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A phase I study of lobaplatin (D-19466) administered by 72 h continuous infusion

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A phase I trial with continuous intravenous infusion of lobaplatin (D-19466; 1,2-diamminomethyl-cyclobutane-platinum (II)-lactate) for 72 h was performed to determine the maximum tolerated dose (MTD). Each patient received a single dose level, the total dose of lobaplatin ranged from 30 to 60 mg/m^2/72 h every 4 weeks. Eleven patients enroled in this study and received a total of 30 courses of lobaplatin (median 2; range 1–6). Thrombocytopenia was the dose-limiting toxicity, it reached WHO grade III in three out of six patients at 45 mg/m^2/72 h, and WHO grade IV in two out of two patients at 60 mg/m^2/72 h. Leucocytopenia was mild, as was nausea and vomiting. Phlebitis at the infusion site was found in three patients. During this trial there were no signs of renal, neuro- or ototoxicity. One patient with ovarian cancer, pretreated with three different platinum complexes, achieved a partial response now lasting for longer than 6 months. In conclusion, thrombocytopenia is the dose-limiting toxicity of lobaplatin administered by 72 h continuous infusion. The recommended phase II dose for this regimen is 45 mg/m^2/72 h every 4 weeks.

Key words: Continuous infusion, D-19466, lobaplatin, phase I study.

Introduction

Cisplatin is one of the most active drugs in the treatment of solid tumors, but has limitations both due to toxicity, especially nephro- and neurotoxicity, and to development of drug resistance. A major goal in this respect is to find new platinum analogs that are less toxic and more effective than second generation analogs such as carboplatin. One of these compounds is lobaplatin (D-19466; 1,2 diamminomethyl-cyclobutane-platinum (II)-lactate). Preclinical *in vitro* and animal data suggest that the anti-tumor activity of lobaplatin is different from that of cisplatin and carboplatin.[1] There is evidence that lobaplatin is non-cross-resistant in a number of cisplatin resistant tumor cell lines.[1,2] The preclinical toxicity data resemble that of carboplatin.[1]

In the first phase I study with lobaplatin administered daily for 5 days, its main toxicity appeared to be on the bone marrow and, in particular, consisted of thrombocytopenia.[3] Gastrointestinal toxicity was mild and renal toxicity did not occur. The thrombocytopenia was clearly related to the renal function of the patients, resulting in different maximal tolerated doses (MTDs) for different renal function cohorts. In a 1 day bolus infusion schedule the toxicity pattern was comparable with that of a 5 day regimen.[4] The optimal doses of lobaplatin in both schedules for patients with a creatinine clearance (CRCL) above 80 ml/min were between 50 and 70 mg/m^2. Preliminary pharmacokinetic analysis of lobaplatin showed a short plasma half-life and rapid urinary excretion.[5]

Continuous infusion of platinum compounds might be beneficial for both activity and toxicity, as indicated by recent studies.[6–8] *In vitro* studies indicate that the cytotoxicity of lobaplatin towards tumor cell lines is altered by prolonged exposure.[2] From these observations, a clinical phase I trial by 72 h continuous infusion was conducted in order to determine the MTD and to characterize the clinical toxicity of lobaplatin.

Materials and methods

Eleven patients entered this study. All patients had histologically proven advanced cancers not amenable to conventional treatment. To be eligible for this study, patients had to fulfil the following criteria: (i) age between 18 and 75 years; (ii) an estimated life expectancy of ≥ 3 months; (iii) a

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WHO performance status of ≤ 2; (iv) complete recovery from all toxic effects from prior treatments with a treatment-free interval of at least 4 weeks; (v) adequate bone marrow function (leucocyte count $\geq 4 \times 10^9$/l and platelet count $\geq 100 \times 10^9$/l); (vi) serum creatinine level ≤ 135 μmol/l and a CRCL ≥ 60 ml/min; (vii) alkaline phosphatase < 1.5 times normal and serum bilirubin ≤ 26 μmol/l; and (viii) no coexisting active medical problems. This protocol was approved by the Medical Ethical Committee of the University Hospital Groningen. Consent was obtained from all patients after being informed of the investigational nature of this treatment.

Lobaplatin was provided by ASTA Medica AG (Frankfurt, Germany) in vials containing 20 mg dried white powder. The proper daily dose of lobaplatin was dissolved in sterile water (2 ml/20 mg) and diluted in 30 ml NaCl 0.9%, divided over two syringes. One syringe with lobaplatin was administered over 12 h right after preparation, the other was stored at 4°C for 12 h until usage. The chemical stability of lobaplatin solutions was tested with a previously described high performance liquid chromatographic (HPLC) technique.[9] Lobaplatin 20 mg was dissolved in 2.0 ml water for injection and further diluted with NaCl 0.9% to 580, 867 and 1153 mg/l, representing concentrations commensurate with those used during continuous infusion. Solutions were stored in 20 ml polypropylene–polyethylene syringes (Omnifix, Braun Medical, Uden, The Netherlands) at room temperature and in normal daylight. At appropriate intervals, 2 ml samples were taken and immediately frozen (−20°C). Samples were analyzed within 1 week. Each experiment was performed in triplicate. The drug stability is shown in Fig. 1. The loss of lobaplatin in NaCl 0.9% solutions was less than 5% over 24 h, and did not differ for the three concentrations. Furthermore, the osmolality of fresh solutions was measured using a cryoscopic osmometer (Osmomat 030, Salm & Kipp, Breukelen, The Netherlands). The osmolalities of the three different solutions (mean ± SD) were 271.5 ± 0.6, 263.8 ± 1.0 and 257.3 ± 1.0 mosmol/kg, respectively (the osmolality of NaCl 0.9% was 287.1 ± 0.7).

Lobaplatin was administered intravenously for 72 h with a portable infusion pump every 4 weeks. No anti-emetic agents were given before or during chemotherapy, except if the patient experienced gastrointestinal toxicity over grade 2 in the WHO criteria.[10]

Each patient received one dose level of 72 h continuous lobaplatin, the total dose of lobaplatin ranged from 30 to 60 mg/m^2. The starting dose was 30 mg/m^2/72 h, which is a dose that did not show toxicity in previous trials.[3,4] Three patients were entered at each dose level. There was no dose escalation in the individual patient. The MTD was defined as the dose at which two patients reached WHO grade 4 hematological toxicity or WHO grade 3 organ toxicity. A total of six patients were entered at the desirable dose level, one step below the MTD.

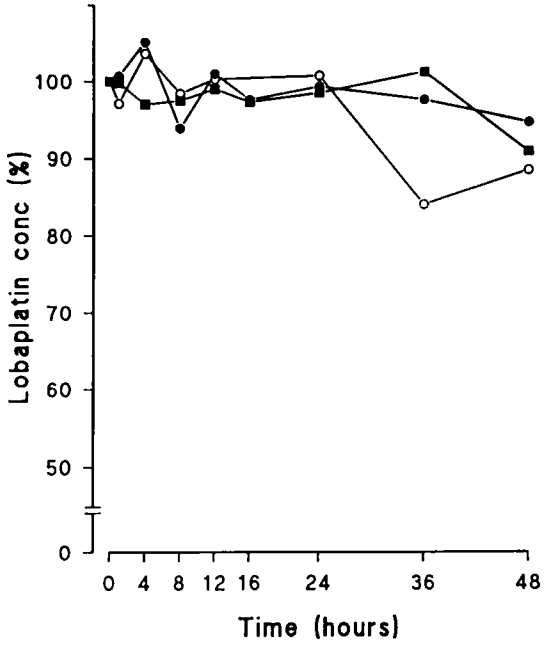

Figure 1. The chemical stability of lobaplatin solutions was tested with a HPLC technique. Lobaplatin solutions of 580 mg/l (●), 867 mg/l (○) and 1153 mg/l (■), representing concentrations commensurate with those used during continuous infusion, were stored at room temperature. The concentrations at $t = 0$ were set at 100%. Data points are the mean of three separate determinations.

During each course, the complete blood cell count, serum electrolytes, liver and renal function, and glucose were measured on each treatment day, and on day 7, 14, 21 and 28. Twenty-four hour urinary CRCLs were performed twice before study entry, twice prior to each lobaplatin course and on day 14 of each course. ECG and chest X-rays were done before each course of lobaplatin.

To be evaluable for response the patient with measurable disease had to receive at least two courses of lobaplatin. Tumor evaluations were performed at entry and after every two treatment cycles. A complete response (CR) was defined as the disappearance of all evidence of the tumor and

no development of new lesions for at least 4 weeks. A partial response (PR) was defined as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions. Stable disease meant a decrease within 50% or an increase of less than 25% in any measurable lesions. Progressive disease was defined as an increase of more than 25% of the lesions or the occurrence of new lesions.

Results

The characteristics of the 11 patients enroled in this study are outlined in Table 1, they received a total of 30 courses of lobaplatin (median 2; range 1–6).

Table 1. Clinical characteristics of 11 patients treated with lobaplatin

	Number of patients
Median age (range)	54 (38–66) years
Sex	
male	6
female	5
Performance status (WHO)	
0	4
1	4
2	3
Primary site	
ovarian carcinoma	3
small cell lung carcinoma	2
malignant melanoma	2
non-small cell lung carcinoma	1
colon carcinoma	1
breast carcinoma	1
adenocarcinoma of unknown primary origin	1
Previous treatment	
chemotherapy	9
radiotherapy and chemotherapy	1
none	1
Prior treatment with cisplatin or carboplatin	3

All patients were evaluable for toxicity and eight for tumor responses. At entry of this trial the mean CRCL of the patients was 91 ml/min (range 83–109 ml/min).

Toxicity

Myelosuppression was the dose-limiting toxicity in this schedule and is detailed in Table 2. Thrombocytopenia WHO grade 4 occurred in two patients at 60 mg/m^2/72 h, this dose level was considered to be the MTD. At 45 mg/m^2/72 h, two patients experienced grade 3 thrombocytopenia during their first or second course of lobaplatin. One patient who started at 60 mg/m^2/72 h was de-escalated to 45 mg/m^2/72 h during his second course and experienced grade 3 thrombocytopenia. The median day of platelet count nadir was day 20 (range 14–28). Blood cell counts usually recovered within 1 week after their nadir. Leucocytopenia was less prominent, only one patient experienced grade 3 leucopenia at a dose level of 45 mg/m^2/72 h. Two patients developed grade 2 anemia during their second and third course of lobaplatin and required a blood transfusion. No relation could be detected between the percent decrease in platelet or leucocyte count nadir and the CRCL of patients at time of lobaplatin administration.

Three patients developed a phlebitis at the infusion site during the lobaplatin administration. In one patient this resulted in an ulcer at this phlebitis site requiring termination of lobaplatin treatment. An extravasation of lobaplatin could not entirely be excluded. Hypertonicity of the lobaplatin solutions could be excluded as a cause for this phlebitis. Nausea and vomiting of WHO grade 2 occurred in only four patients, three of these patients had received other platinum complexes as previous treatment. The nausea and vomiting was not clearly dose related and could easily be controlled with ondansetron. There was no

Table 2. Hematological toxicity: number of courses associated with WHO toxicity grade

Dose (mg/m^2/72 h)	No. of patients	No. of courses	WHO toxicity grades											
			leukocytes				thrombocytes				hemoglobin			
			1	2	3	4	1	2	3	4	1	2	3	4
30	3	7	5	0	0	0	0	0	0	0	0	0	0	0
45	6	21	12	3	1	0	4	2	6	0	2	5	0	0
60	2	2	2	0	0	0	0	0	0	2	2	0	0	0

evidence of renal toxicity expressed as CRCL during the course of this trial. Furthermore, no neurotoxicity, ototoxicity or hepatic toxicity was encountered in this regimen.

Response

In the eight patients evaluable for response, one partial response was observed in a patient with ovarian cancer with normalization of the initially elevated tumor marker CA-125. This response has now lasted for more than 6 months. This patient entered the current trial after the second relapse of her ovarian cancer. She was pretreated with carboplatin and cyclophosphamide as first line therapy with a PR as best response. Her second line treatment consisted of intraperitoneal cisplatin and also resulted in a PR. For her second relapse she initially received the platinum compound Zeniplatin (Lederle), but when she achieved no response she was treated with lobaplatin. One patient with a non-small cell lung carcinoma had a disappearance of three of his four lung metastases during lobaplatin treatment; however, before he possibly could develop a remission this patient had to be removed from the trial because of local phlebitis at the infusion site. Two other patients had stable disease after lobaplatin treatment, the remaining patients were progressive.

Discussion

Continuous intravenous infusion of a platinum compound is one of the interesting strategies to enhance its activity and or to reduce its side effects.[6–8,11] Several reports on continuous infusion of cisplatin have suggested better response rates and less side effects as compared with intermittent drug infusion.[12,13] In the case of platinum complexes with, compared to cisplatin, low protein binding and rapid urinary excretion such as carboplatin, 254-S and lobaplatin, continuous infusion might be a way to enhance cytotoxicity by means of prolonged drug exposure.[11,14]

In this phase I study patients were treated continuously intravenously over 72 h with lobaplatin. The dose-limiting toxicity appeared to be thrombocytopenia and occurred at 60 mg/m^2/72 h. The recommended dose for a phase II trial with lobaplatin is 45 mg/m^2/72 h. The standard dose for intravenous bolus infusion of lobaplatin is reported to be 50 mg/m^2.[4] The recommended dose for a daily $\times 5$ intravenous bolus schedule depended on CRCL and ranged from 30 mg/m^2 for patients with a CRCL of 60–80 ml/min, 55 mg/m^2 for patients with a CRCL of 81–100 ml/min, to 70 mg/m^2 for patients with a CRCL above 100 ml/min.[3] The mean CRCL of patients in the present continuous infusion study was 91 ml/min, the desirable dose level of 45 mg/m^2 is somewhat lower than the phase II dose of the daily $\times 5$ regimen for patients with a CRCL of 81–100 ml/min. For continuous infusion of cisplatin, it has been reported that the myelotoxicity is more pronounced after 5 day continuous infused cisplatin than after intermittent bolus infused cisplatin; this might be related to prolonged exposure to unbound platinum during continuous infusion.[12] This difference in toxicity has also been described for 245-S, a platinum analog with protein binding comparable with carboplatin: 75.5 mg/m^2 of 254-S is the desirable dose level for continuous infusion whereas 100 mg/m^2 is the phase II level for intravenous drip administration. Pharmacokinetic analysis demonstrated that these two different dosages of 254-S produce comparable platinum AUCs. Although we did not perform pharmacokinetic analysis of platinum levels in the present study, the suggested low protein binding could also prolong the retention of the unbound form of lobaplatin when administered by continuous infusion.

In contrast to our earlier phase I study performed with lobaplatin in a daily $\times 5$ bolus infusion schedule, the present study did not show a correlation between CRCL and platelet nadir (expressed as relative to the pretreatment platelet count). This might be caused by the small variation in clearances in these patients.

A promising result of this trial was the clinical anti-tumor activity of lobaplatin in an extensive platinum pretreated patient with ovarian cancer. This patient could be marked as partial resistant to previous platinum chemotherapy. Taking the two responses in ovarian cancer patients from the previous phase I trial into account,[3] lobaplatin might be an active drug in ovarian cancer. A phase II trial with lobaplatin in patients with ovarian cancer is currently in progress at our institution.

Conclusion

The recommended dose for a phase II trial of lobaplatin by continuous infusion is 45 mg/m^2/72 h every 4 weeks; in view of the occurrence of

phlebitis, this regimen is best given through a venous access device.

References

1. Voegeli R, Schumacher W, Engel J, *et al.* D-19466 a new cyclobutane–platinum complex with antitumor activity. *J Cancer Res Clin Oncol* 1990; **116**: 419–22.
2. Meijer C, Mulder NH, Timmer-Bosscha H, *et al.* Role of glutathione in the efficacy of seven platinum compounds in two models of cisplatin resistance. *Cancer Res* 1992; **52**: 6885–9.
3. Gietema JA, de Vries EGE, Sleijfer DTh, *et al.* A phase I study of 1,2-diamminomethyl-cyclobutane-platinum(II)-lactate (D-19466; lobaplatin) administered daily for 5 days. *Br J Cancer* in press.
4. Fiebig HH, Mross K, Henss H, *et al.* Phase I study of the new platinum complex D-19466 on a single intermittent schedule. *Eur J Cancer* 1991; **52**: S197.
5. Mross K, Meyberg L, Fiebig H, *et al.* Pharmacokinetics of the platinum derivate D-19466. *Eur J Cancer* 1991; **52**: S197.
6. Smit EF, Willemse PHB, Sleijfer DTh, *et al.* Continuous infusion of carboplatin on a 21-day schedule: A phase I and pharmacokinetic study. *J Clin Oncol* 1991; **9**: 100–10.
7. Belliveau JF, Posner MR, Ferrari L, *et al.* Cisplatin administered as a continuous 5-day infusion: plasma platinum levels and urine platinum excretion. *Cancer Treat Rep* 1986; **70**: 1215–7.
8. Posner MR, Ferrari L, Belliveau JF, *et al.* A phase I trial of continuous infusion cisplatin. *Cancer* 1987; **59**: 15–8.
9. Guchelaar H-J, Uges DRA, Aulenbacher P, *et al.* Stability of the new anticancer platinum analogue 1,2-diamminomethyl-cyclobutane-platinum(II)-lactate (Lobaplatin; D-19466) in intravenous solutions. *Pharm Res* 1992; **9**: 808–11.
10. WHO. *WHO handbook for reporting results of cancer treatment.* WHO Offset Publication no. 48, Nijhoff: Den Haag 1978.
11. Sasaki Y, Amano T, Morita M, *et al.* Phase I study and pharmacological analysis of *cis*-diammine(glycolato)platinum (254-S; NSC 375101D) administered by 5-day continuous intravenous infusion. *Cancer Res* 1991; **51**: 1472–7.
12. Forastiere AA, Belliveau JF, Goren MP, *et al.* Pharmacokinetics and toxicity evaluation of five day continuous infusion versus intermittent bolus *cis*-diamminedichloroplatinum(II) in head and neck cancer patients. *Cancer Res* 1988; **48**: 3869–74.
13. Reece PA, Stafford I, Abbot RL, *et al.* Two- versus 24-hour infusion of cisplatin: pharmacokinetic considerations. *J Clin Oncol* 1989; **7**: 270–5.
14. Shea TC, Flaherty M, Elias A, *et al.* A phase I clinical and pharmacokinetic study of carboplatin and autologous bone marrow support. *J Clin Oncol* 1989; **7**: 651–61.

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