ORIGINAL

Translational and Randomized Study of 5-HT$_3$ Receptor Antagonists for Evaluation of Chemotherapy-induced Nausea and Vomiting Related Biomarkers

Yukari Tsubata MD, PhD[1], Mika Nakao MD[1], Yoshihiro Amano MD[1], Takamasa Hotta MD[1], Megumi Hamaguchi MD[1], Tamio Okimoto MD, PhD[1], Kiyotaka Miura MD[1], Shunichi Hamaguchi MD[1], Takashige Kuraki MD, PhD[1], Masayuki Itakura MD, PhD[2], and Takeshi Isobe MD, PhD[1]

[1]Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, Shimane, Japan, [2]Department of Surgery, Shimane University Faculty of Medicine, Shimane, Japan

Abstract : *Purpose* We assessed the efficacy of palonosetron (PAL) in comparison to granisetron (GRA) for the treatment of CINV using the self-assessment questionnaires. In addition, we analyzed the serum levels of emetic various biomarkers. *Methods* We conducted a randomized study of 70 patients naïve to chemotherapy. The primary endpoint was the late phase score on the MAT questionnaire. The plasma concentrations of the biomarkers were measured on days 1 and 3. *Results* There were no statistical differences in the scores on the questionnaires, but the mean values in response to PAL were higher than those in response to GRA. The value of ghrelin on day 1 was significantly higher for GRA than for PAL. *Conclusions* For the primary endpoint, the score of the late phase on the MAT questionnaire was not statistically different between the PAL and GRA treatment groups. Further studies are needed to clarify the role of ghrelin for the treatment of CINV. J. Med. Invest. 66 : 269-274, August, 2019

Keywords **:** *Chemotherapy-induced nausea and vomiting (CINV), Self-assessment questionnaire, Quality of life (QOL), Emetic biomarkers, Ghrelin*

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) is among the most feared and distressing side effects of chemotherapy for cancer patients. Inadequate control of CINV may cause treatment delay or discontinuation and impair the patient's quality of life (QOL). Oncologists should recognize that antiemetic therapy is important for the completion of chemotherapy while maintaining the QOL of the patients. The antiemetic guidelines provided by American Society of Clinical Oncology (ASCO) (1), National Comprehensive Cancer Network (NCCN) (2), and the Multinational Association of Support Care in Cancer (MASCC) (3) allow us to control CINV with appropriate antiemetic therapy. These current antiemetic guidelines classify the risks of CINV with anticancer drug by the regimen (e.g., high emetic risk chemotherapy (HEC), moderate emetic risk chemotherapy (MEC), low and minimal emetic risk chemotherapy) and the occurring phase (acute, delayed and anticipatory nausea and vomiting). Moreover, the guidelines list the recommended antiemetic drugs while showing the correct dosage.

CINV has physiologic mechanisms in each occurring phases, and various guidelines are recommended to choose the drug to use accordingly (1-3). For instance, it is thought that the release of serotonin (5-HT) from enterochromaffin cells in the small intestine is related to acute phase CINV. 5-HT$_3$ receptor antagonists (RAs) are reported to have complete response (CR) rates (i.e., no emesis, no use of rescue medication) of 50-70% (4-5) when using these drugs as single agents for antiemetic therapy of acute CINV (occurring within 24 hours of chemotherapy) in patients receiving MEC. However, it has been reported in the prevention of delayed CINV (occurring > 24 hours after chemotherapy) that the effectiveness is low even if 5-HT$_3$ RAs are administered together with a steroid (6).

Recently, new antiemetic agents have been developed such as the 5-HT$_3$RA, palonosetron (PAL) (7-9), and the neurokinin-1 (NK$_1$) RA (10-12), aprepitant. PAL is a highly potent, second-generation selective 5-HT$_3$ RA. It has been shown to have an approximately 100-fold stronger binding affinity for the 5-HT$_3$ receptor compared with other 5-HT$_3$ RAs and an extended plasma elimination half-life of approximately 40 hours (7). The PROTECT study (8), a phase III trial, showed that PAL with dexamethasone exerts efficacy against CINV which is non-inferior to that of granisetron (GRA) with dexamethasone in the acute phase and is better than that of GRA in the delayed phase. Aprepitant is the first approved substance P (SP)/NK1-RA, and it has been shown to significantly improve the prevention of acute and delayed CINV for use in combination with a 5-HT$_3$RA and dexamethasone (10-12).

While the strategy for the prevention of CINV is in progress, the self-assessment of patients using questionnaires is attractive because questionnaires can estimate the patient's QOL objectively. The MASCC Antiemesis Tool (MAT) (13) was developed as a tool for subjective patient self-evaluation of CINV in 2004 in which the patient can easily evaluate the onset time of CINV (14). The Functional Living Index-Emesis (FLIE) questionnaire is a validated patient-reported measure of the impact of CINV on daily living (15-16). However, there are few clinical trials that have examined these questionnaires as a major index of CINV evaluation.

On the other hand, it is well known that various emetic biomarkers, such as 5-HIAA, SP and ghrelin, affect emesis expression or appetite suppression. Serotonin (5-HIAA is a one of the metabolites of serotonin) has long been appreciated as the

Received for publication September 12, 2018 ; accepted May 7, 2019.

Address correspondence and reprint requests to Takeshi Isobe, MD, PhD, Professor and Chairman, Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan and Fax : +81-853-20-2580.

primary mediator of acute vomiting, a conclusion consistent with the efficacy of 5-HT_3 RAs in treating early phase CINV (17-18). SP is a regulatory peptide found in areas of the central nervous system and the gastrointestinal tract and known to cause CINV by binding to the NK-1 receptor of the vagal afferents (19-21). Ghrelin is a growth-hormone-releasing acylated peptide predominately produced by gastric endocrine cells and known to have an intense appetite-enhancing effect in addition to the growth hormone secretion-promoting effect (22-24). Moreover, the association between emetic biomarkers and CINV is unclear.

Therefore, our study was designed to evaluate the effectiveness of PAL compared to GRA using questionnaires in standard antiemetic therapy, especially for delayed phase CINV in which the prevention of CINV is believed to be difficult. Another objective of this study was to assess the plasma biomarker levels (5-HIAA, substance P, ghrelin) of patients who received chemotherapy with antiemetic drugs.

PATIENTS AND METHODS

Design and patients

This study was a prospective, randomized, single-center, comparative phase III trial. Eligible patients were 20 years of age or older with histologically or cytologically confirmed malignant disease, chemotherapy-naive and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2. Each patient was scheduled to receive his first course of HEC or MEC. The classification of HEC and MEC were according to the Japan Society of Clinical Oncology (JSCO) antiemetic guideline. The primary exclusion criteria included the following : dementia, planned whole brain irradiation, active infection, symptomatic brain metastasis, symptomatic hypercalcemia or hyponatremia. The primary endpoint was the score of late phase CINV on the MAT questionnaire. The secondary endpoints were the score of nausea or vomiting in the FLIE questionnaire, the proportion of patients that achieved a CR (defined as no emetic episode and no use of rescue medication) and the plasma concentrations of the biomarkers. Written informed consent was obtained from all patients in this study, which was approved by the institutional review board. This trial was registered with the UMIN (No. 000005268). At the time of registration to UMIN, because there was a patient of lung cancer and the breast cancer to start chemotherapy 80 patients at our hospital in a year, we set number of cases to 60 patients. After an examination start, because most of the enrolled patients were lung cancer patients, we increased the enrollment of the breast cancer patient in consideration of the balance of both groups and the study finished in 70 cases.

Procedures

The patients were randomized 1 : 1 to either the PAL or GRA treatment group, which were stratified by age, gender and the risk of CINV for chemotherapy (HEC or MEC). The standard antiemetic therapy for HEC was consisted to be intravenous PAL (0.75 mg) or GRA (3 mg) and dexamethasone (9.9 mg) on day 1, followed by oral dexamethasone (8 mg daily) on days 2-4. Oral aprepitant (125 mg) was administered on day 1 followed by 80 mg daily on days 2 and 3. The standard antiemetic therapy for MEC was consisted to be intravenous PAL (0.75 mg) or GRA (3 mg) and dexamethasone (9.9 mg) on day 1, followed by oral dexamethasone (8 mg daily) on days 2 and 3, and without oral or intravenous aprepitant. After chemotherapy, rescue medication for the treatment of nausea and vomiting was allowed for all patients.

For the assessment of the biomarkers, blood samples were collected at 1 h and 48 h after chemotherapy, according to the results of our preliminary study (data not shown). Approximately 4 mL of peripheral blood were divided into three tubes. For the measurement of active ghrelin, we used aprotinin/EDTA added tubes. All tubes were immediately centrifuged at 4℃, 3000 rpm for 10 min. The plasma was removed and stored at -80℃ until further use. The plasma concentration of 5-HIAA was measured by SRL Inc. (Tokyo, Japan) using a high-performance liquid chromatography system. SP (Cayman Chemical Co, Ann Arbor, Michigan, USA) and active ghrelin (SCETI Co Ltd, Tokyo, Japan) were measured using an enzyme-linked immunosorbent assay kit according to the protocol supplied by the manufacturer.

Assessments

We used two kinds of questionnaires to evaluate nausea and vomiting. The MAT questionnaire is an eight-item scale for the assessment of acute and delayed CINV that is completed once per cycle of chemotherapy (25). The validated FLIE questionnaire specifically addresses the impact of CINV on daily functioning and quality of life (QOL) (15-16). On days 2 and 5, the patients completed a MAT questionnaire to assess the effect of nausea or vomiting. On day 5, the patients also completed FLIE questionnaires. The study observation period was divided in three distinct phases : the acute phase, from the start of chemotherapy to 24 h post-chemotherapy administration (days 1-2) ; the delayed phase, from 24 h to 120 h (days 2-5) post-chemotherapy administration ; and the overall phase (days 1-5). Higher scores indicated more severe disease on the MAT and FLIE questionnaires.

Statistical analysis

Student's t-test or the Mann Whitney U test was applied to assess the data. All of the statistical calculations were performed using the SPSS software program, version 19 (IBM, Tokyo, Japan). A p value < 0.05 was considered to be statistically significant.

RESULTS

Patient

Patients were evaluated between Oct. 2010 and Jan. 2013. Seventy patients were enrolled and randomized to the PAL or GRA treatment group. Table 1 shows that the patient baseline characteristics, including known risk factors for CINV (gender,

Table 1 Patient characteristics

		PAL (N = 35)		GRA (= 35)	
Age (yr)	≦ 49	3	Median 68 yr	4	Median 68 yr
	50-69	18		17	
	≧ 70	14		14	
Gender	Male	22		22	
	Female	13		13	
Risk of emesis	HEC	20		19	
	MEC	15		16	
Type of cancer	NSCLC	25		24	
	SCLC	3		3	
	BC	6		6	
	Others	1		2	
ECOG PS	0 / 1	24 / 11		23 / 12	
Previous radiotherapy	Yes / No	8 / 27		4 / 31	
Alcohol habits	Yes / No	20 / 15		18 / 17	

alcohol consumption or history of radiation therapy), were similar between the two treatment groups. The majority of patients were male (44/70, 63%) with an average age of 68 years, and 56% of the patients received a HEC regimen. The most common primary types of malignant disease included lung cancer (54/70, 79%) and breast cancer (12/70, 17%).

Efficacy

For the primary endpoint, the score of the late phase on the MAT questionnaire was not statistically different between the PAL and GRA treatment groups (2.7 vs 3.5, P = 0.55) (Figure 1). The acute phase on the MAT questionnaire and emesis and nausea on the FLIE questionnaire (Figure 1) were also not statistically different between the two treatment groups. A subgroup analysis of each treatment group stratified by HEC and MEC also showed no statistically differences. While there were no statistical differences in the overall score of the questionnaires, the mean values in those receiving PAL were lower than those receiving GRA in both the acute and delayed phases. In addition, the CR (51.4% vs 48.6%) and total control (TC) (37.1% vs 40.0%) rates were similar during all phases among the PAL and GRA treatment groups (Table 2). An analysis of the questionnaires and the rate of total control showed that approximately 60% of the patients suffered from any vomiting or nausea, thus these patients required rescue medication throughout the observation period.

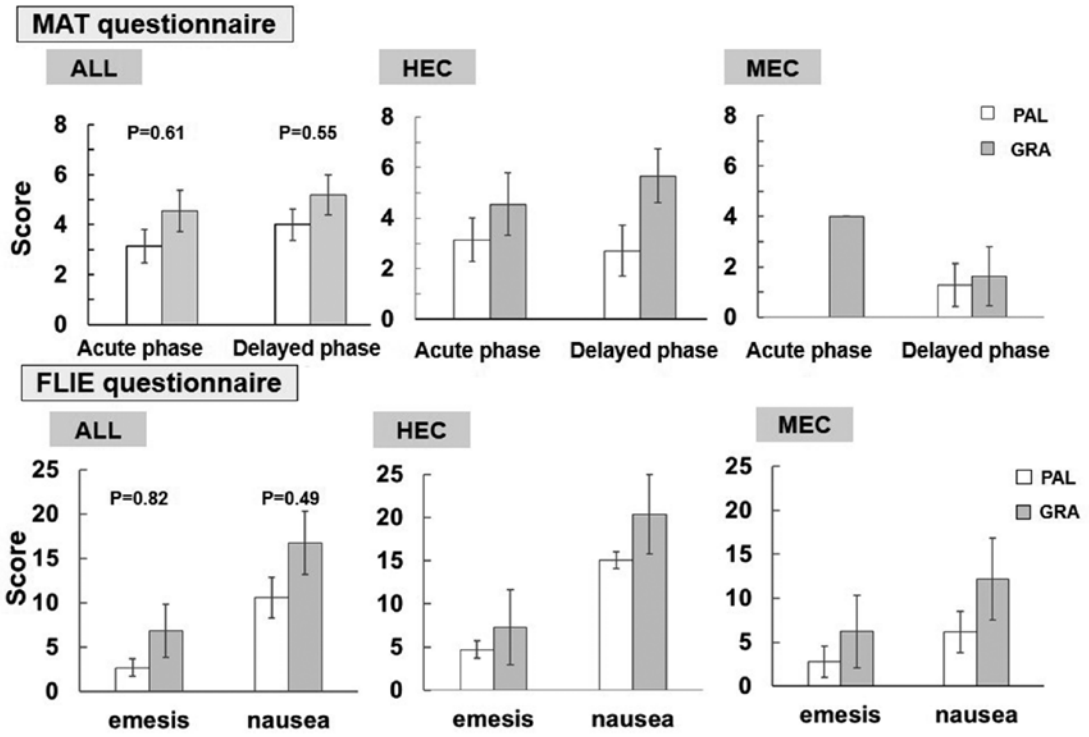

Figure 1 Results of the questionnaires
Data are expressed as the mean ± SE.

Table 2 Evaluation of the responses

Responses (%)		ALL		HEC		MEC	
		PALO (N = 35)	GRA (N = 35)	PALO (N = 20)	GRA (N = 19)	PALO (N = 15)	GRA (N = 16)
Complete Response	Acute	80.0	82.9	70.0	68.4	93.3	100
	Delayed	51.4	48.6	35.0	36.8	66.7	62.5
	Overall	51.4	48.6	35.0	36.8	66.7	62.5
Total Control	Overall	37.1	40.0	25.0	31.6	60.0	50.0

Complete response ; defined as no emetic episodes and no use of rescue medication
Total control ; defined as no emetic episodes, no use of rescue medication, and no nausea Acute ; 0-24 h, Delayed ; 24-120 h, Overall ; 0-120 h

Biomarker assessment

The plasma concentrations of SP and 5-HIAA were not significantly different between the PAL and GRA treatment groups on days 1 and 3, while the plasma ghrelin levels were significantly higher for GRA than PAL on day 1 (Figure 2). The ghrelin levels on day 3 were significantly decreased compared with on day 1 in the GRA group. A subgroup analysis of each treatment group stratified by HEC and MEC, having CINV or not, and a high or low score on the questionnaires also showed no statistically significant differences.

DISCUSSION

For all time points or intervals not mentioned, a similar trend favoring PAL compared with GRA was observed, although this difference did not reach statistical significance. It is especially important to note that at least 50% of the patients experienced CINV following an initial cycle of HEC and MEC, despite substantial recent progress. These patients required rescue medication throughout the observation period. In addition, the results of the biomarker study indicated that the plasma concentration of ghrelin, which is an appetite increaser hormone, may be related to the type or dosage of 5-HT_3RA.

Our results regarding the CR and TC rates are in agreement with previous triple therapy studies. The reason that significant differences were not detected in our study is because the sample size was too small. However, all the scores on the questionnaires showed an advantage with PAL treatment. In particular, because the FLIE questionnaire is a qualifying tool for evaluating the QOL of the patient, the fact that PAL treatment resulted in higher scores is thus considered to be an important finding. These finding suggest the possibility that PAL is useful for QOL maintenance of the patients compared with GRA. The evaluation of CINV is typically subjective, especially during the delayed phase. Clinicians tend to underestimate the incidence of nausea and vomiting, as well as a worsening of a patient's QOL during chemotherapy, and therefore improved communication between medical professionals and patients regarding CINV may help improve the outcomes (25-26). Thus, clinicians are sometimes troubled with the grading decision of the adverse events of CINV because the evaluation is not objective. Although we adopted standard antiemetic therapy in this study, which complied with the guidelines, the FLIE questionnaire clarified that approximately half of the patients felt that their QOL was inhibited by CINV. The MAT and FLIE questionnaires are a short, easy, self-administered instrument containing two domains – one for nausea and one for vomiting. These questionnaires are reliable for assessing the patient's QOL and easy-to-use in the clinical setting, thus they are useful tools for CINV management.

Various reports in the literature have shown that there is cross-talk between ghrelin, NK-1 and the 5-HT receptor signaling pathway (27-31). Rojas *et al*. (28) have shown the possibility that 5-HT_3 RAs can inhibit cisplatin-induced activation of the SP response. Moreover, 5-HT_{2C} receptor gene expression may lead to anorexia in cisplatin-treatment patients, and administration of a 5-HT_{2C} agonist inhibited hypothalamic ghrelin secretion (30). Recent reports indicate that both the 5-HT_{2C} receptor and the 5-HT_{2B} receptor, but not the 5-HT_3 receptor, mediate cisplatin-induced ghrelin suppression in rodents (32). In this study, we showed that there was a difference in the influence on the plasma ghrelin level between the PAL and GRA treatment groups. This phenomenon may be caused by the pharmacologic differences of the affinity of 5-HT_3 RA to the 5-HT_{2C} or 5-HT_{2B} receptor. It was thought that 5-HT_3 RAs, especially GRA, might have the potential to increase the ghrelin level and desacylation through various serotonin receptors. Because half-life is short in GRA with 4-9 hours, it is thought that the blood concentration of the ghrelin of day 3 decreased briefly as for the time to affect

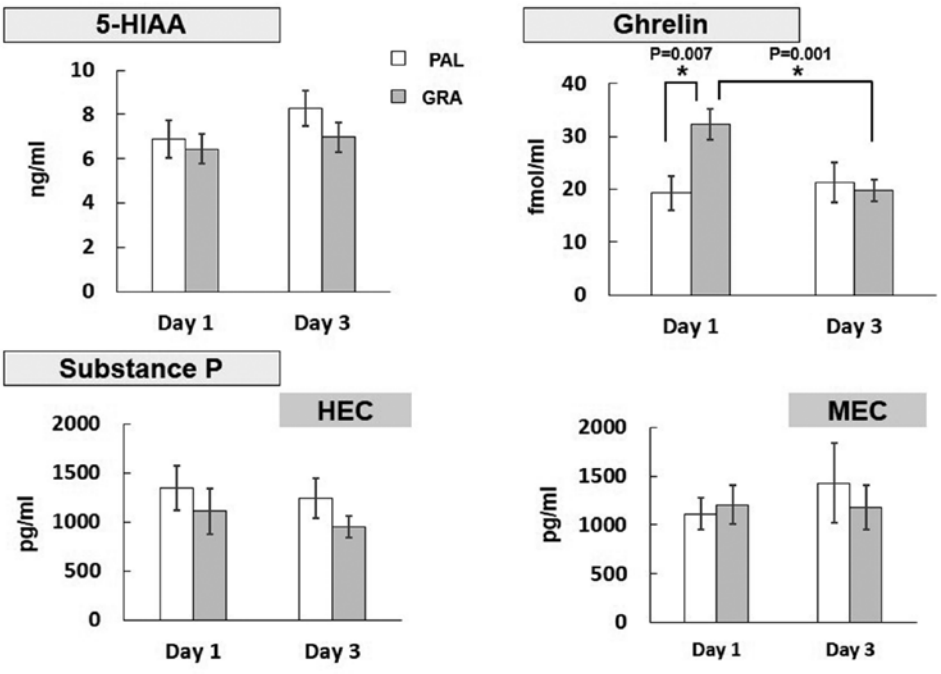

Figure 2 Results of the biomarkers
Data are expressed as the mean ± SE. *Statistically significant by student's t-test.

5-HT receptor. Further studies are needed to clarify any differences in the effects of both 5-HT_{2C} and 5-HT_{2B} and also elucidate their influence on ghrelin secretion and the metabolism during 5-HT_3 RA treatment.

CONCLUSION

However the score of the late phase on the MAT questionnaire was not statistically different between the PAL and GRA treatment groups, this study provided important information on the clinical assessment of CINV, and demonstrated that questionnaires, such as MAT and FLIE, are helpful for improving patient care during cancer chemotherapy. Though we provided treatment according to the antiemetic guidelines as standard therapy, half of the patients felt that their QOL was inhibited by chemotherapy. Further studies should investigate the control of CINV over the duration of cancer therapy and should consider not only the CR rate during the first cycle, but also the QOL of all cancer patients.

CONFLICT OF INTEREST

All authors have no conflict of interest to disclose.

ACKNOWLEDGEMENTS

We thank patients and their families who participated in this trial. This work was supported by efforts from the promotion plan for the platform of human resource development for cancer.

REFERENCES

1. Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacia D, Somefield MR, Lyman GH : Antiemetics : American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35 : 3240-3260, 2017
2. NCCN Clinical Practice Guidelines in Oncology Antiemesis Version 3.2018
3. Roila F, Hesketh PJ, Herrstedt J : Antiemetic subcommitte of the multinational association of supportive care in cancer. Prevention of chemotherapy-and radiotherapy-induced emesis, results of the 2004 Perugia International Antiemetic Conference. Ann Oncol 17 : 20-28, 2006
4. Hesketh PJ, Gandara DR : Serotonin antagonists : a new class of antiemetic agents. J Natl Cancer Inst 83 : 613-620, 1991
5. Chevallier B : Efficacy and safety of granicetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. The Granicetron Study Group. Eur J Cancer 26 : 33-36, 1990
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. Stoltz R, Cyong JC, Shah A, Parisi S : Pharmacokinetic and safety evalution of palonosetron, a 5-hydroxytryptamine-3 receptor antagonist, in U.S. and Japanese healthy subjects. J Clin Pharmacol 44 : 520-531, 2004
8. Aapro MS, 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 palonocetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol 17 : 1441-1449, 2006
9. Saito M, Aogi K, Sekine I, Yoshizawa H, Yanagita Y, Sakai H, Inoue K, Kitagawa C, Ogura T, Mitsuhashi S : Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy : a double-blind, double-dummy, randomized, comparative phase III trial. Lancet Oncol 10 : 115-124, 2009
10. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Rolia F, de Wit R, Chawla SP, Carides AD, Ianus J, Elmer ME, Evance JK, Beck K, Reines S, Horgan KJ, Aprepitant Protocol 052 Study Group : The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting : a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – the Aprepitant Protocol 052 Study Group. J Clin Oncol 21 : 4112-4119, 2003
11. de Wit R, Herrstedt J, Rapoport B, Carides AD, Guoquang-Ma J, Elmer M, Schmidt C, Evans JK, Horgan KJ : The oral NK1 antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy : a combined analysis of two randomizes, placebo controlled phase III clinical trials. Eur J Cancer 40 : 403-410, 2004
12. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, Carides A, Webb T, Schmoll HJ : Aprepitant for the prevention of chemotherapy –induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types : a randomized, double-blind study. Support Care Cancer 18 : 423-431, 2010
13. MASCC Antiemesis Tool (MAT) : http://www.mascc.org/content/126/.html
14. Molassiotis A, Coventry PA, Stricker CT, Clements C, Eaby B, Velders L, Rittenberg C, Gralla RJ : Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting, the MASCC Antiemesis Tool. J Pain Symptom Manage 34 : 148-159, 2007
15. Martin AR, Pearson JD, Cai B, Elmer M, Horgan K, Lindly C : Assessing the impact of chemotherapy-induced nausea and vomiting on paients'daily lives : a modified version of the Functional Living Index-Emesis (FLIE) with 5-day recall. Support Care Cancer 11 : 522-527, 2003
16. Poon M, Dennis K, DeAngelis C, Chung H, Stinson J, Zhang L, Bedard G, Wong E, Popovic M, Lao N, Pulenzas N, Wong S, Cheon P, Chow E : Symptom clusters of gastrointestinal cancer patients undergoing radiotherapy using the Functional Living Index-Emesis (FLIE) quality-of-life tool. Support Care Cancer 23 : 2589-2598, 2015
17. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Malave JJ : Changes in serotonin metabolism in cancer patients : its relationship to nausea and vomiting induced by chemotherapeutic drugs. Br J Cancer 66 : 198-203, 1992
18. Hesketh PJ, Van Belle S, Aapro M, Tattersal FD, Naylor RJ, Hargreaves R, Carides AD, Evans JK, Horgan KJ : Differential involvement of neurotransmitters through the time course of cisplatin-induced emesis as revealed by therapy with specific receptor antagonists. Eur J Cancer 39 : 1074-1080, 2003
19. Diemunsch P, Grelot L : Potential of substance P antagonists as antiemetics. Drugs 60 : 535-546, 2000
20. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Rolia F, de Wit R, Chawla SP, Carides AD, Lanus J, Elmer ME, Evans JK, Beck K, Reines S, Horgan KJ, Aprepitant Protocol

052 Study Group : The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting : a multinational, randomized, double-blind, placebo-contralled trial in patients receiving high-dose cisplatin- the Aprepitant Protocol 052 Study Group. J Clin Oncol 21 : 4112-4119, 2003
21. Higa GM, Auber ML, Altaha R, Piktel D, Kurian S, Hobbs G, Landreth K : 5-Hydroxyindoleacetic acid and substance P profiles in patients receiving emetogenic chemotherapy. J Oncol Pharm Pract 12 : 201-209, 2006
22. Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K : Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402 : 656-660, 1999
23. Wren AM, Small CJ, Ward HL, Murphy KG, Dakin CL, Taheri S, Kennedy AR, Roberts GH, Morgan DG, Ghatei MA, Bloom SR : The novel hypothalamic peptide ghrelin stimulates food intake and growth hormone secretion. Endocrinology 141 : 4325-4328, 2000
24. Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, Matsukura S : A role for ghrelin in the central regulation of feeding. Nature 409 : 194-198, 2001
25. Molassiotis A, Coventry PA, Stricker CT, Clements C, Eaby B, Velders L, Rittenberg C, Gralla RJ : Validation and psychometric assessment of a short clinical scale to measure chemotherapy-induced nausea and vomiting : the MASCC antiemasis tool. J Pain Symptom Manage 34 : 148-159, 2007
26. Escobar Y, Cajaraville G, Virizuela JA, Álvarez R, Muñoz A, Olariaga O, Tamés MJ, Muros B, Lecumberri MJ, Feliu J, Martínez P, Adansa JC, Martínez MJ, López R, Blasco A, Gascón P, Calvo V, Luna P, Montalar J, Del Barrio P, Tornamira MV : Incidence of chemotherapy-induced nausea and vomiting with moderately emetogenic chemotherapy : ADVICE (Actual Data of Vomiting Incidence by Chemotherapy Evaluation) study. Support Care Cancer 23 : 2833-2840, 2015
27. Hu WP, You XH, Guan BC, Ru LQ, Chen JG, Li ZW : Substance P potentiates 5-HT3 receptor-mediated current in rat trigeminal ganglion neurons. Neurosci Lett 365 : 147-152, 2004
28. Rojas C, Li Y, Zhang J, Stathis M, Alt J, Thomas AG, Cantoreggi S, Sebastiani S, Pietra C, Slusher BS : The antiemetic 5-HT3 receptor antagonist palonosetron inhibits substance P-mediated responses in vitro and in vivo. J Pharmacol Exp Ther 335 : 362-368, 2010
29. Rubenstein EB, Slusher BS, Rojas C, Navari RM : New approaches to chemotherapy-induced nausea and vomiting : from neuropharmacology to clinical investigations. Cancer J 12 : 341-347, 2006
30. Hiura Y, Takiguchi S, Yamamoto K, Takahashi T, Kurokawa Y, Yamasaki M, Nakajima K, Miyata H, Fujiwara Y, Mori M, Kangawa K, Doki Y : Effects of ghrelin administration during chemotherapy with advanced esophageal cancer patients. Cancer 118 : 4785-94, 2012
31. Yakabi K, Sadakane C, Noguchi M, Ohno S, Ro S, Chinen K, Aoyama T, Sakurada T, Takabayashi H, Hattori T : Reduced ghrelin secretion in the hypothakamus of rats due to cisplatin-induced anorexia. Endocrinology 151 : 3773-3782, 2010
32. Takeda H, Sadakane C, Hattori T, Katsurada T, Ohkawara T, Nagai K, Asaka M : Rikkunshito, an herbal medicine, suppresses cisplatin-induced anorexia in rats via 5-HT2 receptor antagonism. Gastroenterology 134 : 2004-2013, 2008