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Pattern of carboplatin-induced emesis

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In contrast to the broad experience concerning the therapeutic use of carboplatin, only limited data are available regarding the patterns of carboplatin-induced emesis, one of its most distressing side effects. This study reports frequency, severity and time course of carboplatin-induced vomiting and nausea refractory to 5-HT$_3$ antagonism. A total of 216 patients receiving single-day carboplatin-based chemotherapy regimen were enrolled into an open multicenter study focusing on the safety and efficacy of ondansetron 8 mg t.d.s. Emesis on day 1 occurred in 22% and nausea in 75% of the patients; 44% of patients reported some degree of vomiting within the 5 days observation period. The risk for emesis and nausea over 2–5 days was increased in patients suffering from emesis on day 1 (relative risk 2.25 for vomiting and 2.84 for nausea, respectively). The median cumulative number of emetic episodes was 0 for all patients and 4 for the patients who did vomit at least on 1 day. Vomiting began on average 1.77 days following chemotherapy administration. The mean duration of vomiting was 2 days and 3.1 days for nausea. Carboplatin showed a monophasic prolonged pattern of emesis. The combination with cyclophosphamide led to an earlier onset and a higher frequency of vomiting. The analysis of the pattern of emesis refractory to 5-HT$_3$ receptor blockade should help to describe the course of emesis, which is probably triggered through a 5-HT$_3$ receptor-independent mechanisms.

Key words: Carboplatin, nausea, ondansetron, vomiting.

Introduction

Carboplatin is a second generation platinum analog which provides similar efficacy compared with its parent compound cisplatin in the treatment of several malignancies, especially epithelial ovarian cancer.[1] Carboplatin acts via the same mechanism as cisplatin, i.e. forming DNA adducts, DNA interstrand links and causing DNA strand breaks.[2–4] However, the pharmacokinetic profiles of cisplatin and carboplatin differ with a higher renal elimination rate and a longer plasma half-life for carboplatin.[5–8] Despite the similar mechanism of action, side effects differ markedly between these platinum analogs. Cisplatin is the drug with the highest emetogenic potential. Without antiemetic treatment, nearly all patients suffer from severe emesis following cisplatin therapy.[9,10] Comparison between emesis induced by either cisplatin or carboplatin in animal models as well as clinical studies revealed a lower emetogenic potential for carboplatin.[11–13] Nevertheless, carboplatin is a highly emetogenic drug. One study has reported emesis following carboplatin therapy without antiemetic prophylaxis.[14] Vomiting occurred in 82% of patients and started on average 6.25 ± 2.38 h after carboplatin administration. Eighty-nine percent of the patients suffered from nausea or vomiting. Emesis was severe with a mean number of 13.5 emetic episodes per patient.

Ondansetron, a selective 5-HT$_3$ receptor antagonist, has proven efficacy against acute cisplatin-induced emesis.[15,16] Its role in the management of cisplatin-induced delayed emesis is still not clearly defined.[17] Due to methodological issues there is only limited information available describing antiemetic treatment and patterns of emesis in patients receiving carboplatin-based chemotherapy regimens. The majority of carboplatin-treated patients were enrolled in antiemetic trials together with patients receiving other non-cisplatin-containing regimens. The publications of these studies do not provide enough detailed data for a subgroup analysis of patients receiving carboplatin chemotherapy. A MEDLINE search revealed only four antiemetic trials including 131 patients with carboplatin-based chemotherapy.[13,18–20] The identified studies were open trials in chemotherapy naive and non-naive patients with ondansetron used as antiemetic therapy. Acute emesis was observed in 25–38% of patients and emesis over days 2–5 occurred in 25–59% of patients, whilst over the same period

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nausea of any degree was reported in 50–70% of patients. None of the four studies provide detailed information about the frequency, severity and course of emesis and nausea.

This paper describes the patterns of vomiting and nausea over the 5 days following carboplatin-based chemotherapy which occurred despite antiemetic treatment with ondansetron over the whole observation period. The aim of the study is to identify the patterns (i.e. frequency, severity and time course) of emesis refractory to 5-HT_3 antagonism and thereby identify the area where further improvement of antiemetic therapy is warranted. Furthermore, analysis of emesis refractory to 5-HT_3 antagonism will possibly lead to a better characterization of the clinical course emesis triggered by yet not clearly defined non-5-HT_3-dependent mechanisms.

Methods

All patients were enrolled into an open multicenter study evaluating the safety and efficacy of ondansetron in the prophylaxis of chemotherapy-induced emesis. Prior chemotherapy was allowed, but anticipatory emesis, vomiting within 24 h before study entry, presentation with brain metastasis and use of other drugs with antiemetic potential led to exclusion from the study. Analysis is based on the subgroup of patients who received their first course with ondansetron and were scheduled to receive a carboplatin dose of equal to or more than 300 mg/m^2. Antiemetic prophylaxis consisted of ondansetron 8 mg i.v. given 15–30 min before chemotherapy. Further 8 mg tablets were given twice on the day of chemotherapy. Ondansetron 8 mg tablets were given three times daily on days 2–5. The patients documented any episodes of emesis in a diary over days 1–5. Nausea was graded according to a four-item scale (none – mild – moderate – severe) for each day separately. The patients were under clinical observation for at least the day of chemotherapy and emesis was recorded by study nurses independent from the patients' diary registrations. Diary cards were collected within 1–4 weeks following chemotherapy. Patients were interviewed by the investigator or a study nurse and the diary cards were checked for completion. In case of a discrepancy in the judgement of emesis or nausea between patients and investigator, the patient's report was considered for analysis.

The first analysis includes all patients independent of whether they experienced emesis or not. It describes the course and pattern of emesis for all patients at risk. A second analysis is based only on the patients who experienced at least one emetic episode within the 5 days observation period (non-responder analysis). The latter analysis describes the pattern and course of emesis in patients who are not completely protected by ondansetron. This analysis gives an estimate of the course of emesis insensitive to 5-HT_3 antagonism. Furthermore, a subgroup analysis evaluates the role of cyclophosphamide when added to carboplatin. Therefore, two homogenous groups of patients were formed which did not differ in respect to the following factors which might influence the risk for emesis: carboplatin dose, age, female gender and diagnosis of gynecological neoplasms. One group had received carboplatin as a single agent ($n=39$) and the other had received carboplatin in combination with cyclophosphamide ($n=98$).

Patterns of emesis are analyzed as follows. Frequency of emesis is reported as a percentage of patients experiencing at least one emetic episode for each day separately, for the whole observation period (days 1–5) and for days 2–5, respectively. Nausea is reported both as a percentage of patients experiencing any degree of nausea and patients suffering from more than mild nausea. Median numbers of emetic episodes for each day and cumulative numbers of emetic episodes for the whole observation period describe the severity of emesis. The duration of emesis was calculated by adding the days on which either vomiting or nausea was observed. The incidence of emesis over days 2–5 is analyzed according to the stratification for the antiemetic results on day 1. The two-tailed Fisher's exact test is used to compare different groups. Any day on which comparable degrees of emesis were observed was considered for its contribution to the worst-day pattern.

Results

Patients and chemotherapy regimens

A total of 216 patients receiving carboplatin-containing chemotherapy regimens were recruited. The mean age was 55 years and treatment was given for a variety of malignancies (Table 1). The gender ratio was 5.2 for female:male patients. The mean carboplatin dose was 332 mg/m^2 (250–460 mg/m^2) and 85% of the patients received more than 300 mg/m^2 carboplatin. Eighty-four patients (39%) received carboplatin as a single agent or in combination with cytostatics which possess a low emetogenic poten-

Table 1. Patients characteristics

n	216	100%
Female	184	85%
Male	32	15%
Age (years)	mean 55	range 17–79
Neoplasms		
ovary	149	69%
lung	24	11%
uterus	18	8%
others	25	12%

tial, such as 5-fluorouracil (5-FU), vincristine, bleomycin or low-dose methotrexate. A total of 132 patients (61%) received a carboplatin-based combination regimen containing alkylating agents (i.e. cyclophosphamide or ifosfamide).

The characteristics of the subgroup of gynecological patients who received carboplatin as a single agent or in combination with cyclophosphamide showed no difference with respect to age, diagnosis and carboplatin dose. The groups were unbalanced according to the percentage of patients who had prior chemotherapy experience. One half of the patients receiving the combination regimen compared with 25% of the patients with single-agent carboplatin had no prior chemotherapy; 92 and 93% of the patients received more than or equal to 300 mg/m^2 carboplatin as a single agent and in the combination therapy group, respectively. In the latter group the median dose of cyclophosphamide was 600 mg/m^2 and 96% of the patients received more than 500 mg/m^2 cyclophosphamide.

Frequency of emesis

Acute vomiting on the day of chemotherapy was observed in 47 patients (22%). Frequency of vomiting increased slightly on day 2 and decreased slowly until day 5 (Figure 1). Nearly half of the patients (96/216 patients = 44%) experienced at least one emetic episode within the 5 days observation period (Table 2). More than 50% of the patients who vomited (55/96 patients) experienced emesis lasting longer than 1 day. Vomiting limited to the day of chemotherapy is reported for 17 patients (8% of all patients and 18% of the patients who vomited once, respectively). Fifty percent of the patients who reported at least one emetic episode within the observation period suffered only from vomiting starting later than 24 h after chemotherapy administration. Nausea was observed in a higher percentage of patients (Figure 1). Seventy-five percent of the patients reported some degree of nausea on day 1 and 30% of patients reported more than mild nausea. The incidence of both nausea of any degree and more than mild nausea increased on days 2, and on day 3 it was still larger than on day 1. On days 4 and 5 nausea decreased slowly, but was still a problem for the majority of patients.

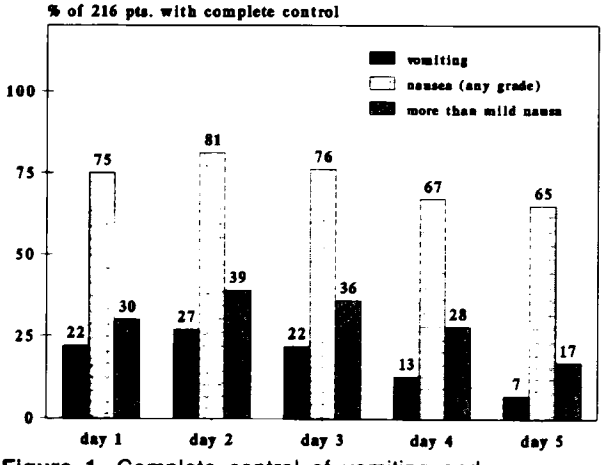

Figure 1. Complete control of vomiting and nausea on days 1–5 (for each day separately).

Table 2. Frequency of emesis for all patients [*n* = 216 (100%)]

	Day 1	Days 2–5	Days 1–5
Vomiting	48 (22%)	79 (37%)	96 (44%)
More than mild nausea	64 (30%)	102 (47%)	110 (51%)
Nausea of any degree	161 (75%)	177 (82%)	180 (83%)

Vomiting and nausea do not imply each other in all patients. Of the 96 patients who vomited, only 70 (73%) suffered from nausea of more than mild grade, and nausea was reported from 40/120 patients (33%) in whom vomiting was totally controlled.

Vomiting later than 24 h after chemotherapy administration was observed in 26% of the patients. The relationship between vomiting on day 1 and vomiting on days 2–5 is shown in Table 3. Only 29% of the 168 patients who did not vomit on day

Table 3. Vomiting on days 2–5 stratified for vomiting on day 1

	Vomiting on days 2–5		
Vomiting on day 1	yes	no	Total
Yes	31	17	48
No	48	120	168
Total	79	137	

1 reported vomiting on days 2–5, whereas 65% of the 48 patients who vomited on day 1 suffered from vomiting later than day 1 ($p < 0.001$). Eighty-six percent of the patients reported at least mild nausea on one or more days following the day of chemotherapy. Again, the incidence of nausea over days 2–5 was higher in patients who experienced nausea on day 1. The difference was statistically significant ($p < 0.001$).

Patterns of emesis

The average interval to the onset of emesis was 40 h. Fifty percent of the patients who did vomit reported their first emetic episode on day 1 and 30% had their first emetic episode on day 2. The mean duration of vomiting was 0.9 days including all patients and 2.0 days for the patients who vomited. Nausea started earlier, lasted longer and showed a later peak than vomiting. The mean duration of nausea of any degree was 3.3 and 4.4 days with regard to all patients and patients who did not vomit, respectively.

A worst-day analysis was performed for 96 patients who reported at least one emetic episode within the observation period. The worst-day analysis for nausea was based on all patients who reported any degree of nausea on at least 1 day. Vomiting and nausea peaked on day 2. Thirty one percent of the patients reported their worst day of vomiting on day 1, 34% on day 2 and 23% on day 3, respectively. The results for nausea were comparable with 24% of the patients reporting their worst day on day 1, 33% on day 2 and 23% on day 3, respectively.

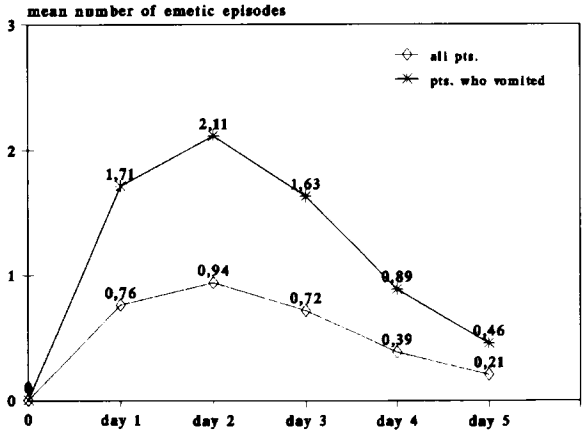

Figure 2. Severity of emesis in all patients and in patients who vomited at least on 1 day.

Severity of emesis

The curves of the mean emetic episodes per day (Figure 2) showed a monophasic shape with a broad peak over days 1–3. The worst day was day 2. The mean number of emetic episodes in patients who vomited at least on 1 day were 2.1 on days 2 and 1.71 and 1.63 episodes on days 1 and 3, respectively. The median cumulative number of emetic episodes over days 1–5 was 0 considering all patients and 4 for the patients who experienced at least one emetic episode. Severe emesis, classified as experiencing more than five emetic episodes within 24 h was observed in 21 patients (9.7%). Eight patients reported severe vomiting lasting longer than 1 day.

Comparison between single-agent carboplatin and combination therapy with carboplatin and cyclophosphamide

The addition of cyclophosphamide to carboplatin resulted in an increased frequency of emesis over days 1–2. The increase was highest on day 1 with a difference in the percentage of patients who were not completely protected from vomiting of 12% (92 and 80% for single-agent versus combination therapy, respectively; $p = 0.08$). The difference in favor of carboplatin single-agent chemotherapy decreased on days 2–5. Significantly less patients receiving carboplatin as a single agent suffered from more than mild nausea on day 1 (13 versus 31% for single-agent versus combination therapy, respectively; $p = 0.03$). Again, the difference decreased from day 2 onwards. Sixty-four percent of patients with monotherapy in contrast to 55% of patients receiving the combination regimen were completely protected from vomiting over days 1–5. There was no significant difference between the two groups with regard to the frequency of vomiting on days 2–5, with 31 and 38% for the monotherapy and the combination regimen, respectively. The onset of vomiting commenced later in patients receiving single-agent carboplatin compared with patients receiving additional cyclophosphamide (2.4 versus 1.8 days; $p = 0.08$), but there was no difference with respect to the duration of emesis. The worst-day analysis revealed a trend for an earlier peak of emesis in the group receiving the combination regimen. The analysis of the severity of emesis including only the patients who vomited within the observation period revealed a distinct differ-

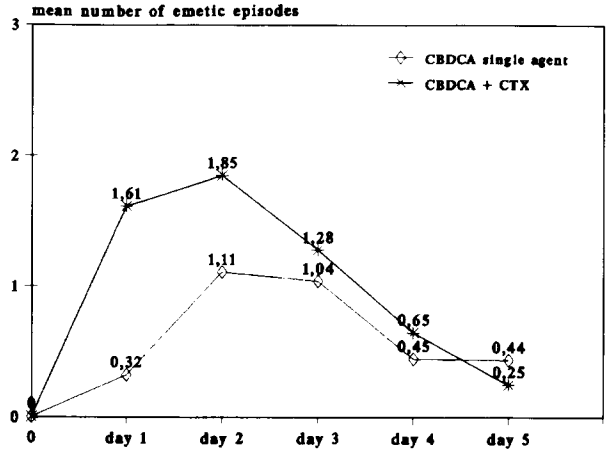

Figure 3. Severity of emesis in gynecological patients receiving carboplatin (CBDCA) as a single agent or in combination with cyclophosphamide (CTX). Analysis based on patients who vomited at least on 1 day (non-responder).

Table 4. Frequency of emesis for gynecological patients receiving carboplatin as a single agent or in combination with cyclophosphamide

	Day 1	Days 2–5	Days 1–5
Single-agent carboplatin			
vomiting	3 (8%)	12 (31%)	14 (36%)
more than mild nausea:	5 (13%)	17 (44%)	18 (46%)
nausea of any degree:	24 (61%)	28 (72%)	29 (74%)
Carboplatin and cyclophosphamide			
vomiting	20 (20%)	37 (38%)	44 (45%)
more than mild nausea	30 (31%)	49 (50%)	52 (53%)
nausea of any degree	73 (74%)	82 (84%)	84 (86%)

ence with respect only to acute emesis in favor for the single-agent therapy (Figure 3 and Table 4).

Discussion

Historical data describing the natural course of emesis following carboplatin-containing chemotherapy revealed a considerable emetogenic potential of this drug. Over 80% of the patients treated with carboplatin without antiemetic prophylaxis suffered from vomiting and nearly 90% of these patients experienced nausea. Emesis was severe with a median of 13.5 emetic episodes for each patient.[14] Compared with historical data, the introduction of the selective 5-HT_3 antagonist ondansetron has led to a remarkable reduction of emesis. The median number of emetic episodes in this study was less than 1 for all patients and 4 for patients who experienced some degree of emesis. The vast majority of patients did not experience acute emesis and less than 50% of the patients reported any degree of vomiting within the 5 day observation period. The proportion of patients suffering from severe vomiting was small and did not exceed 10%. Results concerning nausea were less pronounced. The majority of patients reported some degree of nausea which lasted on average for 3–4 days, but most of them suffered only from mild nausea. The probability for emesis on days 2–5 significantly differs depending on whether emesis on day 1 is observed. Nevertheless, the predictive value of acute emesis for the occurrence of emesis on days 2–5 is only 65%. Therefore, clinical decisions if a patient needs antiemetic treatment on the days following the day of chemotherapy cannot only depend on whether acute emesis occurs. Criteria with a higher predictive value regarding the occurrence of emesis on days 2–5 are warranted, such that patients who are in need for prolonged antiemetic treatment can be identified.

There are only limited data available describing the interaction of different cytostatics regarding their emetogenic potential. Two studies describe an increase in chemotherapy induced emesis when anthracyclines are added to cyclophosphamide.[21,22] Another study failed to demonstrate a similar effect regarding the addition of cyclophosphamide to cisplatin, but could demonstrate an increase of emesis when anthracyclines are added to a combination of cisplatin and cyclophosphamide.[23] In this study we were able to compare two subgroups of patients with either single-agent carboplatin or a combination of carboplatin and cyclophosphamide. Both groups were comparable with respect to age, gender, diagnosis and carboplatin dose, but were unbalanced with respect to prior chemotherapy experience. This imbalance which might have caused a bias in favor of the combination regimen was more than outweighed by the higher emetogenic potential of cyclophosphamide plus carboplatin. Our results indicate that the combination with cyclophosphamide leads to more acute emesis compared with single-agent carboplatin. The mechanism of this 'enhancement' is not clear. Ondansetron has proven efficacy against both cyclophosphamide[21,22] and carboplatin-induced emesis[18–20] (present data), but fails to provide total control of emesis in 100% of the treated patients. A possible explanation of the observed enhancement of acute emesis for the combination of carboplatin and cyclophosphamide is that both drugs involve 5-HT_3 receptor-independent mechanisms of acute emesis;

and, furthermore, that these mechanisms may act synergistically or in an additive manner. Recently published reports have focussed on alternative mediators of cytostatic drug-induced emesis. Results from animal experiments indicate, that there is a potential role for substance P, acting via NK 1 receptors in the central nervous system, in the pathomechanism of emesis.[25] Furthermore, clinical observations as well as some experimental data indicate that endogenous and exogenous steroids play a in the pathophysiology and the management of cytostatic drug-induced emesis.[26–28] Future trials should evaluate the role of both NK 1 receptor antagonists and corticosteroids in the management of carboplatin-induced emesis.

However, the efficacy of 5-HT_3 receptor antagonists in reducing carboplatin-induced emesis indicates that serotonin-related mechanisms are of major importance in the pathophysiology of carboplatin-induced emesis. These observations correspond to experimental data describing measurable changes in serotonin metabolism following carboplatin-containing chemotherapy.[24] This study revealed a decrease of the frequency of emesis after prophylactic treatment with single-agent ondansetron compared with historical data, reporting the natural course of carboplatin-induced emesis without antiemetic treatment.[14] Ondansetron not only reduces the incidence of vomiting, but also reduces the severity of vomiting in those patients who are not completely protected. It is not clear if the beneficial effects of ondansetron are maintained over several days following chemotherapy. The analysis of the course of carboplatin-induced emesis did not reveal any hint for a biphasic pattern of vomiting. Emesis following carboplatin chemotherapy shows a prolonged monophasic pattern with a wide peak between day 1 and 3, with day 2 being the worst day in most patients. There is significant inter-individual diversity concerning the onset of emesis and nearly one-third of patients reported their first emetic episode later than day 2. Although it is likely that ondansetron given for at least 3 days (the interval in which emesis peaks) improves antiemetic results, the data presented do not allow us to draw final conclusions. Further studies, focussing on the efficacy of ondansetron given as single-day versus a multiple-day treatment should help to clarify this issue.

The results of this study suggest that future trials of carboplatin-induced emesis should include multiple-day assessment of emesis and nausea. Furthermore, patients should be stratified according to whether they receive single-agent carboplatin or a combination regimen including cyclophosphamide. Neglecting the interactions of these cytostatics may lead to a bias mainly with respect to acute emesis.

Conclusion

Carboplatin induces a monophasic prolonged pattern of emesis lasting on average over 2–3 days. The addition of cyclophosphamide to carboplatin leads to an earlier onset and a higher frequency of vomiting. Compared with historical data, the 5-HT_3 antagonist ondansetron is effective in controlling carboplatin-induced emesis. Nevertheless, 44% of patients suffer from emesis despite 5-HT_3 antagonism. The analysis of the pattern of 5-HT_3-independent emesis should help to define areas of research in which further improvement of antiemetic treatment is mandatory.

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References

1. Advanced Ovarian Cancer Trialist Group. Chemotherapy in advanced ovarian cancer: an overview of randomized clinical trials. *Br Med J* 1991; **303**: 884–93.
2. Knox RJ, Friedlos F, Lydall DA, *et al.* Mechanism of cytotoxicity of anticancer platinum drugs: evidence that *cis*-diammine-dichloroplatinum (II) and *cis*-diammine (1,1-cyclobutanedicarboxylato) platinum (II) differ only in the kinetics of their interaction with the DNA. *Cancer Res* 1986; **46**: 1972–9.
3. Micetich KC, Barnes D, Erickson LC. A comparative study of the cytotoxicity and DNA-damaging effects of *cis*-(diammino)(1,1 cyclo-butanedicarboxylato)-platinum (II) and *cis*-diamminedichloro-platinum (II) on L 1210 cells. *Cancer Res* 1984; **45**: 4043–7.
4. Terheggen PMAB, Begg AC, Ernondt JY, *et al.* Formation of interaction products of carboplatin with DNA *in vitro* and in cancer patients. *Br J Cancer* 1991; **63**: 195–200.
5. Gaver RC, Deeb G. High-performance liquid chromatographic procedure for the analysis of carboplatin in human plasma and urine. *Cancer Chemother Pharmacol* 1986; **16**: 201–6.
6. Harland SJ, Newell DR, Siddik ZH, *et al.* Pharmacokinetics of *cis*-diammine-1,1cyclobutane dicarboxylate platinum in patients with normal and impaired renal function. *Cancer Res* 1984; **44**: 1693–7.

7. Trump DL, Grem JL, Tutsch KD, *et al.* Platinum analogue combination chemotherapy: cisplatin and carboplatin – a phase I trial with pharmacokinetic assessment of the effect of cisplatin administration on carboplatin excretion. *J Clin Oncol* 1987; **5**: 1281–9.
8. Elfrink F, van der Vijgh WJF, Klein I, *et al.* Pharmacokinetics of carboplatin after iv administration. *Cancer Treat Rep* 1987; **71**: 1231–7.
9. Cupissol DR, Serrou B, Caubel M. The efficacy of granisetron as a prophylactic anti-emetic and intervention agent in high-dose cisplatin-induced emesis. *Eur J Cancer* 1990; **26**(Suppl 1): S23–7.
10. Cubeddu LX, Hoffman IS, Fuenmayor NT, *et al.* Efficacy of ondansetron (GR 32038F) and the role of serotonin in cisplatin induced nausea and vomiting. *N Engl J Med* 1990; **322**: 810–6.
11. Schurig JE, Florczyk AP, Bradner WT. Evaluation of platinum complexes for emetic potential. *Proc 4th Int Symp Platinum Coordination Complexes* 1984; 184–99.
12. Adams M, Kerby IJ, Rocker I, *et al.* Carboplatin (Paraplatin) clinical trials: assessment of nausea and vomiting. In: Lapis, Eckhardt, eds. *Anticancer drug research.* Karger, Basel/Akademiai Kiado, Budapest 1987: 33–44.
13. Du Bois A, Vach W, Thomssen C, *et al.* Comparison of the emetogenic potential between cisplatin and carboplatin. *Acta Oncol* 1994; **33**: 531–5.
14. Martin M, Diaz-Rubio E, Sanchez A, *et al.* The natural course of emesis after carboplatin treatment. *Acta Oncol* 1990; **29**, 593–7.
15. Marty M, Pouillart P, Scholl S, *et al.* Comparison of the 5-hydroxytryptamine (serotonin) antagonist ondansetron (GR 32038F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990; **322**: 816–21.
16. De Mulder PHM, Seynaeve C, Vermorken JB, *et al.* Ondansetron compared with high-dose metoclopramide in the prophylaxis of acute and delayed cisplatin-induced nausea and vomiting — a multicentre randomised, double-blind crossover study. *Ann Intern Med* 1990; **113**: 834–40.
17. Kris MG, Tyson LB, Clark RA, *et al.* Oral ondansetron for the control of delayed emesis after cisplatin. *Cancer* 1992; **70**: 1012–6.
18. Gridelli C, Incoronato P, Airoma G, *et al.* Ondansetron in the prophylaxis of nausea and vomiting induced by carboplatin combination chemotherapy. *Eur J Cancer* 1993; **29A**: 651.
19. Smith DB, Rustin GJS, Howells N, *et al.* A phase II study of ondansetron as antiemetic prophylaxis in patients receiving carboplatin for advanced ovarian cancer. *Ann Oncol* 1991; **2**: 607–8.
20. Harvey VJ, Evans BD, Mitchell PLR, *et al.* Reduction of carboplatin induced emesis by ondansetron. *Br J Cancer* 1991; **63**: 942–4.
21. Cubeddu LX, Pendergrass K, Ryan T, *et al.* Efficacy of oral ondansetron, a selective antagonist of 5-HT_3 receptors, in the treatment of nausea and vomiting associated with cyclophosphamide-based chemotherapies. *Am J Clin Oncol* 1994; **17**: 137–46.
22. Beck TM, Ciociola AA, Jones SE, *et al.* Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med* 1993; **118**: 407–13.
23. Du Bois A, Meerpohl HG, Vach W, *et al.* Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin pretreated patients: a study with ondansetron. *Eur J Cancer* 1992; **28**: 450–7.
24. Du Bois A, Cramer-Giraud U, Vach W, *et al.* Pathophysiology, severity pattern and risk-factors for carboplatin-induced emesis. *Oncology* 1995; in press.
25. Bountra C, Bunce K, Dale T, *et al.* Anti-emetic profile of a non-peptide neurokinin NK_1 receptor antagonist, CP 99,994, in ferrets. *Eur J Pharmacol* 1993; **249**: R3–4.
26. Fredrickson M, Hursti T. Endogenous cortisol exerts antiemetic effect similar to that of exogenous corticosteroids. *Br J Cancer* 1993; **68**: 112–4.
27. Fredrickson M, Hursti T. Nausea in cancer chemotherapy is inversely related to urinary cortisol excretion. *Br J Cancer* 1992; **65**: 779–80.
28. Hesketh PJ, Harvey WH, Harker WG, *et al.* A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. *J Clin Oncol* 1994; **12**: 596–600.

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