Comparison of Antiemetic Effects of Ondansetron, Granisetron and Tropisetron in Treatment of Acute Emesis Caused By Cisplatin/Paclitaxel Chemotherapy

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OBJECTIVE: Emesis is significant side effect of chemotherapy. In this study we aimed to compare prophylactic effect of ondansetron (OND), granisetron (GRA) and tropisetron (TRO) on acute emesis induced by cisplatin/paclitaxel combine chemotherapy.
STUDY DESIGN: Between years 1993 and 2005, 172 patients have been operated for gynecologic malignancy and who had first-line chemotherapy (cisplatin-paclitaxel) were evaluated retrospectively. Chemotherapy was started with paclitaxel (175 mg/m^2, 3 hours infusion) followed by cisplatin (75 mg/m^2, 2 hours infusion). Dexamethasone (24 mg) was given 60 min before chemotherapy and infused until chemotherapy. 5 HT3 antagonist (OND=8 mg/TRO = 5 mg/GRA=3 mg) is started 1 hour before chemotherapy and given in 30 minutes. The second dose of OND also was given before cisplatin (8 mg, 30 min infusion). Chemotherapy toxicity was assessed according to WHO criteria. According to this, grade 0 was accepted as a complete response while grade 1 and more toxicity were accepted as nonresponse.
RESULTS: 172 patients received 968 chemotherapy courses. OND, TRO, GRA were given 23.8% of patients and 23.3% of courses, 16.7% of patients and 15.7% of courses, 60.5% of patients and 59.9% of courses, respectively. Grade 3 toxicity was developed in 3.5% of patients and 0.8% of courses. None of the patients developed grade 4 toxicity. Complete response occurred in 28.5% of patients and 63% of courses. If it has been evaluated only for courses GRA is more effective than TRO. Other than there was no significant difference in antiemetic potency between the drugs for courses and patients.
CONCLUSION: Although this study is not prospective, it is homogenous for treatment modalities and patient selection. Complete response was observed in 63% of courses; however this antiemetic affect is not found to be satisfactory. In order to develope better protocols there is need for prospective studies on homogenous group. Antiemetic efficiency has to associate for chemotherapy protocols.
(Gynecol Obstet Reprod Med 2006; 12:197-201)

Key Words: Cisplatin, Emesis, 5 HT3 receptor antagonists

Chemotherapy-induced emesis has an effect on the quality of life and prevents maintenance of the effective cancer-treatment.[1-3] Success of antiemetics used nearby chemotherapy was not at required level until end of 1980s. 5 HT3 receptor antagonists developed after this period and have greatly overcome the nausea-emesis due to chemotherapy.

Cisplatin-paclitaxel protocol is used often in especially first-line chemotherapy in gynecological malignancies even though not as often as it was in the past. Emetogenic feature of cisplatin which is a cytotoxic agent, is quite strong.[4,5] Emetogenic feature of paclitaxel is not obvious as that of cisplatin. However, emesis caused by paclitaxel may become significant in the chemotherapy process.[4,6]

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Submitted for Publication: 25.09.2006

Accepted for Publication: 21.12.2006

5 HT3 receptor antagonists are effective antiemetic agents in prophylaxis and treatment of emesis developed in chemotherapy media having strong emetogenic feature.[6,7] Comparative studies carried out with such antiemetic agents are in limited number. For this reason, information on superiority of these medicines to one another is not clear.

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

Materials and Methods

Data of 172 patients operated due to gynecological malignancy diagnosed between years 1993-2005 and applied a first-line cisplatin/paclitaxel combined chemotherapy in follow-up, received the same antiemetic (OND/TRO/GRA) during first-line chemotherapy, applied no dose reduction due to chemotherapy toxicity, not received any adjuvant chemotherapy and not applied previously any chemotherapy or radiotherapy due to another malignancy, have been evaluated retrospectively, Chemotherapy, initiated with paclitaxel 175 mg/m² after premedication was infused in three hours. Then,

Table I. Patient Characteristics

Parameter			N	%
Number of courses	3		12	7
	4		11	6.4
	5		7	4.1
	6		142	82.6
Histopathological diagnosis	Epithelial ovarian cancer		143	83.7
	Fallopian tube carcinoma		4	2.3
	Endometrial adenocancer		17	9.9
	Mix tumor [1]		7	4.1
$5HT_3$ Receptor Antagonist	Ondansetron	Per Patient	41	23.8
		Per Course	226	23.3
	Tropisetron	Per Patient	27	15.7
		Per Course	162	16.7
	Granisetron	Per Patient	104	60.5
		Per Course	580	60
Acute CINV[2]	Grade 0	Per Patient	49	28.5
		Per Course	610	63
	Grade 1	Per Patient	61	35.5
		Per Course	254	26.2
	Grade 2	Per Patient	56	32.6
		Per Course	96	9.9
	Grade 3	Per Patient	6	3.5
		Per Course	8	0.8

[1]Endometrial Adenocancer + Epithelial Ovary Cancer, [2] CINV: Chemotherapy Induced Nausea and Vomiting

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

Per Courses	Grade 0, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
Ondansetron	137 (60.6)	69 (30.5)	19 (8.4)	1 (0.4)
Granisetron	382 (65.9)	152 (26.2)	43 (7.4)	3 (0.5)
Tropisetron	91 (56.1)	33 (20.4)	34 (21)	4 (2.5)
Per Patient				
Ondansetron	8 (19.5)	17 (41.5)	15 (36.6)	1 (2.4)
Granisetron	33 (21.7)	42 (40.4)	27 (26)	2 (1.9)
Tropisetron	8 (29.6)	2 (7.4)	14 (51.9)	3 (11.1)

cisplatin was given in 75 mg/m^2 by infusion in two hours. It is known that giving the therapy in this order, is tolerated by the patients better.[8] 24 mg of Dexamethasone was infused for an hour before chemotherapy. 5 HT3 receptor antagonist (OND= 8 mg / TRO= 5 mg / GRA= 3 mg) commenced one hour before the chemotherapy and infused within 30 minutes. In addition, OND was given one more dose before cisplatin (8 mg, 30 minutes infusion).

The emesis which developed within the first 24 hours of chemotherapy was defined as acute emesis. Toxicity was evaluated according to WHO criteria.[9] According to this, grade 0 toxicity was accepted as complete response whereas, grade 1 and higher toxicity was accepted as nonresponse. Response in the study was examined per course and per patient.

Statistical evaluation was made by utilizing Chi-Square test in SPSS (Statistical Package for Social Sciences) 12.0 program working under Windows XP operating system. The expression $p < 0.05$ was accepted as meaningful.

Results

Mean age of patients was 54.4.[18-81] A total of 968 courses of chemotherapy were given to 172 patients. The minimum applied chemotherapy course was three and 142 patients (82.6%) received six courses of chemotherapy (Table I). Pathological diagnosis of 143 patients (83.7%) was epithelial ovarian carcinoma.

OND, TRO and GRA was applied in 41 patients (23.8%) and 226 courses (23.3%), 27 patients (15.7%) and 162 courses (16.7%) and 104 patients (60.5%) and 580 courses (60%) respectively (Table I).

Table 3. Comparison of antiemetic efficacies of 5 HT3 receptor antagonists per course and per patient

Comparison	Antiemetic	Per Course		Per Patient	
		CR, n (%)	NR, n (%)	CR, n (%)	NR, n (%)
Ondansetron	Ondansetron	137 (60.6)	89 (39.4)	8 (19.5)	33 (80.5)
vs	Granisetron	382 (65.9)	198 (34.1)	33 (21.7)	71 (78.3)
Granisetron	P	0.163		0.141	
Ondansetron	Ondansetron	137 (60.6)	89 (39.4)	8 (19.5)	33 (80.5)
vs	Granisetron	91 (56.2)	71 (43.8)	8 (29.6)	19 (70.4)
Tropisetron	P	0.380		0.336	
Ondansetron	Ondansetron	382 (65.9)	198 (34.1)	33 (21.7)	71 (78.3)
vs	Granisetron	91 (56.2)	71 (43.8)	8 (29.6)	19 (70.4)
Tropisetron	P	0.023		0.834	

CR: Complete response, NR: Nonresponse

Table 4. Emetogenic risk of chemotherapeutic agents

High-risk;	Intermediate-risk;	Low-risk;
emesis that has been documented to occur in >30 % of patients	emesis that has been documented to occur in 10-30 % of patients	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

Grade 4 toxicity was not developed. In 49 patients (28.5%) in none of chemotherapy cycles nausea-emesis was seen. In 61 of patients (35.5%) grade 1 toxicity was developed in at least one of the course, in 56 (32.6%) grade 2 toxicity and in 6 (3.5%) grade 3 toxicity was observed (Table 1).

Full response was obtained in 610 cycles (63%). In eight courses (0.8%) grade 3 toxicity was developed (Table I). Grade 3 toxicity was obvious in the group receiving TRO and in 3 of the patients (11.1%) (Table 2).

When effectiveness of antiemetics is compared, it was determined that GRA was more effective than TRO only in course basis (Table 3). Although it is not meaningful statistically, the best antiemetic activity was obtained in GRA in course basis and in TRO in patient basis.

Discussion

Emesis is an important side effect of chemotherapy. Emesis developed within first 24 hours following the chemotherapy is defined as acute emesis whereas, emesis developed within first 5-7 days after 24 hours, is defined as delayed emesis.[10,11]

The emetogenic features of chemotherapeutic 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[12] (Table 4). According to this cisplatin is accepted in

high-risk category. Cisplatin has the dose-depended strong emetogenic effect. Nausea–vomiting is seen in almost all of the patients in case no antiemetic is given.[4] Grade 3-4 toxicity develops in 33% of patients.[5]

Approximately 30 years ago, thanks to the development of 5 HT3 receptor antagonists, prophylaxis and treatment of emesis caused by chemotherapy was significantly ensured. In cisplatin based chemotherapies antiemetic effects of OND, TRO and GRA on acute and delayed emesis, were proved.[10,13,14] Full response rate obtained with these three agents were reported to change between rates of 52%-85%.[3,10,11,13,15-18]

Comparative studies carried out are few in number and most of these are dual comparisons. In Martoni's study which is one of these dual comparisons, to patients receiving cisplatin from minimum 50 mg/m^2, prior to chemotherapy 3 mg GRA was given to one of the groups through intravenous (IV) infusion, to another group 24 mg (in the form of 3 x 8 mg) OND was given through IV infusion.[19] Although there is not any difference statistically in this study of Martoni et al, it was reported that a better result was obtained with OND. Gebbia et al, in his study where he used the antiemetics in a dose similar to that of Martoni et al, obtained with OND a higher rate of success than with GRA in a patient group he gave cisplatin from minimum 70 mg/m^2.[11] Including of dexamethasone in the treatment increases the anti emetic effectiveness.[16,10,17]

There are two significant studies as similar to this study however, organized prospectively and where triple comparison was made.[16,20] In these two studies, effects of OND, TRO and GRA on acute emesis developed as connected to cisplatin were investigated. TRO and GRA in both studies were given respectively in doses of 5 mg and 3 mg through IV infusion as it was in this study. However, while Chua et al in their study, they conducted, applied the OND before chemotherapy in 8 mg through IV infusion and following the chemotherapy at 4 th and 8 th hours in 8 mg as orally,[20] Mantovani et al gave 24mg OND through IV infusion prior to chemotherapy.[17] Moreover, Mantovani et al didn't use any steroids. Results of both studies are similar to each other. However, Chua et al reports that GRA is more effective than TRO whereas Mantovani et al reports that OND is more effective than TRO. In this study, GRA was superior to TRO as similar to Chua et al.

The most often seen side effect with antiemetics is headache. It was shown in the studies that there is not any difference between antiemetics regarding the side effects developed.[11,19,20] However, headache reported with OND and TRO has a higher rate than that reported with GRA.

At present, aprepitant in addition to 5 HT3 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 5 HT3 receptor antagonist plus dexamethasone prior to cisplatin chemotherapy improved the control of acute emesis compared to 5 HT3 receptor antagonist plus dexamethasone. Subsequent studies showed that the combination of aprepitant and dexamethasone was similar to 5 HT3 receptor antagonist plus dexamethasone in controlling acute emesis but was worse in controlling acute emesis compared with triple therapy (aprepitant + 5 HT3 receptor antagonist + dexamethasone).[21,22] NCI does not advice aprepitant for intermediate or low-risk group. 5 HT3 receptor antagonist plus dexamethasone combination is recommended for moderately emetogenic chemotherapy.

Patient groups used in most of the studies carried out regarding 5 HT3 antagonists, are not homogeneous in respect of patients and treatment doses applied. Therefore, the success obtained can't become a fixed ratio and exhibits differences among studies. Such a state leads to an uncertainty of results regarding the effectiveness of antiemetics. Although it is a retrospective work, this study is a homogeneous study in respect of the treatment applied and the patient group. However, a better protocol has to be developed as related to effectiveness. For this, there is a need for prospective works performed with homogeneous patient groups. The results have to be presented as per the chemotherapy protocols applied.

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