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Course, Patterns, and Risk-factors for Chemotherapy-induced Emesis in Cisplatin-pretreated Patients: a Study with Ondansetron*

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Vomiting and nausea are the most distressing side-effects of cancer chemotherapy. With standard antiemetic regimens (e.g. metoclopramide based combinations) sufficient antiemetic control is achieved in 50–70% of cisplatin treated patients. Ondansetron, a selective 5-HT$_3$-receptor antagonist has shown efficacy in cisplatin-induced emesis. In the present study, we evaluated the safety and efficacy of ondansetron in cisplatin pretreated patients who had suffered from severe emesis in spite of antiemetic prophylaxis. Complete antiemetic control was reached in 43.5% on the day of treatment and in 27.2% of the patients regarding a worst day analysis. 25% of the patients suffered from severe cisplatin-induced emesis (> 5 emetic episodes per 24 h). We try to characterise risk-factors for cisplatin-induced emesis by performing a multivariate analysis. Sex, cisplatin dose, and combination therapy with cisplatin plus anthracyclines seem to be independent risk-factors for vomiting on day 1 and on worst day. Delayed emesis occurred less often when sufficient antiemetic protection from acute vomiting had been obtained. Female sex, cisplatin dose and recurrent disease seem to influence the probability for occurrence of delayed vomiting.
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INTRODUCTION

NAUSEA AND vomiting are distressing side-effects of tumour drug therapy [1] and are held responsible for discontinuation of therapy in 3–19% of cancer patients [2, 3]. Cisplatin leads to nausea and vomiting in almost all patients [4, 5]. Without any antiemetic medication, cisplatin-induced vomiting will commence after 1–4 h [6–8]. If antiemetic drugs are given, vomiting will on average start after 4, 5h (metoclopramide), and only after 6–24 h using 5-HT$_3$-antagonists [9–12]. Besides acute vomiting, cisplatin will also cause delayed emesis, which has been observed even if acute vomiting was completely suppressed [13]. However, sufficient therapy of acute vomiting seems to affect delayed emesis in a positive way [14]. Assumed risk factors for increased chemotherapy-induced vomiting under cisplatin therapy are female sex [10, 15, 16], patient age [17], a history of prior chemotherapy [16, 18], and a combination of cisplatin with anthracyclines [14].

Serotonin-receptors, and among them especially 5-HT$_3$-receptors seem to play a central role in chemotherapy-induced emesis [19]. The latter have been shown to be present in the chemotherapy trigger zone (CTZ), and on peripheral afferent vagal neurons. Blocking of 5-HT$_3$-receptors or of serotonin synthesis will prevent cisplatin induced emesis in animal models

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[20–23], and both are as efficient as an ablation of the area postrema, or a peripheral vagotomy [24, 15].

Under high-dose metoclopramide, a complete protection (CR) from acute cisplatin induced vomiting has been reported in about 50% of patients while in about 20% of patients a vomiting frequency of > 5 has been observed [4, 9, 10, 16, 17, 26–29]. Delayed emesis has on average been reported in 55% of patients [4, 9, 10, 14, 21]. In several clinical trials the 5-HT_3-receptor antagonist ondansetron was used for antiemesis in chemotherapy naive patients receiving cisplatin. A CR has been reported in about 50% of patients, while in 10% of patients more than five episodes of vomiting were observed [6, 9, 10, 31–34]. Delayed emesis was reported in 40–85% of patients [6, 9, 10]. In two controlled, randomised trials, ondansetron was superior to metaclopramide in the prophylaxis of acute cisplatin induced vomiting but showed no advantage concerning delayed emesis [9, 10].

In the present study, efficacy and safety of ondansetron was investigated in patients who had suffered from therapy-refractory vomiting during prior cisplatin chemotherapy courses. In addition, risk-factors for the incidence of vomiting under cisplatin are characterised.

PATIENTS AND METHODS

Patients

The present open prospective multi-centre study was performed at 15 institutions in Germany (see acknowledgements). Inclusion criteria were age of consent, experience with cisplatin-containing chemotherapy regimens, and severe emesis (≥ five episodes of vomiting/24 h) in spite of antiemetic treatment. No restrictions were made with respect to tumour localisation. 143 chemotherapy cycles in 92 patients were studied. Age, sex, diagnosis and disease status are shown in Table 1. On average, patients had been pretreated with 153.7 mg/m² cisplatin. Metoclopramide in different dose and schedules had been used for antiemesis in 69% of the patients.

Table 1. Patients' characteristics

Patients	n = 92	
Age	mean:	55.6 years (20–75 years)
Sex	Female:	76 (82.6)
	Male:	16 (17.4)
Diagnosis	Ovarian carcinoma	70 (76.1)
	Lung carcinoma	7 (7.6)
	Endometrial carcinoma	3
	Testicular carcinoma	2
	Soft tissue sarcoma	2
	Miscellaneous	8
Status	1st-line chemotherapy	50 (54.3)
	2nd-line chemotherapy	30 (32.6)
	Recurrence	12 (13.0)
Dose of cisplatin	mean	75.5 mg/m²
	≤ 75 mg/m²	33 patients
	> 75 mg/m²	59 patients
Chemotherapy regimens	Cisplatin mono*	29 (31.5)
	Cisplatin + alkylating agents	42 (45.7)
	Cisplatin + anthracycline	21 (22.8)
Previous chemotherapy	1–2 courses	54 (58.7)
	3 courses	19 (20.7)
	> 3 courses	19 (20.7)
	Mean	2.8 courses
Previous cisplatin (cumulative dose)	≤ 160 mg/m²	63 (68.5)
	> 160 mg/m²	29 (31.5)
	Mean	153.7 mg/m²
Previous antiemetics	MCP > 1 mg/kg†	47 (51.1)
	Others	45 (48.9)

* or in combination with non/very low emetogenic cytostatics as 5-FU, etoposide, vincristine.
† Alone or in combination with other antiemetics.
(%)

Chemotherapy

Single-day cisplatin mono or cisplatin-containing combination-chemotherapies with cisplatin dose ≥ 50 mg/m² were used. The mean cisplatin dose was 75.5 mg/m² per course and infusion time was 1–3 h. 29 patients (31.5%) received cisplatin alone or in combination with non- or low-emetogenic cytostatic drugs (e.g. 5-FU 2 patients, vincristine 1 patient, etoposide 13 patients). 42 patients (45.7%) received a combination of cisplatin and cyclophosphamide, and 21 patients (22.8%) were given a combination of cisplatin and an anthracycline (e.g. cisplatin + doxorubicin or epirubicin + cyclophosphamide 15 patients, cisplatin + doxorubicin + 5-FU 1 patient, cisplatin + doxorubicin or epirubicin 5 patients).

Study medication

Antiemetic study medication contained 8 mg of ondansetron in 100 ccl NaCl 0.9%, given intravenously as a short infusion 30 min prior to chemotherapy, followed by continuous infusion of 1 mg/h for 8–24 h. On days 2–6, 3 × 8 mg ondansetron were given orally. If more than five vomiting episodes within 24 h were observed, rescue-medication was administered as judged suitable by the physician.

Response evaluation

Informed consent was achieved from all patients. A history was taken and a physical examination was performed before each therapy cycle. Laboratory parameters for the evaluation of renal, liver, and bone marrow function were obtained before and after therapy. On the day of chemotherapy, patients were observed, and every bout of vomiting or retching as well as adverse events were taken down by a study nurse or a physician. During days 2–5, nausea, vomiting, and side-effects were entered into a patient-diary. Efficacy of antiemetic therapy was classified according to the following criteria: complete response (CR) = no vomiting or retching; major response (MR) = 1–2 × vomiting in 24 h; minor response (mR) = 3–5 × vomiting in 24 h; failure (F) = > 5 emetic episodes in 24 h. If multiple vomiting or retching occurred during 5 min, this was judged as one emetic episode (EE).

Evaluation criteria for statistical analysis

Main target criteria were response on the day 1, and on the worst day, i.e. the day during which most EEs were counted. We focused on cases with CR. In the CR group only, therapy may be judged as completely successful, and thus the percentage of CR is the paramount parameter for evaluation of antiemetic therapy [35]. In addition the incidence of delayed emesis was studied. The cut-off time-period to distinguish between acute and delayed emesis was 48 h after start of cisplatin administration. For the analysis of emetic patterns, the time-lapse between chemotherapy and the first vomiting was considered.

The duration of emesis was measured by the number of days between start of therapy and last day with vomiting or nausea. For analysis of risk-factors for cisplatin induced emesis, the following parameters were considered: sex, age (≤ 50 vs. > 50 years), chemotherapy combinations (cisplatin-mono or in combination with low emetogenic cytostatics versus cisplatin + cyclophosphamide versus cisplatin in combination therapy containing anthracyclines), status of disease (primary chemotherapy versus 2nd-line therapy versus chemotherapy for recurrence), cumulative cisplatin dose in previous chemotherapy (≤ 160 mg/m² vs. > 160 mg/m²), number of previous chemotherapy courses (1–3 cycles vs. > 3 cycles) and previous antiemetic therapies (metoclopramide > 1 mg/kg vs. other antiemetic regimens). In 29 patients 51 subsequent courses were given maintaining identical study conditions. However, these courses were not considered for statistical analysis of ondansetron efficacy.

All chemotherapy cycles were considered for analysis of treatment safety. Adverse events were graded according to WHO criteria.

Statistical analysis

All data were compiled on case report forms, then coded, and analysed using the SAS and BMDP statistical software. *P* values for the comparison of frequencies between two groups are based on Fisher's exact probability test. *P* values for the comparison of frequencies between different groups of status of disease (i.e. 1st line, 2nd line, recurrence chemotherapy) are based on the χ^2 test. Computation of the *P* values were performed with PROC FREQ of SAS. *P* values for the comparison of the distribution of the variables onset and duration of emesis are based on the Wilcoxon rank sum test, using the normal approximation (PROC NPAR1WAY of SAS). All *P* values refer to two-sided tests. PROC CORR of SAS was used to compute Spearman's correlation coefficient. The program BMDPLR of BMDP was used for the logistic regression and variable selection. The backward elimination was based on a remove limit of 0.1.

RESULTS

Antiemetic response

A complete response (CR) on day 1 was observed in 40 patients (43.5%). CR was reduced to 25 patients (27.2%) if worst-day analysis was performed. The percentage of patients with more than 5 emetic episodes on day 1 rose from 12% to 25% on worst day (see Table 2). In half of the patients who experienced vomiting during the chemotherapy cycle, day 1 was the worst day. The number of CR patients continuously decreases up to day 3. No patient started to vomit or changed for the worse in such a way, that he/she had to be judged a "failure", later than day 3. If only patients who experienced vomiting were considered, a mean of 3.8 emetic episodes on day 1, and of further 10.2 emetic episodes on days 2–6 were found. The median time to start of vomiting was 9 h, and on average vomiting lasted for 4 days. After 48 h 46 patients (50%), and after 120 h 24 patients (26%) still complained about vomiting or marked nausea.

Patterns of emesis

Onset of emesis was influenced by the drug combined with cisplatin, and it was markedly accelerated if cisplatin was combined with anthracyclines. Statistical significance was only reached on a 10% level ($P = 0.087$), however. Early onset of emesis (< 6 h after cisplatin) leads to failure on the worst day more frequently ($P = 0.005$). Patients receiving cisplatin plus cyclophosphamide complained the longest about vomiting and nausea. However, no statistical significance was reached.

Table 2. Antiemetic response, onset and duration of emesis/nausea

		Day 1 patients (%)	Worst Day patients (%)	
Complete response		40 (43.5)	25 (27.2)	
Major response		18 (19.6)	25 (27.2)	
Minor response		23 (25.0)	19 (20.7)	
Failure		11 (12.0)	23 (25.0)	
		All patients	Patients with emesis	
Number of vomits: Median (day 1)		1	3	
	Mean	2.2	3.8	
Number of vomits: Median (sum of day 2–6)		1	6	
	Mean	6.0	10.2	
Worst day*	Day 1	59 (64.1%)	34 (50.7%)	
	Day 2	23 (25.0%)	23 (34.3%)	
	Day 3	10 (11.9%)	10 (14.9%)	
Mean duration of emesis/nausea (days)†		All patients	Patients with emesis	*P* value ‡
Cisplatin ≤ 75 mg/m²		1.3/1.8	2.3/3.3	
Cisplatin > 75 mg/m²		3.8/4.5	4.6/5.3	0.005 §
Cisplatin mono‖		2.6/2.9	4.1/4.6	
Cisplatin + alkylans		3.5/4.1	4.6/5.4	0.711 ¶
Cisplatin + anthracycline		2.2/3.2	2.7/3.9	0.105 ¶
Onset of vomiting**		*n*	Median	*P* value
Total		67	9 h	
Cisplatin mono‖		18	10 h	
Cisplatin + alkylans		32	11 h	0.832 ¶
Cisplatin + anthracycline		17	7 h	0.087 ¶

* First day with worst response.
† Last day analysis.
‡ Comparison of duration of emesis for patients who vomited.
§ Significant at level $P < 0.05$.
‖ Or in combination with non/very low emetogenic cytostatics.
¶ Compared with cisplatin mono therapy.
** Only patients who vomited ($n = 67$); time to start of cisplatin infusion.

The more acute observed vomiting was on day 1/worst day, the more frequently patients suffered from delayed emesis (Table 3).

Correlation between response variables

Only a low correlation was found between response on day 1 and duration of emesis ($r = 0.171$). Comparing the response on day 1 and on worst day, a correlation of $r = 0.67$ was found, however, first day and worst day coincided for only half of these patients. Comparing the response rates on day 1 and on worst day with the total number of vomits, and the duration of emesis, a markedly higher correlation was found for the worst day results (Table 4).

Univariate analysis of risk-factors for cisplatin induced emesis

The frequency of events in the outcome variables (response on day 1 and on worst day, delayed emesis later than day

Table 3. Emesis > 48 h after cisplatin therapy (delayed emesis)

		Delayed emesis patients (%)	*P*-value
Response (day 1)	CR	11 (27.5)	
	MR	6 (33.3)	
	mR	16 (69.6)	
	Failure	8 (72.7)	0.002 *
	Total	41 (44.6)	
Response (worst day)	CR	—	
	MR	9 (36.0)	
	mR	13 (68.4)	
	Failure	19 (82.6)	0.003 *‡
Sex	Female	38 (50.0)	
	Male	3 (18.8)	0.027 *
Age	≤ 50 years	9 (36.0)	
	> 50 years	32 (47.8)	0.353
Status	1st-line CT	17 (34.0)	
	2nd-line CT	19 (63.3)	
	Recurrence	5 (41.7)	0.037 *
Dose of cisplatin	≤ 75 mg/m²	7 (21.2)	
	> 75 mg/m²	34 (57.6)	0.001 *
Regimen	Cisplatin mono †	13 (44.8)	
	DDP + alkylating agent	21 (50.0)	0.810 §
	DDP + anthracycline	7 (33.3)	0.560 §
Previous courses	≤ 3	32 (43.8)	
	>3	9 (47.4)	0.783
Previous cisplatin	≤ 160 mg/m²	29 (46.0)	
	> 160 mg/m²	12 (41.4)	0.677
Previous antiemetics	Metoclopramide > 1 mg/kg	24 (51.1)	
	Others	17 (37.8)	0.216

* Significant at level $P < 0.05$.
† Or in combination with non/very low emetogenic cytostatics as 5-FU, bleomycin, methotrexate, vincristine.
‡ Only patients who vomited.
§ Compared with cisplatin mono therapy.

2) were compared between subgroups defined by risk-factors (Tables 3 and 5). Considering the factors age and extent of chemotherapeutic/antiemetic pretreatment no striking differences were found. Female patients suffered more from emesis compared with men at all points in time ($P < 0.05$). A CR on day 1 was found more rarely in patients treated for recurrent disease ($P < 0.05$). Worst day analysis showed a similar trend,

Table 4. Spearman correlation coefficient between response variables for patients with emesis

Response variables	No. of vomits day 1	No. of vomits worst day	No. of vomits (days 1–6)	Duration of emesis
No. of vomits day 1	—	0.668	0.622	0.171
No. of vomits worst day	0.668	—	0.953	0.568
No. of vomits (days 1–6)	0.622	0.953	—	0.724
Duration of emesis (d)	0.171	0.568	0.724	—

($n = 67$).

but no statistical significance was reached. Analysing failure rates, no significant differences were found in relation to disease status. A higher percentage of patients receiving a 2nd-line therapy suffered from delayed emesis, as compared with patients receiving primary treatment ($P < 0.05$).

The cisplatin dose was the strongest therapy-related risk-factor. Patients receiving > 75 mg/m² cisplatin exhibited less frequently a CR. The actual cisplatin dose was a good predictor of delayed emesis ($P < 0.001$). On day 1 and worst day, a smaller portion of patients receiving cisplatin plus anthracycline was found to be CR, while more patients were in the F groups, as compared with the other chemotherapy regimens. Univariate analysis of the differences between drug combinations with respect to delayed emesis showed no significance.

Multivariate analysis of risk-factors for cisplatin induced emesis

Considering response on day 1 and on worst day, differences between different therapy regimens cannot be explained by different cisplatin dosage. Patients receiving a combination therapy with cisplatin plus anthracyclines were given the lowest mean cisplatin dose but showed the worst response, nevertheless. A stratified analysis (Table 6) demonstrates that the difference between cisplatin dose groups appears uniformly within the therapy regimen groups and vice versa. The only exception concerned the failure rates under cisplatin plus anthracyclines, however, in this subgroup only few patients received high dose cisplatin. This uniformity of the effects of cisplatin dose and chemotherapy regimen with respect to CR rates allows for the analysis of both effects simultaneously in a logistic regression model. *P* values of 0.008 for day 1 and 0.033 for the worst day were obtained for the differences between the therapy regimens. For the different cisplatin doses *P* values of 0.003 and 0.001 were calculated—for day 1 and worst day, respectively.

The worse response in patients treated for recurrent disease may possibly be explained by the increased frequency of cisplatin plus anthracycline combination therapy (5/12 patients), and by regimens containing high cisplatin doses (10/12 patients) in this subgroup, whereas the high response rate in male patients cannot be explained by the distribution of other risk-factors.

These considerations are supported by the results of an automatic variable selection. Based on a model with all eight previously defined risk-factors, the variables cisplatin dose, therapy combination, and sex are selected, both for evaluation of CR on day 1 and on the worst day. Comparing cisplatin plus anthracyclines and cisplatin monotherapy in the final model estimation of the relative risk for the occurrence of vomiting are 6.4 and 4.1 (day 1 and worst day, respectively). The concerning 95% confidence intervals are 1.97–17.21 and 1.37–12.2. In a similar fashion, the relative risk for cisplatin dose > 75 mg/m² vs. ≤ 75 mg/m² is 2.8 on day 1 and 2.7 on worst day, with 95% confidence intervals being 1.35–5.25 and 1.47–5.12. Finally the relative risk of females vs. males is 2.3 and 2.6 (95% confidence intervals 0.94–3.82 and 1.26–5.56).

Multivariate analysis considering delayed emesis as target parameter was difficult. If data were stratified according to status of disease and cisplatin dose, no hint for an interaction could be found, but stratification according to cisplatin dose and therapy regimens or disease status and therapy regimens showed such hints. The difference between the two groups with different cisplatin doses among the patients with cisplatin plus cyclophosphamide therapy was markedly bigger than for the remaining combination therapies. Patients receiving primary treatment developed delayed emesis almost exclusively if they were admin-

Table 5. Analysis of day of chemotherapeutic treatment and worst day

		Day of treatment				Worst day			
		CR (%)	*P* value	Failure (%)	*P* value	CR (%)	*P* value	Failure (%)	*P* value
Sex	Female	29 (38.2)		11 (14.5)		15 (19.7)		23 (30.3)	
	Male	11 (68.8)	0.030*	0	0.201	10 (62.5)	0.001 *	0	0.009 *
Age	≤ 50 years	10 (40.0)		3 (12.0)		8 (32.0)		7 (28.0)	
	> 50 years	30 (44.8)	0.814	8 (11.9)	1.000	17 (25.4)	0.601	16 (23.9)	0.788
Status	1st-line chemotherapy	25 (50.0)		5 (10.0)		17 (34.0)		10 (20.0)	
	2nd-line chemotherapy	14 (46.7)		4 (13.3)		7 (23.3)		9 (30.0)	
	Recurrence chemotherapy	1 (8.3)	0.030 *	2 (16.7)	0.783	1 (8.3)	0.169	4 (33.3)	0.470
Dose cisplatin	≤ 75 mg/m²	19 (57.6)		5 (15.1)		15 (45.4)		5 (15.1)	
	> 75 mg/m²	21 (35.6)	0.050 *	6 (10.1)	0.515	10 (16.9)	0.006 *	18 (30.5)	0.134
Regimen:	Cisplatin mono †	16 (55.2)		1 (3.5)		11 (37.9)		5 (17.3)	
	Cisplatin + alkylating agent:	19 (45.2)	0.474 ‡	4 (9.5)	0.642 ‡	10 (23.8)	0.290 ‡	12 (28.6)	0.397 ‡
	Cisplatin + anthracycline	5 (23.8)	0.042 ‡*	6 (28.6)	0.033 ‡*	4 (19.1)	0.215 ‡	6 (28.6)	0.491 ‡
Previous courses	1–3:	33 (45.2)		10 (13.7)		20 (27.4)		18 (24.6)	
	> 3	7 (36.8)	0.608	1 (5.3)	0.449	5 (26.3)	1.000	5 (26.3)	1.000
Previous cisplatin dose	≤ 160 mg/m²	29 (46.0)		9 (14.3)		16 (25.4)		17 (27.0)	
	> 160 mg/m²	11 (37.9)	0.505	2 (6.9)	0.492	9 (31.0)	0.618	6 (20.7)	0.610
Previous antiemetics	Metoclopromide > 1 mg/kg	21 (44.7)		3 (6.4)		14 (29.8)		11 (23.4)	
	Others:	19 (42.4)	0.836	8 (17.8)	0.116	11 (24.4)	0.642	12 (26.7)	0.811

* Significant at $P < 0.05$.
† Or in combination with non-emetic cytostatics as 5-FU, etoposide, vincristine.
‡ Compared with cisplatin mono therapy.
n = 92 patients.

Table 6. Antiemetic response in different chemotherapy regimens stratified for cisplatin dose

Dose of cisplatin (mg/m²)	Patients	Day of treatment CR	Day of treatment Failure	Worst day CR	Worst day Failure
Cisplatin monotherapy					
≤ 75	8	7 (87.5)*	0 (0.0)	5 (62.5)	0 (0.0)
> 75	21	9 (42.9)	1 (4.8)	6 (28.6)	5 (23.8)
Cisplatin + cyclophosphamide					
≤ 75	9	7 (77.8)	0 (0.0)	6 (66.7)	0 (0.0)
> 75	33	12 (36.4)	4 (12.1)	4 (12.1)	12 (36.4)
Cisplatin + anthracycline					
≤ 75	16	5 (31.3)	5 (31.3)	4 (25.0)	5 (31.3)
> 75	5	0 (0.0)	1 (20.0)	0 (0.0)	1 (20.0)

*(%).

istered cisplatin plus cyclophosphamide. Statistical confirmation of this interaction was impossible due to the small numbers in the concerning subgroups. It may be concluded from our data that a complex interaction of risk-factors affects the incidence of delayed emesis.

Analysis of the above mentioned factors was also performed for female patients only, in order to assess a possible effect of a different spectrum of diagnosis among the two sexes. No differences were found as compared with analysis of all patients.

Adverse events

The most frequently observed side effects under the study medication were headaches (16.1%), abdominal pain or epigastric discomfort (9.8%), constipation (8.4%), and an asymptomatic elevation of liver enzymes (7.6%). Rarely sleeplessness, tiredness, a dry mouth and diarrhoea were encountered (Table 7). Therapy had to be discontinued in one patient with a history of cardiac arrhythmia because of recurrent bradyarrhythmia. Constipation was severe in some patients and in 1 patient, a combined small- and large-bowel ileus which required surgical intervention was observed. In this patient a marked intra-abdominal tumour spread with bowel conglomerate tumours was present. The involved physicians judged the constipating effect of ondansetron to be only contributing to the ileus while bowel function was already largely impaired. Elevation of liver enzymes was without symptoms and subsided within 4 weeks, and no clinical consequence was necessary in any of the patients.

DISCUSSION

Animal experiments and clinical studies of patients without previous chemotherapy experience have shown ondansetron to be effective against cisplatin induced emesis [31–34], and to be superior to metoclopramide in the prophylaxis of acute emesis [9, 10]. Thus far only limited data exist concerning the sequential use of ondansetron in cisplatin pretreated patients who had suffered from therapy-refractory cisplatin induced vomiting under standard antiemetic medication. Our study shows that in the latter patients, antiemetic protection can be ensured by ondansetron in 55% of patients (CR + MR on worst day).

Table 7. Adverse events during ondansetron therapy (143 courses) without haematological toxicity due to chemotherapy

		WHO Grade			
	Courses (%)	I	II	III	IV
Headache	23 (16.1)	9	10	4	
Abdominal pain	14 (9.8)	2	11	1	
Constipation	12 (8.4)	2	5	4	1
Elevation of liver enzymes	10 (7.6)*	6	3	1	
Tiredness	4 (2.8)				
Sleeping disorders	4 (2.8)				
Diarrhoea	3 (2.1)				
Dry mouth	3 (2.1)				
Heat flush	3 (2.1)				
Arrhythmia	2 (1.4)				
Paresthesia	2 (1.4)				
Vertigo	2 (1.4)				
Ear pain	2 (1.4)				
Roughness of voice	1				
Hypersalivation	1				
Cough	1				
Tremendous hunger	1				

* Biochemistry controls within a week after therapy only in 131 courses available.

Nevertheless, 25% of patients still suffer from severe emesis in spite of ondansetron (> 5 vomits on worst day), and half of the patients complain about nausea or vomiting 48 h after chemotherapy. Our data emphasise the importance of performing a worst day analysis even in single-day therapy protocols. The worst response was found later than on day 1 in half of the patients. In 1/3 of patients, day 2 is the worst day, and in 1/6 of patients the worst day is even later. As a consequence the rate of CR or failure is markedly different depending on whether day 1 or worst day analysis are being performed. In addition, looking at failure rates in relation to cisplatin dose, the rates are much higher on the worst day compared with day 1. For high cisplatin doses the failure rate on worst day is three times higher than on day 1, whereas for low cisplatin doses no such difference is found. In addition, correlation analysis of the different response variables showed a low correlation between response on day 1, and the total number of emetic episodes or duration of emesis. Response on worst day correlates more strongly with the remaining response variables (number of emetic episodes and duration of emesis), and thus reflects the clinical situation more clearly. Assessment of antiemetic response on day 1 favours antiemetic therapies which delay onset of vomiting without considering absolute antiemetic effectiveness.

Delayed emesis and nausea are a typical side-effect of cisplatin, but they have also been observed in conjunction with other cytostatic drugs [21]. Delayed emesis needs to be distinguished from a late onset of acute emesis. In the literature, delayed emesis has mostly been defined as onset of vomiting later than 24 h after cisplatin. The potential of ondansetron to delay the peak of emesis leads to a shift of several patients with late onset acute emesis into the former category of delayed emesis if the abovementioned criteria are applied. We have tried to more precisely separate both forms of emesis and have set the cut-off times between acute and delayed emesis at 48 h after chemotherapy. At that time 85% of patients have already experienced the peak of emesis (worst day). In the present study delayed emesis was found much less often if good control of acute emesis had been achieved. It is remarkable that none of the patients started to vomit later than day 3.

Analysis of risk-factors for nausea and emesis after cisplatin therapy showed a higher risk for female patients for both acute and delayed emesis. This is a phenomenon known in the literature [10, 15, 16], however, so far no explanation has been found. In our study, patient age does not play a role as a risk-factor for acute or delayed emesis.

The extent of prior therapy (as measured by number of cycles and by cumulative cisplatin dose) did not show any effect on antiemetic response in our collective. Thus neither the cumulative toxicity of cisplatin nor the extent of chemotherapy experience seems to be responsible for an increased rate of emesis and nausea in pretreated patients—as has been reported in the literature [16, 18]. Disease status (first-line vs. second-line therapy or treatment for recurrent disease) shows an effect on emesis in the univariate analysis. Psychological effects may be responsible for this phenomenon. Expectation of patients—cure in the case of primary therapy but "only" palliation in the case of second-line therapy or treatment of recurrent disease—seems to enhance the readiness to react by vomiting to emetogenic stimuli of chemotherapy. However, on multivariate analysis, the influence of disease status can not be shown clearly. The actual cisplatin dose is the strongest therapy-related risk-factor for emesis and nausea in our study. The relative risk not to reach a CR under cisplatin-containing chemotherapy is about 2.75 if cisplatin doses of > 75 mg/m^2 were given as compared with lower doses. In contrast the percentage of failure cases seems to be less cisplatin dosage dependent. It is possible that patients experiencing > 5 vomits belong to a subgroup of individuals who are ondansetron-refractory and thus respond even to low doses of cisplatin for lack of protection mechanisms. This is supported by the observation that a majoritiy of these patients also experience severe vomiting in subsequent cycles.

The different combination partners of cisplatin affect onset and duration of chemotherapy-induced emesis, and, in the case of a combination of cisplatin with an anthracycline, seemingly represent an independent risk-factor for the absolute extent of emesis. Anthracycline-containing combinations lead to an earlier onset of emesis, while cyclophosphamide-containing combinations lead to a somewhat prolonged emesis. The relative risk for developing emesis under study medication is about 5 times higher in the group of patients receiving cisplatin plus anthracyclines as compared with cisplatin mono therapy. The combination of cisplatin and cyclophosphamide did not lead to increased acute emesis in our collective. Future studies should clarify this problem.

Our results differ partly from data which were gathered from a comparable analysis in a study using metoclopramide-containing antiemetic regimens [16]. The assessed variables were diagnosis, age, sex, general physical condition, previous therapy, and a history of vomiting-experience. Only patient age showed an effect on emesis both on univariate and multivariate analysis. The different results may be explained by the larger number of patients in the present study, but may also be explained by different mechanisms of 5-HT$_3$ antagonist effects as opposed to those of metoclopramide, diphenhydramine, droperidol, and lorazepam in patients belonging to different subgroups (e.g. age or sex).

The overall side-effect spectrum of ondansetron in our study does not differ from the data reported in the literature [6, 9, 31, 34]. The main difference in the side-effect profiles of

ondansetron and metoclopromide is the lack of extrapyramidal reactions after ondansetron, which has been reported in 1.6–14% of patients who received high-dose metoclopramide [4, 16, 17, 27, 29, 30]. The adverse events observed under study medication were usually mild and rarely required medical treatment or discontinuance of therapy. Ondansetron-induced constipation may be troublesome, as reported elsewhere [10]. In one patient, an ileus was observed under therapy, and surgical intervention was necessary. On laparotomy large- and small-bowel conglomerate tumours were found which could explain for the ileus. The constipating effect of ondansetron constitutes an increased risk for a disturbance of bowel motility especially in patients with intra-abdominal tumour burden or in a situation post-laparotomy or post-abdominal irradiation. This risk should in our opinion be countered by a synchronous prophylactic administration of laxatives.

It may be concluded from our data, that ondansetron is remarkably effective in 50% of patients who have suffered from therapy-refractory emesis under standard antiemesis. However, further efforts are necessary to render cisplatin therapy tolerable for all patients. Risk-factor analysis may help to define high-risk collectives, in which new combinations of 5-HT_3 antagonists with other antiemetic drugs (e.g. dexamethasone) may lead to improved results. It seems to be important for the planning of future studies to emphasise stratification of data according to the established risk-factors. Multivariate analysis should also be applied in order to assess the independence of each single factor. Besides clinical trials, further efforts are necessary for the clarification of the different pathophysiological mechanisms in effect in the different forms of emesis. The role of serotonin as a possible mediator will be a main focus of interest.

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Parotid Gland Function During and Following Radiotherapy of Malignancies in the Head and Neck

A Consecutive Study of Salivary Flow and Patient Discomfort

Lars Franzén, Ulrika Funegård, Thorild Ericson and Roger Henriksson

Radiotherapy of tumours in the head and neck region usually involves the salivary glands in the treatment volume with ensuing dryness and discomfort. In the present study, a prospective evaluation of the same patients were performed before, during radiotherapy and 6, 12 and 18 months after the end of treatment. Three different groups were outlined, one receiving doses not exceeding 45 Gy, another 47–52 Gy and a third group treated with doses over 64 Gy. All but one of the patients receiving doses less than 52 Gy showed a recovery of secretion beginning after 2 months with a continuous improvement of the salivary flow up to 18 months. Doses exceeding 64 Gy caused irreversibly depressed parotid function in the vast majority of glands. The subjective experience of discomfort with dry mouth was not at all correlated to the initial flow rate. Treatment with unilateral technique and doses below 52 Gy caused just no or slight dryness and 3 out of 4 patients with bilateral involvement of the glands displayed problem with subjective dryness even after 18 months. Doses over 64 Gy with one gland involved had only slight dryness, however, patients with both glands affected showed severe problems with dryness. it has to be emphasised that there were relatively large interindividual differences with respect to salivary flow and discomfort of dryness. It is obvious that these patients need a careful dose planning and a close follow up with co-operation between radiotherapeutists and dentists.
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INTRODUCTION

RADIOTHERAPY OF tumours in the head and neck region usually involves the salivary glands in the irradiated volume. The inherent radiosensitivity, especially of parotid glands, is manifested by very early signs of hampered salivary flow [1–4]. A sharp decrease in the salivary flow rate occurs already in the first week with conventional fractionation, i.e. 2 Gy/day [5–9]. The decrease in flow rate continues throughout the treatment period and when both parotid glands are affected by radiation to full dose (66 Gy) the mouth usually becomes permanently dry [10–12]. Subsequently, this leads to chronic oral disease with subjective distress and loss of taste and a pronounced decrease in quality of life [2–4, 8, 13]. In addition to the direct influence on salivary glands the discomforts in speaking, mastication and swallowing are further aggravated by the effects of irradiation on the oral mucosa with the development of erythema, plaque formation and in severe cases ulceration and bleeding.

The present study is a prospective continuous evaluation, as far as we know one of the first, on the effects of different irradiation schedules on parotid gland function and its correlation to patients distress of dryness of the mouth when treating malignancies in the head and neck region. The results of the effects were continuously followed in the patients. Although, the total radiation dose is most important the radiosensitivity of the parotid gland function and recovery varied considerably between the individuals during and 18 months following the end of irradiation.

PATIENTS AND METHODS

Patients and irradiation

25 of the patients treated at the department of Oncology, University Hospital, Umeå, Sweden during 1985–1989 for

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