Comparison of Antiemetic Effects of Ondansetron Granisetron and Tropisetron For Acute Emesis In Ovarian Cancer Patients Receiving Chemotherapy With Paclitaxel and Carboplatin

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OBJECTIVE: Emesis is a critical adverse effect of cancer treatment. In this study, prophylactic activity of ondansetron (OND), tropisetron (TRO) and granisetron (GRA) on acute emesis following carboplatin-paclitaxel chemotherapy was compared.

STUDY DESIGN: Charts of 277 patients, who had been treated with first-line carboplatin-paclitaxel combined chemotherapy after being operated with a diagnosis of gynecologic malignancy in between 1993 and 2005, were evaluated retrospectively. After premedication, chemotherapy was initiated with paclitaxel 175 mg/m², infused in three hours. Then, carboplatin was infused in one hour (AUC=6). 90 minutes before the onset of chemotherapy, dexamethasone, 24 mg was infused within an hour. 5 HT3 receptor antagonist (OND=8 mg / TRO=5 mg / GRA=3 mg) were infused for a duration of 30 minutes, one hour before the chemotherapy. Toxicity was evaluated according to WHO criteria. Grade 0 toxicity was accepted as complete response, grade 1 and higher toxicity was accepted unresponsive.

RESULTS: The mean age was 55 years. Overall 1582 courses of chemotherapy were given. 241 patients (87%) received six courses. OND was given to 57 (20.6%) patients at 321 (20.3%) courses, TRO to 57 (20.6%) patients at 330 (20.9%) courses and GRA to 163 (58.8%) patients at 931 (58.8%) courses. Grade 3-4 toxicity did not develop in any of the patients. Complete response was achieved in 41.2% of the patients in 77.1% of the cycles. Antiemetic activities of TRO and GRA were stronger than OND.

CONCLUSION: Even though this study was retrospective, the treatment and patient groups were homogeneous. Both the discovery of an antiemetic that is much more effective and a protocol that is improved are essential. An emerging need for prospective studies achieved with homogeneous patient groups does exist.

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Key Words: Carboplatin, Emesis, 5 HT3 receptor antagonists

Emesis is a critical adverse effect of cancer treatment. Nausea and vomiting associated with chemotherapy have an effect on the quality of life and adjourn maintenance of the treatment.[1-3] The development of $5HT_3$ receptor antagonists at the end of 1980's was an important step at the prophylaxis and treatment of emesis linked with chemotherapy.

The carboplatin and paclitaxel combination is frequently used as first-line chemotherapy for gynecologic malignancies. Emetogenic characteristic of carboplatin, a cytotoxic agent is not as apparent as cisplatin, another member of platin species.[1,4] But emesis arising because of carboplatin could be important at the administration of chemotherapy.[5,6] Paclitaxel has a potent emetogenic characteristic too.[7,8]

The success of the 5 HT_3 receptor antagonists in carboplatin-based chemotherapy protocols was reported.[9-14] But data on superiority of one of these agents to others is restricted, as a consequence of lack of comparative studies on the activity of antiemetic agents. Additionally, most of comparative studies had evaluated antiemetic activity in patients who received cisplatin based chemotherapy.

In this study it was planned to compare prophylactic activity of ondansetron (OND), tropisetron (TRO) and granisetron (GRA) on acute emesis (first 24 hours of chemotherapy) resultant of carboplatin-paclitaxel chemotherapy.

Materials and Methods

Charts of 277 patients, who had been treated with first-line carboplatin-paclitaxel combined chemotherapy and single agent antiemetic (OND/TRO/GRA), after being operated with a diagnosis of gynecologic malignancy in between 1993 and 2005, were evaluated retrospectively. Patients received neoadjuvant chemotherapy was not eligible. They neither did go through dosage reduction, nor did receive chemotherapy or radiotherapy because of prior malignancy.

Chemotherapy, initiated with paclitaxel 175mg/m² after

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premedication was infused in three hours. Then carboplatin was infused in one hour (AUC=6). 24 mg of dexamethasone was infused for an hour, 90 minutes before the onset of chemotherapy. $5HT_3$ receptor antagonist (OND= 8mg / TRO= 5mg/GRA= 3mg) commenced one hour before the chemotherapy and infused within 30 minutes.

The emesis which developed within the first 24 hours of chemotherapy was defined as acute emesis. Toxicity was evaluated according to WHO criteria.[15] While complete response was accepted as grade 0 toxicity, nonresponse was accepted as grade 1 and higher toxicity. The response was calculated per course and per patient. The assessment per course was carried out in two conditions. The effects of $5HT_3$ receptor antagonists at primary course and after termination of courses were compared, trying to understand whether a change of antiemetic drug was necessary or not.

Descriptive statistics were calculated using the SPSS (Statistical Package for Social Sciences) 12.0 package program (SPSS Inc, Chicago IL, USA). Chi-square test was used to evaluate proportions for statistical significance. The cut-off for statistical significance was set at $P < 0.05$.

Results

The mean age at presentation was 55 years (range 18-79). A total of 1582 courses of chemotherapy were given to 277 patients. At least 3 chemotherapy courses were given. 241 patients (87%) received six courses (Table 1). Histopathological diagnosis was epithelial ovarian carcinoma in 218 patients (78.8%).

Table 1. Patient Characteristics

Parameter			n	%
Number of courses	3		17	6.1
	4		10	3.6
	5		9	3.2
	6		241	87
Histopathological diagnosis	Epithelial Ovarian Cancer		218	78.7
	PPSCP[1]		9	3.2
	Endometrial Adenocarcinoma		38	13.8
	Mixed Tumor[2]		9	3.2
$5HT_3$ Receptor Antagonist	Ondansetron	Patient number	57	20.6
		Course number	321	20.3
	Tropisetron	Patient number	57	20.6
		Course number	330	20.9
	Granisetron	Patient number	166	58.8
		Course number	931	58.8
CINV[3]	Grade 0	Per Patient	114	41.2
		Per Course	1220	77.1
	Grade 1	Per Patient	132	47.7
		Per Course	325	20.5
	Grade 2	Per Patient	31	11.2
		Per Course	37	2.3

[1]Primary Papillary Serous Carcinoma of Peritoneum, [2]Endometrial Adenocancer + Epithelial Ovarian Cancer, [3]Chemotherapy Induced Nausea and Vomiting

OND was given to 57 patients (20.6%) at 321 courses (20.3%), TRO to 57 patients (20.6%) at 330 courses (20.9%) and GRA, to 163 patients (58.8%) patients at 931 courses (58.8%) respectively.

Grade 3-4 toxicity did not develop in any patient. Nausea and vomiting did not develop in any course in 114 patients (41.2%). Grade 1 toxicity was observed at least in one course in 132 patients (7.7%). Grade 2 toxicity was observed in 31 patients (11.2%) (Table 1).

Complete response was achieved in 1220 courses (77.1%) (Table 1). Grade 2 toxicity developed in 37 courses (2.3%) (Table1) Grade 2 toxicity apparent in OND group was observed in 13 patients (22, 8%) in 16 courses (5%) (Table 2).

Table 2. Toxicity levels of emesis with respect to selected antiemetic

Per Course	Grade 0, n	Grade 1, n	Grade 2, n
Ondansetron	211 (65.7%)	94 (29.3%)	16 (5%)
Granisetron	750 (80.6%)	165 (17.2%)	16 (1.7%)
Tropisetron	259 (78.5%)	66 (20%)	5 (1.5%)
Per Patient			
Ondansetron	14 (24.6%)	30 (52.6%)	13 (22.8%)
Granisetron	72 (44.2%)	77 (47.2%)	14 (8.6%)
Tropisetron	28 (49.1%)	25 (43.9%)	4 (7%)

No significant difference at antiemetic effect between the primary course and after termination of courses was observed (Table 3). It was concluded that an antiemetic replacement in further courses had not been validated. But antiemetic activity of TRO and GRA were stronger than OND both in primary course and after completion of final course (Table 3). No difference between TRO and GRA was found. Complete response rate was 65.7% in OND, 78.5% in TRO and 80.6% in GRA for total courses.

Table 3. Comparison of antiemetic efficacies of $5HT_3$ receptor antagonists per course

Comparison	Antiemetic	Emesis, First course		Emesis, Total courses	
		CR, n	NR, n	CR, n	NR, n
Ondansetron	Ondansetron	35 (61.4%)	22(38.6%)	211 (65.7%)	110 (34.3%)
vs	Granisetron	127 (77.9%)	36 (22.1%)	750 (80.6%)	181 (19.4%)
Granisetron	p	0.015		0.000	
Ondansetron	Ondansetron	35 (61.4%)	22 (38.6%)	211 (65.7%)	110 (34.3%)
vs	Tropisetron	45 (78.9%)	12 (21.1%)	259 (78.3%)	71 (21.5%)
Tropisetron	p	0.041		0.000	
Granisetron	Granisetron	127 (77.9%)	36 (22.1%)	750 (80.6%)	181 (19.4%)
vs	Tropisetron	45 (78.9%)	12 (21.1%)	259 (78.3%)	71 (21.5%)
Tropisetron	p	0.871		0.418	

***CR:** Complete response, **NR:** Nonresponse*

Nausea and vomiting did not develop in any cycle in 28 patients (49.1%) who received TRO (Table 4). This rate was 44.2 in GRA and 24.6% in OND. Antiemetic activities of TRO and GRA were stronger than OND in some cases.

Table 4. Comparison of antiemetic efficacies of 5HT$_3$ receptor antagonists per patient

Comparison	Drug	Emesis, per patient	
		CR, n	NR, n
Ondansetron vs Granisetron	Ondansetron	14 (24.6%)	43 (75.4%)
	Granisetron	72 (44.2%)	91 (55.8%)
	p	0.009	
Ondansetron vs Tropisetron	Ondansetron	14 (24.6%)	43 (75.4%)
	Tropisetron	28 (49.1%)	29 (50.8%)
	p	0.007	
Granisetron vs Tropisetron	Granisetron	72 (44.2%)	91 (55.8%)
	Tropisetron	28 (49.1%)	29 (50.8%)
	p	0.558	

***CR:** Complete response, **NR:** No Response*

Discussion

Emesis is a paramount adverse effect of chemotherapy. It may develop either after the chemotherapy or while waiting for chemotherapy (anticipatory emesis), observed in approximately 25% of the patients.[16] The emesis which developed within the first 24 hours of chemotherapy was defined as acute emesis. Delayed emesis was defined as emesis developing after 24 hours and within first 5-7 days.[16,17]

The emetogenic features of antiemetic agents are different. The American Society of Clinical Oncology (ASCO) has developed a rating system for chemotherapeutic agents and their respective risk of acute and delayed emesis [18] (Table 5). Although cisplatin has a higher emetogenic characteristic than carboplatin [1,4], du-Bois et al reported 75% nausea and 22% vomiting in patients who received carboplatin at acute period [6]. However, Martin et al presented these rates as 89% and 82% respectively.[5]

Table 5. Emetogenic risk of chemotherapeutic agents

High-risk Emesis that has been documented to occur in >30 % of patients	Intermediate-risk Emesis that has been documented to occur in 10-30 % of patients	Low-risk Emesis that has been documented to occur in <10 % of patients
Cisplatin	Paclitaxel	Vinorelbine
Carboplatin	Docetaxel	Fluorouracil
Oxaliplatin	Irinotecan	Methotrexate
Dacarbazine	Mitoxantrone	Thioguanine
Mechlorethamine	Mitomycin	Mercapturine
Streptozocin	Topotecan	Bleomycin
Hexamethilmelamine	Gemcitabine	L-asparaginase
Cyclophosphamide	Etoposide	Vindesine
Lomustine	Teniposide	Vinblastine
Carmustine		Vincristine
Daunorubicin		Busulphan
Doxorubicin		Chlorambucil
Epirubicin		Melphalan
Idarubicin		Hydroxyurea
Cytarabine		Fludarabine
Ifosfamide		2-Chlorodeoxyadenosine
		Tamoxifene

Paclitaxel produce especially hematologic toxicity and neuropathy. But emesis may be an important problem in patients who receive this agent.[19] Mild and moderate emesis develop in 37-50% [7,20] and grade 3-4 emesis develop in 8-10% of patients who received paclitaxel.[8,21]

The prophylaxis and treatment of chemotherapy related emesis achieved by and large with the advancement of 5HT$_3$ receptor antagonists approximately 30 years before. Addition of dexamethasone to the treatment increases the antiemetic activity. [22-24]

The studies about the effect of 5HT$_3$ receptor antagonists to carboplatin related emesis are not enough. Successful results have been reported in these studies. Markman et al employed intravenous infusion of OND 8 mg and 20 mg dexamethasone before the chemotherapy to the patients who were receiving single agent carboplatin or carboplatin based combined chemotherapy (carboplatin-paclitaxel). 90% complete response was observed in this study with evaluation of only one cycle.[9] Nevertheless, the doses of carboplatin and paclitaxel were not invariable. Markman et al reported 93% complete response with 16 mg oral OND,[16] 83% complete response with constant-low dose 0,5 mg intravenous GRA infusion[10] and 94% complete response with low dose 1 mg oral GRA[12] in other prospective studies made in the same patient groups, evaluating only the primary chemotherapy. Similarly 94% complete response was reported by Smith et al at the acute period with OND.[14] Harvey et al who did not use a homogeneous group like Markman's studies has reported that in 68% of the patients vomiting was not observed and complete response was achieved in 20% of them.[13]

Studies comparing the antiemetic activity of 5HT$_3$ receptor antagonists at carboplatin based chemotherapy could not be found. There are two studies which compare antiemetic activities of OND, TRO and GRA at cisplatin based chemotherapy related acute emesis.[25,26] In both of them the worst results were obtained with TRO. The undetermined issue in the studies with antiemetic agents is whether the antiemetic activity changes or not in further cycles. Markman et al reported that there was no change.[27]

The patient groups of almost all of the studies which investigated 5HT$_3$ receptor antagonists activity on the carboplatin and cisplatin's emetogenic toxicity are not homogeneous. While a group of these patients received only single agent (carboplatin or cisplatin), another group received combined chemotherapy (mostly paclitaxel). Furthermore, the doses of the chemotherapeutic agents given during the study were not constant. In addition; some of the patients had been given chemotherapy or radiotherapy before. All of these factors resulted in contradictory nature of results related with antiemetic efficacy.

At present, aprepitant in addition to $5HT_3$ receptor antagonist plus dexamethasone is advised for acute and delayed emetogenic effect of high-risk chemotherapy by National Cancer Institute (NCI). Aprepitant (MK-0869) is NK-1 receptor antagonist. The initial studies using aprepitant demonstrated that the addition of aprepitant to $5HT_3$ receptor antagonist plus dexamethasone prior to cisplatin chemotherapy improved the control of acute emesis compared to $5HT_3$ receptor antagonist plus dexamethasone. Subsequent studies showed that the combination of aprepitant and dexamethasone was similar to $5HT_3$ receptor antagonist plus dexamethasone in controlling acute emesis but was inferior in controlling acute emesis compared with triple therapy (aprepitant + $5HT_3$ receptor antagonist + dexamethasone).[28,29] NCI is not advice aprepitant for intermediate or low-risk group. $5HT_3$ receptor antagonist plus dexamethasone combination is recommended for moderately emetogenic chemotherapy like as paclitaxel/carboplatin protocol.

Even though this study was retrospective, the treatment and patient groups were homogeneous. Both the discovery of an antiemetic that is much more effective and a protocol that is improved are essential. An emerging need for prospective studies achieved with homogeneous patient groups does exist. However, the outcome of these studies must be submitted with respect to the chemotherapy protocols instead of specific agent.

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