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COMPARISON OF THE EMETOGENIC POTENTIAL BETWEEN CISPLATIN AND CARBOPLATIN IN COMBINATION WITH ALKYLATING AGENTS

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Platinum-based polychemotherapy is widely used in the treatment of gynecological cancer. Emesis is one of the most disturbing side-effects of platinum therapy. We performed a study to evaluate and compare the emetogenic potential and the different emesis pattern after cisplatin and carboplatin under antiemetic treatment with ondansetron. One hundred and twenty-two patients with either cisplatin-containing (n = 70) or carboplatin-containing (n = 52) first-line chemotherapy were included. Treatment with cisplatin led more frequently to emesis and patients suffered from more severe emesis than carboplatin treated patients. Delayed emesis was observed after both platinum analogues but occurred more frequently and lasted longer after cisplatin.

During the last decade, cisplatin-containing chemotherapy regimens have become the treatment of choice for ovarian cancer. In patients with advanced ovarian cancer, a recently published metaanalysis showed equal efficacy for carboplatin-containing regimens compared to cisplatin-based chemotherapy (1). The role of platinum-based chemotherapy in the treatment of advanced cervical cancer is under investigation (2, 3). Both platinum analogues induce severe vomiting and nausea which are only partially controlled by antiemetic prophylaxis. Without antiemetic medication, emesis occurs in nearly all cisplatin-treated patients (4, 5). Under the treatment with metoclopramide, emesis occurs in 30–93% (6–9), whereas under prophylactic medication with the 5-HT_3-receptor antagonist ondansetron emesis is reported to occur in 24–86% of the patients (4, 6, 7, 10). Carboplatin-induced emesis is reported in 56–100% of patients without antiemetic prophylaxis (2, 11–13). Ondansetron reduced emesis to 44% in this group of patients (14).

There are common clinical impressions, but only limited data available concerning the comparison of the emetogenic potential of cisplatin and carboplatin. Data from animal studies, as well as a few clinical studies, showed a tendency to less emesis after carboplatin compared with cisplatin (15–18). The difference between the two platinum analogues seems to be more pronounced when looking at the severity of emesis than compared with the frequency of complete protection from chemotherapy-induced emesis.

Material and Methods

The aim of the present study was to compare the emetogenic potential and the pattern of emesis between cisplatin and carboplatin-based chemotherapy regimens. Besides that, the efficacy of ondansetron given as antiemetic prophylaxis to patients with platinum-containing chemotherapy was evaluated.

Chemotherapy-naïve patients who received single-day chemotherapy with either cisplatin ($\geqslant 75$ mg/m^2) or carboplatin ($\geqslant 300$ mg/m^2) in combination with alkylating agents (cylophosphamide or ifosfamide) were included. Informed consent was obtained from every patient. The patients were under observation for at least 24 h after

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chemotherapy administration. During this period, every episode of vomiting was documented by a nurse. Diaries were given to the patients, and they were asked to document vomiting, retching, and nausea on days 2–6. The number of vomits and the time of the first vomit were noted for each day. Emesis was defined as vomiting and/or retching and/or nausea. Every vomiting or retching within 5 min was counted as one emetic episode. Nausea was graded according to a 4-point scale (none = no nausea; mild = nausea not interfering with normal daily activity; moderate = nausea interfering with normal daily activity; severe = bedridden due to nausea). Every emetic episode or episode of nausea interfering with normal daily activity (i.e. moderate or severe nausea) were regarded as an emetic event. Antiemetic response was defined as complete response (CR) when no emetic event was observed. A major response (MR) was considered if only nausea or 1–2 emetic episodes within 24 h were observed. Antiemetic efficacy was judged as minor response (mR) if 3–5 emetic episodes within 24 h were observed. If more than 5 emetic episodes were counted, antiemetic efficacy was judged as failure (F).

Medication. In the cisplatin group the patients received 75–80 mg/m^2 cisplatin as a 1-h infusion, followed by 600–1 000 mg/m^2 cyclophosphamide i.v. Both drugs were diluted in 500 ml normal saline. Pre- and posthydration consisted of 1 000 ml of normal saline. Diuresis was supported with mannitol. Mesna 200 mg given as bolus injection for bladder protection was administered before and 4 and 8 h after start of chemotherapy. In the carboplatin group patients received 300–350 mg/m^2 carboplatin as 1-h infusion followed by either 600–750 mg/m^2 cyclophosphamide i.v. or 5 000 mg/m^2 ifosfamide as 24-h infusion. Carboplatin was diluted in 500 ml glucose 5% and cyclophosphamide and ifosfamide were diluted in normal saline. Mesna for bladder protection and pre- and posthydration were only administered in patients receiving ifosfamide. All patients received ondansetron 24 mg per day for antiemetic prophylaxis. Ondansetron 8 mg was given as a short i.v. infusion 15 min prior to chemotherapy and repeated 4 and 8 h after the platinum infusion. From day 2 to day 6 ondansetron 8 mg was given orally three times a day. If more than 5 vomits occurred within 24 h, or if demanded by the patient, rescue medication was administered as judged suitable by the physician. Ondansetron was provided by GLAXO GmbH Germany.

Patients. One hundred and twenty-two patients receiving a first-line chemotherapy for the treatment of a gynecological cancer were included into the study; 110 patients suffered from advanced ovarian cancer stages FIGO III and IV. The remaining 12 patients had cervical cancer stages FIGO I and II. A cisplatin-containing regimen (cisplatin plus cyclophosphamide) was given to 70 patients whereas 52 received a carboplatin-containing regimen (carboplatin plus cyclophosphamide or carboplatin plus ifosfamide). All patients took part in an open multicenter trial evaluating the efficacy of ondansetron. Eighty patients also took part in two randomized trials of chemotherapy for advanced ovarian cancer and advanced cervical cancer respectively. The mean age was similar in both platinum groups. The patient characteristics and drug dosages are shown in Table 1. The cyclophosphamide dosage in the cisplatin group is slightly higher than that in the carboplatin group.

Table 1

Patient characteristics

	Cisplatin	Carboplatin
No. of patients	70	52
Mean age (years)	57.9	55.7
Diagnosis		
Ovarian cancer (n) [a]	70	40
Cervical cancer (n) [b]	—	12
Mean dosage		
Cisplatin	79.4 mg/m^2	—
Carboplatin	—	335.8 mg/m^2
Cyclophosphamide	850.3 mg/m^2	678.4 mg/m^2 [a]
Ifosfamide	—	5000.0 mg/m^2 [b]

Analysis and statistics. We performed a univariate analysis to see whether diagnosis, stage of disease, or dosage and type of alkylating agent used in combination with platinum therapy had any influence on the pattern of emesis within the carboplatin group. No significant influence of either of the above mentioned factors was shown. Thereafter we compared the two platinum groups. Three qualities of emesis were analyzed: severity, frequency, and duration of emesis. Severity was measured as number of emetic episodes per day (days 1–6) and number of emetic episodes on the worst day (i.e. the day with the highest number of emetic episodes). The frequency of emesis was measured by the proportion of patients with a complete response either regarding the whole observation period (worst day analysis) or when looking at each day. Duration of emesis was measured by adding the days with emetic events. In a second analysis we looked at the time from start of chemotherapy to the last emetic event (time to end of symptoms). In addition, an analysis of the interaction between onset of vomiting and severity and duration of emesis was performed. For this analysis patients with emesis were divided into two groups: those with an early onset of vomiting (within 24 h after start of chemotherapy) and those with a late onset of vomiting (later than 24 h after chemotherapy). Duration and severity of emesis was compared between these two groups, stratified for each platinum analogue. Fisher's exact test and the Wilcoxon rank-sum test were applied for comparison between two groups. The Kaplan-Meier estimate and the log-rank test was used for evaluating the variable 'duration of emesis'. The comparison of the distribution of the worst day is based on the χ^2-test. The computations

were made with the SAS procedures FREQ, NPAR1WAY and LIFETEST.

Results

The univariate analysis of the factors diagnosis, dose and type of alkylating agent used as combination partner of platinum revealed no significant influence on the emesis pattern within the two platinum groups. Therefore we decided to compare the two platinum groups as to different patterns of emesis induced by either carboplatin or cisplatin.

Comparison of the frequency of emesis. Regarding the 'worst day' analysis, more patients suffered from emesis after cisplatin therapy than with carboplatin therapy (Table 2). There was a significant difference in favour of carboplatin concerning patients without vomiting (17% versus 40%) and patients without vomiting and nausea (13% versus 31%). This difference was also present when each day was analysed separately. Analysis of the subgroup of carboplatin-treated patients revealed no difference whether cyclophosphamide or ifosfamide was used as combination partner. In the cisplatin group nausea without vomiting occurred in 15–25% of all patients during days 3–6. The proportion of patients with nausea alone is rather small in the carboplatin group, indicating that delayed nausea is more a problem seen after cisplatin therapy.

Severity of emesis. Of the 122 patients 89 (73%) suffered from at least one episode of vomiting within the observation period. Patients with cisplatin-containing therapy had more emetic episodes compared with carboplatin-treated patients (mean 12.6 versus 5.5 emetic episodes within 6 days). Regarding the worst day, the mean number of emetic episodes was 5.5 in the cisplatin group and 3.3 in the carboplatin group. Statistical significance was reached considering vomiting on the worst day and vomiting during the whole observation period ($p < 0.05$; Table 3). These results indicate that emesis due to cislatin was more severe compared with carboplatin, even when only those patients who experienced any degree of emesis were analysed. Again no difference was found with respect to the alkylating agent combined with carboplatin.

Table 2

Antiemetic response (worst day analysis)

	Cisplatin n = 70 (%)	Carboplatin n = 52 (%)	p-value
No vomiting or nausea	12.9	30.8	0.023
No vomiting (CR)	17.1	40.4	
1–2 vomits/d (MR)	21.4	30.8	
3–5 vomits/d (mR)	27.4	21.2	
> 5 vomits/d (F)	34.3	7.7	0.0001

Table 3

Comparison between cisplatin and carboplatin in patients with vomiting

	Cisplatin n = 58	Carboplatin n = 31	p-value
Emetic episodes days 1–6	12.6	5.5	0.0025
Emetic episodes on worst day	5.5	3.3	0.0120
Days with vomiting	3.29	2.29	0.0049
Days with emesis	4.12	2.55	0.0001
Last day of emesis	5.02	2.58	0.0013

Duration of emesis. Patients treated with cisplatin suffered longer from emesis than carboplatin-treated patients (Table 3). Significant differences were seen for the number of days with vomiting, the days with vomiting and nausea, and the time from start of chemotherapy to the last symptom of emesis ($p < 0.005$ for each variable). The Kaplan-Meier curves for the patients with emesis (duration of emesis) after cisplatin differed significantly from the curve obtained from patients receiving carboplatin ($p = 0.007$). There was a parallel decrease in the proportion of patients who still suffered from emesis up to day 4 in both groups. From day 5 on, the decrease in the percentage of patients with emesis in the carboplatin group was faster compared with the cisplatin group. The differences between both curves indicate, that patients with cisplatin therapy suffered longer from emesis compared with patients with carboplatin therapy.

Distribution of the worst day. The distribution of the worst day after cisplatin therapy showed a single peak on day 2, when 60% of the patients who vomited experienced their worst day. Another 26% of these patients had their worst day on the day of treatment and only 14% had their worst day on day 3. No worst day later than day 3 was observed in the cisplatin group. The distribution of the worst day differed significantly between the cisplatin and the carboplatin groups ($p = 0.001$); 45% of the patients receiving carboplatin experienced their worst day on the day of treatment, 20% on day 2, 22% on day 3, and 13% on day 4.

Relation between onset of vomiting and severity and duration of emesis. The median time for start of platinum infusion to the occurrence of the first episode of vomiting was 17 h after cisplatin and 19 h after carboplatin-containing chemotherapy regimens. There was no significant difference between the two groups regarding the onset of vomiting. Forty-one patients in the cisplatin group and 19 patients in the carboplatin group were considered to have an early onset of vomiting (first vomit within 24 h after start of chemotherapy) whereas 17 patients in the cisplatin group and 12 in the carboplatin group were considered to have a late onset of vomiting. When comparing patients with an early and those with a late onset of vomiting, large differences were observed with respect to severity and

Table 4

Vomiting patterns after DDP and CBDCA (stratified for time of onset of vomiting)

	Cisplatin			Carboplatin		
	early onset (n = 41)	late onset (n = 17)	p-value	early onset (n = 19)	late onset (n = 12)	p-value
Vomits days 1–6	14.95	7.06	0.0010	5.74	5.17	0.9675
Vomits on worst day	6.41	3.47	0.0009	3.16	3.42	0.7716
> 5 vomits on worst day	53.7%	11.8%	0.0035	10.5%	16%	0.8510
Days with vomiting	3.71	2.29	0.0022	2.53	1.92	0.2214

duration of emesis in patients treated with cisplatin (Table 4). More than 50% of the patients with an early onset of vomiting suffered from severe emesis on their worst day. The mean number of vomits in this subgroup was 15 within the observation period. Patients with a late onset of vomiting after cisplatin therapy showed an emesis pattern similar to that of the patients treated with carboplatin. In the carboplatin group no differences concerning severity and duration of emesis could be detected between patients with an early onset of vomiting compared with patients with a late onset of vomiting (Table 4). These results clearly indicate, that patients treated with DDP, who start vomiting within the first 24 h after chemotherapy run a very high risk for severe and long-lasting emesis. Patients with a later onset of vomiting after cisplatin and patients with carboplatin therapy, regardless of the onset of vomiting, showed a similar emesis pattern. The difference in emesis patterns regarding patients with an early onset and those with a late onset of vomiting was highly significant in the cisplatin group, whereas no significance was reached in the carboplatin group.

Discussion

In our study the number of patients completely protected from emesis after cisplatin therapy is small compared with some data reported in the literature (6, 7), but similar to data of another published multicentre report studying the efficacy of continuous infusion ondansetron in patients with chemotherapy experience (10). When interpreting our data, consideration has been taken to the fact that the patients included into the present analysis per se run a high risk of drug-induced emesis (female gender, cisplatin dose $\geqslant 75$ mg/m^2). The analysis of the interaction between onset of vomiting and severity and duration of emesis revealed a high risk of severe and long-lasting emesis for cisplatin-treated patients with an early onset of vomiting. This group of patients is not sufficiently protected by ondansetron monotherapy. Since the completion of the present study, other groups have published their results, indicating a superior antiemetic efficacy for a combination regimen containing ondansetron plus dexamethasone compared with ondansetron alone (19). Further studies should be made to evaluate the effect of this antiemetic combination regimen on the different characteristics of emesis induced by platinum-containing chemotherapy.

Our results confirm the clinical impression, that cisplatin-containing chemotherapy has a significantly higher emetogenic potential compared with carboplatin-containing regimens. Cisplatin more often produces emesis, leads to more severe emesis, and causes a longer duration of vomiting and nausea compared with carboplatin. Although the antiemetic results in carboplatin-based chemotherapy are superior compared with those in cisplatin therapy, we are far from a satisfying solution of the problem. The number of patients suffering from carboplatin-induced emesis was higher than expected by the authors. With the experience of severe emesis in nearly all patients receiving cisplatin therapy in mind, the obviously less emesis induced by carboplatin led to an underestimation of the emetogenic potential of carboplatin. Our results clearly indicate the need for an improvement of antiemetic therapy not only for cisplatin-treated patients, but also for patients receiving carboplatin. Studies on combination regimens, including ondansetron plus dexamethason and metoclopramide plus dexamethason, are under way to evaluate if there is a benefit for carboplatin treated patients comparable with the improvements reported in cisplatin-therapy (19).

One possible bias between both study groups is the imbalance of the dose and type of the alkylating agents used in combination with either cisplatin or carboplatin. Univariate analysis within the carboplatin group revealed no significant influence of dose or type of the alkylating agent on the pattern of emesis. These data are consistent with the results of another analysis of the influence of anthracyclines and alkylating agents used in combination with cisplatin. This analysis did not reveal any influence on the cisplatin-induced emesis patterns by addition of cyclophosphamide to cisplatin compared to cisplatin monotherapy (10). The emetogenic potential of platinums seems to be so strong, that the additional emetogenic stimulus of an alkylating agent is hard to detect. Nevertheless, the number of patients in each subgroup in the present study is too small to perform a multivariate analy-

sis of the influence of dose and type of alkylating agent combined with either cisplatin or carboplatin.

Investigations of the pathophysiology of drug-induced emesis and analysis of risk factors for emesis should help to improve our understanding of the physiological mechanisms involved. First results of investigations of the role of serotonin metabolism in patients receiving platinum chemotherapy (4, 20, 21) showed some evidence for the hypothesis that serotonin plays an important role in the pathogenesis of cisplatin-induced emesis. Whether serotonin plays a role in carboplatin-induced emesis is still unclear. Further investigations are necessary to evaluate if different clinical features of emesis are based on different alterations of serotonin metabolism after chemotherapy.

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