment and may continue for several days. The three phases of CINV are[1]: (a) acute emesis which occurs in the first 24 h following treatment; (b) delayed emesis which typically describes the time period from 24 h onward and can persist as long as 5-7 days; and (c) anticipatory emesis, where vomiting occurs before chemotherapy in patients with poorly controlled emesis from previous cycles of chemotherapy.

During the decade of the 1990's, selective antagonists of the type three 5-hydroxytryptamine receptor (5-HT_3R) quickly became the cornerstone of antiemetic management[1]. However, the ability to prevent emesis in most patients receiving emetogenic chemotherapy created the perception among medical oncologists that CINV was no longer a significant problem. A recent survey showed that experienced oncologists and oncology nurses underestimate substantially the extent to which CINV occurs, especially in case of delayed symptoms, when the problem becomes apparent when the patient is already at home[2]. Physicians accurately predicted acute CINV but overestimat-

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ed control rates for delayed emesis after both highly (HEC) and moderately emetogenic chemotherapy (MEC) by up to 30%. It should be noted that the strongest predictor of delayed CINV is the occurrence of symptoms in the acute phase, but delayed emesis arises in the absence of acute symptoms in 18-24% of patients[2,3].

Recently, a meta-analysis confirmed no difference in efficacy for acute CINV among the first-generation, short-acting 5-HT_3R antagonists (ondansetron, granisetron, dolasetron, tropisetron), except that granisetron may be more efficacious than tropisetron during the first 24 h following chemotherapy[4]. Combination of a 5-HT_3R antagonist with a corticosteroid is more effective than monotherapy for prophylaxis against CINV[5]. However, a major problem is that short-acting 5-HT_3R antagonists have a modest impact on symptoms in the delayed phase. A recent meta-analysis of 10 studies of 5-HT_3R antagonists supports the lack of a benefit for prevention of delayed CINV[6]. Delayed emesis induced by cancer chemotherapy can significantly decrease the patient's quality of life, as shown in a study of nearly 300 patients receiving HEC or MEC[7].

Recent developments in antiemetic care include the approval of the first neurokinin-1 (NK_1) receptor antagonist for acute and delayed CINV for use in combination with standard antiemetic regimens and the approval of palonosetron, the newest agent in the 5-HT_3R antagonist class. This paper provides an update on the clinical experience gained with palonosetron to date in the management of CINV, with a special emphasis on more significant clinical data recently reported in the literature. Ongoing trials with palonosetron are also outlined.

Palonosetron: a 5-HT_3R antagonist for acute and delayed CINV

Palonosetron, a second-generation 5-HT_3R antagonist, differs from conventional serotonin antagonists in that it has a markedly longer terminal half-life of elimination (40 h) and a higher binding affinity for 5-HT_3R[8]. Recent results indicate that palonosetron exhibits both competitive and allosteric interactions with the 5-HT_3R, in contrast to the first-generation antagonists ondansetron and granisetron, which display strictly competitive antagonism[9]. As allosteric interactions may induce changes in the receptor conformation, it has been speculated that palonosetron's dual action on the 5-HT_3R could induce amplification of its inhibitory effect at the primary receptor binding site.

Currently, three large phase III trials have been conducted to compare palonosetron to older 5-HT_3R antagonists. Two trials with an identical non-inferiority design using MEC compared a single intravenous dose of palonosetron (0.25 mg or 0.75 mg) with a single intravenous dose of ondansetron or dolasetron, all given immediately prior to chemotherapy on day 1[10,11]. The third study compared single intravenous doses of palonosetron (0.25 mg and 0.75 mg) with a single dose of ondansetron immediately prior to chemotherapy in patients receiving HEC[12]. All three randomized studies defined the primary end point as complete response (no emesis/no rescue antiemetics) in the acute phase. A number of secondary end points, including complete response for the delayed phase were also assessed. Efficacy results from phase III trials with palonosetron given at the approved dose are shown in Table 1.

In all three studies, antiemetic treatment was well tolerated and the most commonly reported side effects were mild headache and constipation. Results of registration trials showed that palonosetron is equally as, or more efficacious than are older 5-HT_3R antagonists in the prevention of acute and delayed CINV. The functional living index-emesis (FLIE) measurement of quality of life data from phase III trials also showed that significantly more patients treated with palonosetron experienced no impact on daily life from CINV than did patients treated with ondansetron or dolasetron during the acute and delayed time periods after MEC administration[13]. Palonosetron is the first and, at present the only, 5-HT_3R antagonist to have a specific indication for the prevention of delayed emesis in patients receiving MEC. However, the ability of palonosetron to prevent delayed CINV could be simply a carryover effect from better control of symptoms in the acute phase.

Table 1 - Complete response rates from phase III trials with palonosetron at the approved dose

Type of treatment	Reference	n	Comparator (dose in mg)	Study period	Response rate (%)		*P* value
					Palonosetron 0.25 mg	Comparator	
MEC	10	374	OND (32)	Day 1	81	69	0.008
				Days 2-5	74	55	<0.001
MEC	11	380	DOL (100)	Day 1	63	53	0.049
				Days 2-5	54	39	0.004
HEC	12	444	OND (32)	Day 1	59	57	0.701
				Days 2-5	45	39	0.180

MEC, moderately emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; OND, ondansetron; DOL, dolasetron.

Analysis of pooled data from two phase III trials using MEC showed that 500 patients in all treatment groups had no acute CINV, and 75% of them also experienced no delayed emesis[14]. Among emesis-free patients in the acute phase, a greater proportion receiving palonosetron had no delayed CINV compared with those who received ondansetron or dolasetron (80% *vs* 69%; $P = 0.005$). A similar trend was noted for those patients who experienced acute CINV. These findings suggest that the improved ability of palonosetron to prevent delayed CINV is unlikely to be simply a carryover effect. However, significant shortcomings in randomized studies of palonosetron are the absence of corticosteroids and the lack of repetitive day dosing for the comparator 5-HT_3R antagonists.

Recommendations for antiemetic therapy in patients receiving chemotherapy outlined both by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) did not select a 5-HT_3R antagonist as a preferred agent. ASCO recognizes that palonosetron outperformed other 5-HT_3R antagonists in comparative studies, but the primary end points only established non-inferiority[15]. Since palonosetron is the only 5-HT_3R antagonist approved for delayed CINV, the NCCN suggests the use of a single dose of palonosetron prior to the start of a 3-day chemotherapy regimen instead of multiple daily doses of oral or intravenous 5-HT_3R antagonists[16].

Recent clinical data on palonosetron

An open-label, multicenter, phase II study evaluated the safety and efficacy of intravenous palonosetron admixed with dexamethasone to prevent CINV in patients receiving MEC[17]. The antiemetic regimen consisted of palonosetron (0.25 mg) plus dexamethasone (8 mg) on day 1 prior to chemotherapy administration. Most of the 32 enrolled patients were women; the most common tumor types involved the breasts, colon, and lungs. More than half of the patients had not received prior chemotherapy. Complete response (defined as no emesis and no rescue medication) was achieved in 84% of patients during the acute phase, and in nearly 60% of the patients during the delayed phase (Table 2)[17-19]. A total of 23 (72%) patients had no emetic episodes, 16 (50%) had no nausea, and 21 (66%) used no rescue medication throughout the 5-day study period. The combination was well tolerated. When compared with pooled data from two phase III palonosetron trials in a similar population receiving MEC, the addition of dexamethasone resulted in a 12% increase in benefit during the acute phase (complete response rate 84% *vs* 72%)[20]. It is noteworthy that prevention of acute CINV is paramount to successful control of delayed and subsequent cycle emesis.

Aprepitant, the first NK_1 receptor antagonist available for clinical use, can increase the antiemetic efficacy of treatment with HT_3R antagonist plus dexamethasone for prevention of acute and delayed CINV[21]. An open-label, multicenter, phase II study assessed the efficacy of a single intravenous dose of palonosetron (0.25 mg on day 1 of chemotherapy), along with 3 daily oral doses of aprepitant (125 mg on day 1, 80 mg on days 2 and 3), and dexamethasone (12 mg on day 1, 8 mg on days 2 and 3) in patients receiving MEC[18]. Fifty-eight patients were assessable; 47% were women with breast cancer and 55% had received prior chemotherapy. Anthracycline/cyclophosphamide-based chemotherapy was the most commonly administered regimen (41%). Complete response occurred in 88% of patients during the acute phase and in 78% of patients during the delayed phase (Table 2). More than 90% of patients during all time intervals had no emetic episodes, and 57% to 71% of patients reported no nausea during each of the 5 days following chemotherapy administration. In addition, most patients (79%) did not receive rescue medication during the study period.

Table 2 - Complete response rates from recent phase II palonosetron trials in patients receiving MEC

Author (reference)	n	Antiemetic regimen (dose in mg)	Study period	Response rate (%)	95% CI
Hajdenberg *et al.*[17]	32	PALO (0.25) on day 1 DEX (8) on day 1	Day 1 Days 2-5 Days 1-5	84 59 59	67-95 41-76 41-76
Grote *et al.*[18]	58	PALO (0.25) on day 1	Day 1	88	77-95
		DEX (12) on day 1 then (8) on days 2-3	Days 2-5	78	65-88
		APRE (125) on day 1 then (80) on days 2-3	Days 1-5	78	65-88
Navari *et al.*[19]	32	PALO (0.25) on day 1	Day 1	97	84-100
		DEX (8) on day 1	Days 2-5	75	57-88
		OLA (10) on day 1 then (10) on days 2-4	Days 1-5	72	53-86

MEC, moderately emetogenic chemotherapy; 95% CI, 95% confidence interval; PALO, palonosetron; DEX, dexamethasone; APRE, aprepitant; OLA, olanzapine.

The most common adverse events (whether or not related to study treatment) were constipation (21% of patients), diarrhea (17%), fatigue (16%), insomnia (14%), and thrombocytopenia (10%), mostly mild in severity. These results suggest the potential for improved control of both acute and delayed CINV with the use of palonosetron and dexamethasone plus aprepitant.

Concern has been expressed about the potential side effects associated with multiple-day dexamethasone to control CINV[22]. Olanzapine, an atypical antipsychotic drug, has an affinity for several neurotransmitter receptors including HT_3R and has been shown to be an effective agent in controlling delayed CINV[23]. A recently published open-label, phase II study evaluated whether acute and delayed CINV can be effectively controlled in patients receiving MEC and HEC with the use of palonosetron plus olanzapine with dexamethasone given only before chemotherapy[19]. Eligible patients received on day 1 of chemotherapy an antiemetic regimen consisting of dexamethasone (8 mg orally or intravenously for MEC or 20 mg for HEC) and palonosetron (0.25 mg) before chemotherapy. Patients also began olanzapine, 10 mg orally, on day 1 and continued 10 mg daily for days 2-4 following chemotherapy administration. Forty patients who were chemotherapy-naïve entered the study. Most of the patients were women; the most common tumor types involved the lungs, breasts, and colon. Sixty-five percent of patients received at least four cycles of chemotherapy on study. For the first cycle of chemotherapy, the complete response for the acute phase was 100% and for the delayed phase, 75% of 8 patients receiving HEC. Complete response rates for each study period in 32 patients receiving MEC are shown in Table 2. The proportion of patients with no nausea for the acute phase was 100% and for the delayed phase, 78% in patients receiving MEC, and was respectively 100% and 50% in those receiving HEC. There was no grade 3 or 4 toxicity attributable to the study drugs for any of the cycles of chemotherapy. Olanzapine induced no significant sedation, weight gain, or induction of significant hyperglycemia during the study. The shortcoming in this study is that the relative contribution of olanzapine and palonosetron to the effective control of CINV cannot be determined.

Patients treated with multiple-day chemotherapy are at risk of emesis with each day's treatment. Repeat dosing of palonosetron in the clinical setting of multiple-day chemotherapy has not been studied and is not recommended despite palonosetron's safety profile at high doses[16,24]. A recently reported open-label, multicenter, phase II trial assessed the safety and efficacy of multiple-day dosing of palonosetron plus dexamethasone in patients receiving multiple-day cisplatin-based chemotherapy for testicular cancer[25]. Forty-one patients entered the study; 85% of patients were chemotherapy naïve, and all but one patient received chemotherapy consisting of bleomycin weekly, etoposide and cisplatin, both on days 1-5. The antiemetic regimen consisted of palonosetron, 0.25 mg once daily shortly before chemotherapy on days 1, 3, and 5, plus dexamethasone: 20 mg intravenously before chemotherapy on days 1 and 2, 8 mg orally twice daily on days 6 and 7, and 4 mg twice daily on day 8. Safety and efficacy were assessed at 24-h intervals for 9 days. Efficacy end points included emesis, intensity of nausea and its interference with patient functioning (evaluated by the Osoba nausea module), and rescue medication. The multiple-day antiemetic regimen was safe, and the most common adverse events were headache and constipation, mostly mild in severity. More importantly, there was no evidence of cumulative toxicity or any increase in the number or intensity of adverse events as a result of systemic accumulation of palonosetron when the drug was given three times over 5 days. Most of the patients had no emesis at any time throughout days 1-5 (51%) or days 6-9 (83%). Even on days 4 and 5 when an overlap of acute and delayed cisplatin-induced emesis was most likely present, 68% and 71% of patients, respectively, were emesis free. The antiemetic regimen also prevented severe nausea for most patients, with at least 59% of patients experiencing no or only mild nausea at any time on each study day. More than 60% of patients required no rescue medication on any study day except day 4, when 46% of patients had no rescue medication. Most patients reported that nausea had little interference with daily functioning on days 1-4 (72%) and days 5-9 (85%). Efficacy results of the study are comparable to those of published studies evaluating 5-day treatment with ondansetron plus either a day 1 through 5 regimen or a day 1 and day 2 regimen of dexamethasone during multiple-day cisplatin-based chemotherapy[26,27] (Figure 1).

Ongoing studies with palonosetron

Among patients receiving MEC, the efficacy of a single intravenous dose of palonosetron plus dexamethasone (8 mg intravenously) on day 1 will be compared with the same regimen on day 1, followed by dexamethasone (4 mg orally twice daily) given also on days 2 and 3 in two non-inferiority trials. In an open-label, multicenter, randomized, controlled, phase III trial launched by the ITMO oncology group, patients are eligible who have a confirmed diagnosis of a solid malignancy, who have received no prior chemotherapy treatment, who have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and who are scheduled to receive a single dose of a MEC on day 1. A similar disease-oriented study is a double-blind, placebo-controlled, multicenter, randomized trial conducted at European oncology clinics including patients who are females, have a confirmed diagnosis of mammary carcinoma, have received no prior chemotherapy, and are scheduled to receive a single dose of a MEC on day 1. The primary end point of both studies is the proportion of patients achieving a complete response during the 5 days following the first cycle of chemotherapy. Secondary efficacy end points include the following: the proportion of pa-

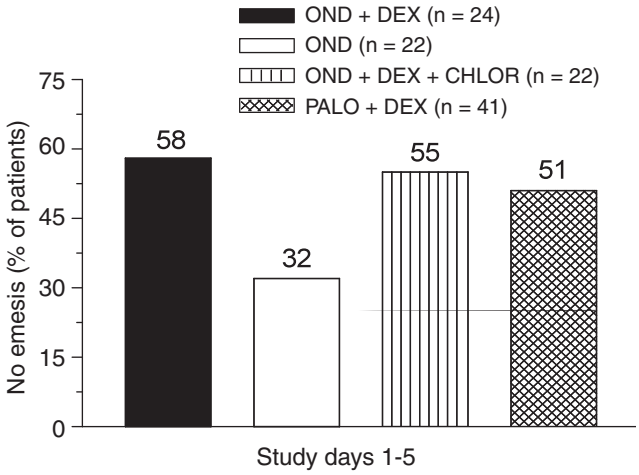

Figure 1 - Proportion of emesis-free patients from studies with multiple-day dosing of ondansetron or ondansetron plus dexamethasone compared with that of multiple-day dosing of palonosetron plus dexamethasone.

OND+DEX, ondansetron 0.3 mg/kg twice daily on days 1-5 plus dexamethasone 20 mg once daily on days 1-5 (Baltzer, 1993[26]); OND, ondansetron 0.15 mg/kg three times per day on days 1-5 (Einhorn, 2007[25]); OND+DEX+CHLOR, ondansetron 0.15 mg/kg three times per day on days 1-5 plus dexamethasone 8 mg before chemotherapy then 4 mg twice daily on days 1-2 plus chlorpromazine 50 mg four times per day on days 1-5 (Fox, 1993[27]); PALO+DEX, palonosetron 0.25 mg once daily on days 1, 3, 5 plus dexamethasone 20 mg once daily on days 1 and 2; 8 mg twice daily on days 6 and 7; 4 mg twice daily on day 8.

tients achieving complete control (defined as no emesis, no rescue medication, and no more than mild nausea); the severity of nausea; patient global satisfaction with antiemetic therapy, as measured by a visual analog scale throughout the 5-day study; and quality of life, measured via the FLIE questionnaire (only in the breast cancer trial). Patient diaries are used to record emetic episodes, use of rescue medication, patient global satisfaction, and severity of nausea. Estimated number of patients to be included in the ITMO study will be 330, whereas it is planned that 300 patients will be enrolled in the breast cancer trial.

Another disease-oriented study is an open-label, multicenter, phase II trial designed by the GOIM oncology group to evaluate the efficacy of a single dose of palonosetron plus dexamethasone (8 mg intravenously) on day 1 in patients with colon cancer who are scheduled to receive MEC. Eligible patients have histologically confirmed stage III colon carcinoma excised by curative surgery, have an ECOG performance status ≤1, and are scheduled to receive adjuvant chemotherapy with the FOLFOX4 (fluorouracil, folinic acid, and oxaliplatin) regimen. The primary end point of the study is the proportion of patients achieving a complete response during the 5 days following the first cycle of chemotherapy. Patient diaries are used to record study parameters. The estimated number of patients to be included in the study is 81.

Preliminary results from the above studies are anticipated in 2008.

Conclusions

Palonosetron is an effective and safe new 5-HT_3R antagonist with provocative activity compared with the older agents ondansetron and dolasetron in patients receiving MEC and HEC. However, there is a need to study the effectiveness of palonosetron in combination with dexamethasone and perform properly designed trials in which the short-acting, older 5-HT_3R antagonist is repetitively dosed. Further studies are awaited, as is the evaluation of the use of palonosetron in the clinical setting of multiple-day chemotherapy. Although the clear-cut superiority of palonosetron remains to be seen in future investigations, it may offer advantages of convenience over the short-acting 5-HT_3R antagonists due to its ability to be given as a single intravenous dose prior to chemotherapy.

References

1. Sharma R, Tobin P, Clarke SJ: Management of chemotherapy-induced nausea, vomiting, oral mucositis, diarrhea. Lancet Oncol, 6: 93-102, 2005.
2. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, Daniele B, De Pouvourville G, Rubenstein EB, Daugaard G: Incidence of chemotherapy-induced nausea and emesis after modern antiemetics: perception versus reality. Cancer, 100: 2261-2268, 2004.
3. Italian Group for Antiemetic Research. Prevention of cisplatin-induced delayed emesis: still unsatisfactory. Support Care Cancer, 8: 229-232, 1999.
4. Jordan K, Hinke A, Grothey A, Voigt W, Arnold D, Wolf HH, Schmoll HJ: A meta-analysis comparing of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. Support Care Cancer, 15: 1023-1033, 2007.
5. Grunberg SM: Antiemetic activity of corticosteroids in patients receiving cancer chemotherapy: dosing, efficacy, and tolerability analysis. Ann Oncol, 18: 233-240, 2007.
6. Geling O, Eichler HG: Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. J Clin Oncol, 23: 1289-1294, 2005.
7. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J: Delayed nausea and vomiting continue to reduce patient's quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol, 24: 4472-4478, 2006.
8. Aapro M: 5-HT(3)-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. Oncology, 69: 97-109, 2005.
9. Rojas C, Stathis M, Alt J, Rubenstein E, Cantoreggi S, Sebastiani S, Slusher B: Additional binding mechanism of palonosetron to the 5-HT3 receptor versus first generation 5-HT3 receptor antagonists. J Clin Oncol, 25: (Abstract 19583), 2007. Available at http://www.asco.org; accessed October 23, 2007.
10. Gralla R, Lichinitser M, Van der Vegt S, Sleeboom H, Mezger J, Peschel C, Tonini G, Labianca R, Macciocchi A, Aapro M: Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol, 14: 1570-1577, 2003.
11. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, Macciocchi A, Grunberg S: Im-

proved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor anatagonist. Results of a phase III, single-dose trial versus dolasetron. Cancer, 98: 2473-2482, 2003.
12. Aapro M, Grunberg SM, Manikhas GM, Olivares G, Suarez T, Tjulandin SA, Bertoli LF, Yunus F, Morrica B, Lordick F, Macciocchi A: A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol, 17: 1441-1449, 2006.
13. Decker GM, DeMeyer ES, Kisko DL: Measuring the maintenance of daily life activities using the functional living index-emesis (FLIE) in patients receiving moderately emetogenic chemotherapy. J Support Oncol, 4: 35-41, 2006.
14. Grunberg SM, Vanden Burgt JA, Berry S, Rubenstein EB, Berry D: Prevention of delayed nausea and vomiting (D-CINV): carryover effect analysis of pooled data from 2 phase III studies of palonosetron (PALO). Proc Am Soc Clin Oncol, 23: 738 (Abstract 8051), 2004.
15. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM: American Society of Clinical Oncology guidelines for antiemetics in oncology: update 2006. J Clin Oncol, 24: 2932-2947, 2006.
16. National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology: Antiemesis, version 1.2007. Available at http://www.nccn.org; accessed September 18, 2007.
17. Hajdenberg J, Grote T, Yee L, Arevalo-Araujo R, Latimer LA: Infusion of palonosetron plus dexamethasone for the prevention of chemotherapy-induced nausea and vomiting. J Support Oncol, 4: 467-471, 2006.
18. Grote T, Hajdenberg J, Cartmell A, Ferguson S, Ginkel A, Charu V: Combination therapy for chemotherapy-induced nausea and vomiting in patients receiving moderately emetogenic chemotherapy: palonosetron, dexamethasone, and aprepitant. J Support Oncol, 4: 403-408, 2006.
19. Navari RM, Einhorn LH, Loehrer PJ Sr, Passik SD, Vinson J, McClean J, Chowhan N, Hanna NH, Johnson CS: A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier oncology group study. Support Care Cancer, 15: 1285-1291, 2007.
20. Rubenstein EB, Gralla RJ, Eisenberg P, Sleeboom O, Vtoraya A, Macciocchi A, Olivares G, Berry D: Palonosetron (PALO) compared with ondansetron (OND) or dalasetron (DOL) for prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV): combined results of two phase III trials. Proc Am Soc Clin Oncol, 22: 729 (Abstract 2932), 2003.
21. Roila F, Fatigoni S: New antiemetic drugs. Ann Oncol, 17 (Suppl 2): ii96-ii100, 2006.
22. Vardy J, Chiew KS, Galica J, Pond GR, Tannock IF: Side effects associated with the use of dexamethasone for prophylaxis of delayed emesis after moderately emetogenic chemotherapy. Br J Cancer, 94: 1011-1015, 2006.
23. Navari RM, Einhorn LH, Passik SD, Loehrer PJ Sr, Johnson C, Mayer ML, McClean J, Vinson J, Pletcher W: A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier Oncology Group study. Support Care Cancer, 13: 529-534, 2005.
24. Hunt TL, Gallagher SC, Cullen MT Jr, Shah AK: Evaluation of safety and pharmacokinetics of consecutive multiple-day dosing of palonosetron in healthy subjects. J Clin Pharmacol, 45: 589-596, 2005.
25. Einhorn LH, Brames MJ, Dreicer R, Nichols CR, Cullen MT Jr, Bubalo J: Palonosetron plus dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy for germ cell cancer. Support Care Cancer, 15: 1293-1300, 2007.
26. Baltzer L, Pisters KMW, Kris MG, Tyson LB, Potanovich LM, Rigas JR, Bajorin DF, Motzer RJ, Pfister DG, Bosl GJ: High-dose ondansetron (OND) plus dexamethasone (DEX) for the prevention of nausea and vomiting with multiple-day cisplatin chemotherapy. Proc Am Soc Clin Oncol, 12: 462 (Abstract 1607), 1993.
27. Fox SM, Einhorn LH, Cox E, Powell E, Abdy A: Ondansetron versus ondansetron, dexamethasone, and chlorpromazine in the prevention of nausea and vomiting associated with multiple-day cisplatin chemotherapy. J Clin Oncol, 11: 2391-2395, 1993.