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Original article

Clinical and pharmacological phase I study with accelerated titration design of a daily times five schedule of BBR3464, a novel cationic triplatinum complex

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Summary

Objectives: To define the maximum tolerated dose (MTD), the toxicity and pharmacokinetic profile of BBR3464, a novel triplatinum complex.

Patients and methods: Fourteen patients with advanced solid tumors not responsive to previous antitumor treatments received BBR 3464 on a daily × 5 schedule every twenty-eighth day. The drug was given as a one-hour infusion with pre-and post-treatment hydration (500 ml in one hour) and no antiemetic prophylaxis. The starting dose was 0.03 mg/m^2/day. A modified accelerated titration escalation design was used. Total and free platinum (Pt) concentrations in plasma and urine were assessed by ICP-MS on days 1 and 5 of the first cycle.

Results: Dose was escalated four times up to 0.17 mg/m^2/day. Short-lasting neutropenia and diarrhea of late onset were dose-limiting and defined the MTD at 0.12 mg/m^2. Nausea and vomiting were rare, neither neuro- nor renal toxic effects were observed. BBR3464 showed a rapid distribution phase of 1 hour and a terminal half-life of several days. At 0.17 mg/m^2 plasma Cmax and AUC on day 5 were higher than on day 1, indicating drug accumulation. Approximately 10% of the equivalent dose of BBR3464 (2.2%–13.4%) was recovered in a 24-hour urine collection.

Conclusions: The higher than expected incidence of neutropenia and GI toxicity might be related to the prolonged half-life and accumulation of total and free Pt after daily administrations. Lack of nephrotoxicity and the low urinary excretion support the use of the drug without hydration. The single intermittent schedule has been selected for clinical development.

Key words: BBR3464, phase I, platinum analog, pharmacokinetics

Introduction

BBR3464 is a charged (+4), triplatinum complex (Figure 1) with notable preclinical characteristics. It is approximately fourty- to eighty-fold more potent than cisplatin (CDDP) on a molar-dose basis and is active *in vivo* in CDDP-sensitive and resistant tumors, as well as in insensitive xenografts. In addition, BBR3464 was shown to be more active than CDDP in *p53* mutant tumors [1].

The characteristic DNA-interaction of BBR3464 results in an inhibition of DNA replication and RNA transcription, with triggering of the apoptotic cascade leading to cell death. Unlike cisplatin, BBR3464 leads to prolonged tumor growth inhibition after discontinuation of treatment, suggesting that the two drugs could

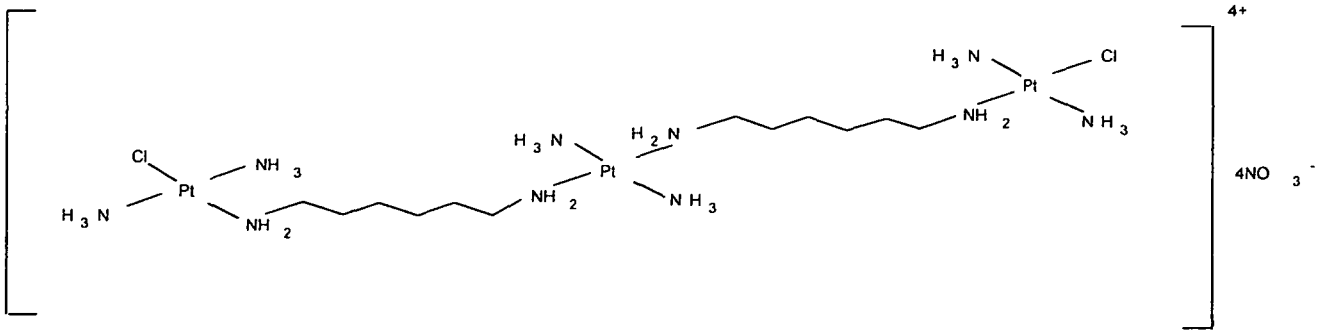

Figure 1. Chemical structure of BBR3464.

differ significantly in their ability to perturb the cell cycle [2].

As a distinctive feature, BBR3464 achieves a high proportion of interstrand and intra-strand DNA adducts in contrast to the effects of CDDP, which predominantly produces predominantly the latter type of DNA damage. While CDDP-damaged DNA is recognized by HMG-proteins, the conformational changes resulting from BBR3464 interaction with DNA are not. This observation might explain resistance to CDDP, and lack of resistance to BBR3464 in tumors expressing mutations of the *p53* oncosuppressor gene [3].

The preclinical toxicology in mice, rats and dogs treated on a single or daily × 5 refracted schedule showed that target organs for BBR3464 toxicity were bone marrow, resulting in leukopenia, and intestines, while renal tubulopathy was only minimal or slight. A slight pulmonary interstitial reaction, with fibroblast proliferation and inflammatory infiltration, was observed in mice and dogs. This unusual effect was more extensive after intravenous bolus, given as a single or weekly dose, than after slow infusion or every two-week bolus [1]. The schedule dependency of the lung toxicity prompted the clinical evaluation of a daily times 5 refracted schedule in addition to a single dose schedule. The present report describes the clinical and pharmacological findings of a phase I investigation of the daily × 5 refracted schedule.

Patients and methods

Patients

Adult patients, aged 18–75 years, with histologically/cytologically confirmed advanced solid tumors, not amenable to conventional local or systemic treatments, were candidates for this study. Eligibility criteria also included a WHO performance status $\leqslant 2$, life expectancy of $\geqslant 3$ months, adequate bone marrow (Hb $\geqslant 10$ g/dl; neutrophil count (ANC) $\geqslant 2.0 \times 10^9$/l, platelet count $\geqslant 100 \times 10^9$/l), liver (total bilirubin $\leqslant 1.5 \times$ upper normal limit, ALAT and/or ASAT $\leqslant 2.5 \times$ upper normal limit, unless due to tumor) and kidney (Creatinine Clearance $\geqslant 60$ ml/min) function. Patients could be eligible provided that: chemotherapy or radiotherapy had not been given in the four weeks (six weeks in case of mitomycin C, nitrosoureas or large-field radiotherapy) preceeding the start of the treatment; they received a maximum cumulative dose of 800 mg/m^2 of cisplatin; they had no clinically significant abnormalities (NCIC-Common Toxicity Criteria (CTC) grade 3–4) of the cardiovascular system; no peripheral neuropathy $\geqslant$ grade 2; no chronic airways disorder or interstitial lung disease (dyspnea grade $\geqslant 2$ NCIC-CTC); no other coexisting medical problems of sufficient severity to limit compliance with the study. Written informed consent was obtained from all patients. For the purpose of data analysis patients were considered heavily pretreated if they had at least one of the following conditions: two or more prior chemotherapy regimens or one prior chemotherapy regimen and radiotherapy.

Study design

The starting dose was 0.03 mg/m^2/daily, corresponding to 1/10 of the mouse equivalent MTD (MEMTD).

The dose was escalated according to the 4B version of the accelerated titration design for phase I studies [4], with single patient cohorts, double-dose step escalation, intra-patient dose escalation, and evaluation of the number of grade 2 toxicities episodes over the total number of cycles given. The maximum tolerated dose (MTD) was defined as the dose at which one third or more of the patients (i.e., at least 2 patients) developed dose limiting toxicities (DLT) after the first cycle. Escalation to the subsequent dose level was allowed only when the last patient in the prior cohort had been observed for at least three weeks following the administration of his/her first course. During the accelerated phase of the trial only one patient per cohort was treated until one patient experienced a DLT or two patients experienced toxicities of grade $\geqslant 2$ according to the NCI-CTC. Definition of hematological DLT included: CTC grade 4 thrombocytopenia and anemia, CTC grade 4 neutropenia lasting $\geqslant 7$ days, febrile neutropenia (ANC $< 0.5 \times 10^9$/l with fever either as two elevations of oral temperature > 38 °C with one-hour interval or as single oral temperature > 38.5 °C). Non-hematological DLT included all episodes of CTC grade 3 or grade 4 toxicity, with the exclusion of: nausea, vomiting and alopecia, prolonged (> 2 week duration) CTC grade 2; renal ($\leqslant 60$ ml/min), neurological, pulmonary, defined as a $> 50\%$ decrease of baseline value of carbon monoxide diffusion capacity (CMDC).

After the first cycle, patients were eligible for retreatment if they still met the entry criteria with a maximum delay of two weeks with respect to the day planned for retreatment. The dose was decreased by one level in instances of DLT and re-escalation at subsequent cycles was not allowed.

Chemistry (including electrolytes, calcium, magnesium, creatinine, total protein, albumin, bilirubin, alkaline phosphatase, glucose, transaminases, uric acid, clotting factors, creatinine clearance and urinalyses) were performed at least weekly, and more often in instances of toxicity. Audiogram, ECG, and chest X-ray were done before therapy and repeated when clinically indicated. CMDC was performed before therapy and repeated before each cycle.

Toxicity was evaluated according to the CTC scale. Patients were evaluable for hematological toxicity if at least weekly CBC counts with differential were available for a minimum of three weeks. Patients were evaluable for non-hematological toxicity after at least one day of treatment.

At each dose level, safety analyses were performed on the total number of evaluable cycles at that particular dose, regardless of previous intrapatient dose escalations. In patients with measurable or evaluable disease, tumor response was assessed after two cycles and classified according to WHO criteria [5]. Responding patients or patients with stable disease continued treatment until tumor progression or unacceptable toxicity whichever occurred first, while patients with progressive disease went off study.

Drug administration

BBR was supplied by Novuspharma (Milano, Italy) as 0.5 mg/1 ml vials to be stored at 2–8 °C. The requested daily amount of drug was diluted and administered in 500 ml of normal saline as an intravenous infusion over one hour for five consecutive days. Therapy was repeated every 28 days. A pre- and post-hydration of 1000 ml of normal saline given over one hour was administered on all days of treatment. Antiemetic prophylaxis was not routinely administered. Intravenous 5-HT$_3$ antagonists were prescribed in instances of vomiting on the days of treatment. Oral thiethylperazine (6.5 mg t.i.d.) for nausea, oral loperamide (4 mg after the first stool, then 2 mg every 2 hours up to 12 hours after the last stool) was prescribed in case of diarrhea. Finally, antibiotic prophylaxis (ciprofloxacin 500 mg b.i.d.) was recommended in case of ANC of $< 0.5 \times 10^9$/l up to a ANC of $> 1.0 \times 10^9$/l.

Pharmacokinetics

Pharmacokinetic studies of BBR3464 were performed in nine patients on days 1 and 5 of the first cycle.

Blood samples (8 ml) from indwelling catheters in the arm contralateral to the one with drug infusion were collected into heparinized

tubes before and then at 60', 90', 2, 3, 4, 6, 8, 10, 24 hours from the start of the infusion Additional samples were taken before the daily administration on days 3 and 4, and in selected cases on days 8 and 15. Urines were collected on day 1 as eight-hour fractions, and two aliquots of 8 ml each were taken from each fraction and stored at −20 °C or colder until analysis.

Blood was immediately centrifuged after collection (2000 × *g* for 10 min at 4 °C), plasma was separated from pellets and divided in two aliquots. One aliquot of 1 ml was stored at −20 °C or colder for total Pt analysis, and the other for preparation of plasma ultrafiltrate using Millipore Ultrafree Filters (10,000 MW cut off) for free platinum analysis. The filters were centrifuged at 4000 × *g* for 15 minutes at 4 °C and the ultrafiltrate stored frozen at −20 °C or colder.

Total and free Pt concentrations in plasma, tissue and urine were assessed by ICP-mass spectrometry (ICP-MS), and expressed as BBR3464 equivalent concentrations.

A calibration curve in the range of platinum concentrations 0.01–200 ng/ml was prepared using the standard addition method by adding Pt standard solution to plasma for the determination of total Pt and to ultrapure water for the analysis of ultrafiltrate and urine. Linear responses were observed in the working range with a correlation coefficient $r > 0.998$. The quantitation limit (LOQ) was 0.01 ng/ml, with an inter-days precision expressed as coefficient of variation (CV) of 7.5%. The inter-assays CV determined at the upper point (200 ng/ml) of the calibration curve was 0.3%.

Biological samples were diluted in the range of concentrations of the calibration curve to varying degrees (1/10 or 1/100 v/v) with ultrapure water (Milli-Ro, Mill/Q, Millipore). Analytical procedure and validation data will be reported in details in a separate paper. The method has been validated according to international standards [6].

Pharmacokinetic parameters were derived from the individual plasma BBR 3464 concentration-time profiles on days 1 and 5, according to a non-compartmental approach using a general non-linear fitting program [7]. Samples taken on days 8 and 15 were not included in the evaluation of pharmacokinetic parameters.

Table 1. Patient characteristics.

Total number of patients	14
Sex	
Female	10
Male	4
Age (in years)	
Median	51
Range	41–70
Prior therapy	
Chemotherapy alone	11
Chemo- and radiotherapy	3
Prior platinum compounds	8
Prior extensive therapy	10[a]
Tumor types	
Ovary	5
Colorectal	3
Non-small-cell lung	1
Other	5

[a] ⩾ 2 chemotherapy regimens ± radiotherapy.

Table 2 Number of evaluable patients and cycles per dose level.

Dose level	Dose (mg/m²/d)	Number of patients/cycles		
		Total	Entry dose	Dose modified
1	0.03	1/1	1/1	
2	0.06	4/6	2/4	1/1 escalated from level 1; 1/1 deescalated from level 3
3	0.12	6/12	5/10	1/2 escalated from level 2
4	0 14	3/3	3/3	
5	0.17	3/3	3/3	

Results

From November 1998 to September 1999, 14 patients entered the trial, 5 in the accelerated dose escalation phase and 9 in the standard phase. The patient characteristics are reported in Table 1. Their median age was 51 years (range 41–70), and the median PS 0 (range 0–2). All patients had already received chemotherapy, 8 of them with cisplatin and/or carboplatin, with a median of 131 days since the last course (range 31–490 days).

Table 2 lists the number of patients and cycles, either initial or subsequent, at entry or modified dose, administered at each of the five dose levels, from 0.03 mg/m² to 0.12 mg/m². A total of 25 cycles were administered, of which one at 0.06 and two at 0.12 mg/m² were due to intrapatient dose escalation from the previous dose level, while an additional one at 0.06 mg/m² was due to dose-reduction because of severe abdominal pain, nausea and vomiting.

Hematological toxicity

Neutropenia, which represented the main toxicity, was dose-limiting and short-lasting. At all doses, the median time to ANC nadir was 14 days (range 9–18 days) and the median time to ANC recovery was 18 days (range 12–28 days). Time to recovery was longer at the higher dose levels. No other hematological toxicities were observed.

Together with diarrhea, neutropenia was one of the toxicities on which dose escalation was based. The dose was first doubled from 0.03–0.06 and then to 0.12 mg/m². No DLT was observed in the first three patients treated at 0.12 mg/m², with grade 1 neutropenia in one out of two patients receiving 0.12 as entry dose and grade 3 neutropenia in one patient already treated at 0.06 mg/m². However, because of the occurrence of diarrhea grade 1 in one patient and grade 2 in two patients, the dose was cautiously escalated by 25% only to 0.17 mg/m². At this level, two of three patients developed febrile neutropenia and grade 3 diarrhea, prompting the assessment of an intermediate dose of 0.14 mg/m² in three additional patients, all of whom had received three prior chemotherapy regimens. Also at this dose, two patients suffered a DLT consisting of grade 4 diarrhea in one case and febrile neutropenia in the other. The dose level of 0.12 mg/m² was therefore expanded by treating three further patients with a maximum of two prior chemotherapy regimens. One patient developed grade 4 neutropenia and a second one febrile neutropenia after the first cycle. Based on these findings, and on the observations made in the other patients initially treated at the same level, the dose of 0.12 mg/m² was defined as the MTD.

Table 3 Hematologic toxicity.

Dose level	Dose ($mg/m^2/d$)	No. of cycles	Hemoglobin at nadir (g/dl), median (range)	Platelets at nadir ($\times 100/mm^3$), median (range)	Neutrophiles at nadir ($/mm^3$)					
					Median (range)		Number of courses with grade 3		Number of courses with grade 4	
					First cycle	Subsequent cycles	First cycle	Subsequent cycles	First cycle	Subsequent cycles
1	0.03	1/0	13.2	227	2470	–	–	–	–	–
2	0.06	2/4	10.3 (9–13.2)	297 (243–412)	468, 1702	1658 (864–2332)	0	1	1	0
3	0.12	5/7	9.1 (8.3–13.7)	246 (128–420)	1800 (153–3141)	392 (176–1536)	0	2	2 (1)[a]	4
4	0.14	3/0	8.8 (8.5–9.4)	196 (139–225)	545 (81–2442)	–	1	–	1 (1)	–
5	0.17	3/0	10.8 (7.9–11.2)	155 (129–247)	370 (198–549)	–	1	–	2 (2)	–

[a] In brackets, number of cycles with febrile neutropenia.

Febrile neutropenia requiring hospitalization, also because of concomitant diarrhea, was reported in four occasions during the first cycle, at 0.12 and 0.14 mg/m^2 in one case each, and in two out of three patients treated at 0.17 mg/m^2 (Table 3). Neutropenia was not cumulative, and with a steep dose-response curve.

Thrombocytopenia was never observed while anemia was only mild to moderate.

Non-hematological toxicity

Diarrhea, the main non hematological side effect, represented the other DLT with features of late appearance, almost concomitantly with neutropenia, preceded by abdominal cramps, and steep dose-response curve. Drug-related diarrhea was first observed at 0.06 mg/m^2, became universal at the two highest dose levels and could be controlled if loperamide was introduced early. Possible risk-factors such as previous treatment with 5-FU, pelvic RT and Irinotecan could not be identified because very few patients had received that type of treatment before BBR3464 administration. Hospitalization due to GI symptoms occurred in seven cycles: diarrhea was the main symptom in three, and abdominal cramps in four cases.

Other toxicities included: paresthesia grade 1 in one patient treated at 0.12 mg/m^2; alopecia grade 1 in three patients and grade 2 in one patient, all treated at 0.12 mg/m^2; nausea grade 3 in one patient at 0.12 mg/m^2 and in one at 0.14 mg/m^2; vomiting grade 3 in one patient at 0.12 mg/m^2 and in one at 0.14 mg/m^2.

Neither renal nor neurological toxicity were observed.

Antitumor response

No objective responses were observed. One patient with pancreatic adenocarcinoma, pretreated with gemcitabine and abdominal irradiation, presented a decrease of CA 19.9 after BBR at 0.12 mg/m^2 with stabilization of tumor recurrence for four months. One patient treated at 0.12 mg/m^2 for ovarian carcinoma and tumor progression after paclitaxel, carboplatin and topotecan showed a 50% decrease of CA125 levels with stabilization of abdominal and pelvic recurrence. Treatment was discontinued after three courses because of cumulative diarrhea and GI symptoms.

Pharmacokinetic results

The pharmacokinetics of BBR3464 on days 1 and 5 were studied in nine patients treated at doses ranging from 0.03–0.17 mg/m^2. Figure 2 shows the plasma pharmacokinetic profile of total and free Pt of three patients treated at 0.06 mg/m^2 (1 patient) and 0.17 mg/m^2 (2 patients). Both platinum species showed a similar plasma disposition with a distribution phase of 1–2 hours followed by a prolonged elimination phase longer than 24

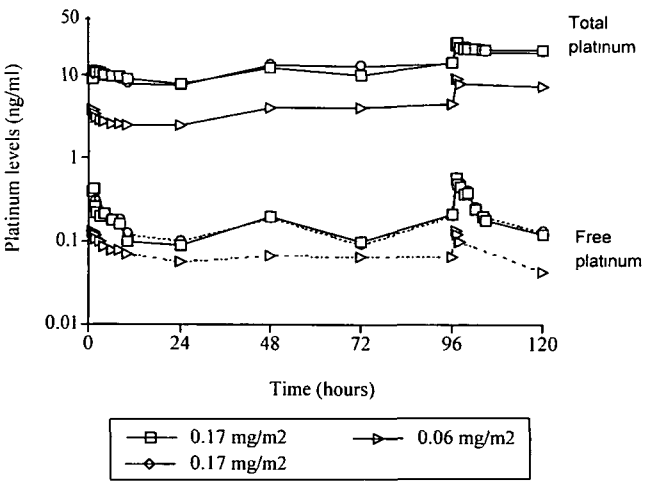

Figure 2. Plasma levels of total and free platinum in three patients receiving BBR3464 daily for five consecutive days.

Table 4. Non-hematologic toxicity.

Dose level	Dose ($mg/m^2/d$)	Number of patients/ cycles	Cycles with all grades toxicity (grade 3, 4 or worst grade)						
			Nausea	Vomiting	Diarrhea	Abdominal pain	Fatigue	Mucositis	Others
1	0.03	1/1	0	0	0	2	0	0	0
2	0.06	4/6	1	1	3	1	2	0	1 infection (1)
3	0.12	6/12	6 (1)	5 (1)	7 (1)	4 (1)	2	3	2 fever (1) 2 hypertension (1)
4	0.14	3/3	2 (1)	2 (1)	3 (1)	1	1	1	1 loss of appetite (1) 1 infection (1)
5	0.17	3/3	1	1	3 (2)	0	1 (1)	1	1 loss of appetite (1)

In brackets, number of cycles with grade 3–4 toxicity.

Table 5. Pharmacokinetic parameters of total and free Pt after treatment with BBR3464 daily for five consecutive days.

Patient number	Dose ($mg/m^2/d$)	Total platinum					Free platinum				
		Cmax (ng/ml)		AUC (ng/ml/h)			Cmax (ng/ml)		AUC (ng/ml/h)		
		Day 1	Day 5	Day 1	Day 5	D5/D1[a]	Day 1	Day 5	Day 1	Day 5	D5/D1[a]
1	0.03	1.5	2.9	18	42	2.4	0.02	0.02	–	–	–
2	0.06	3.9	9 1	62	–	–	0.13	0.14	1.7	–	–
3	0.06	3.7	8.2	57	148	2.6	0.12	0.12	1.8	1.4	0.8
4	0.12	6.9	16.4	116	318	2.7	0.22	0.23	3.2	2.7	0.8
5	0.12	8.1	23.5	158	466	2.9	0.31	0.28	3.6	3.9	1.1
6	0.14	7.3	15.4	133	270	2.0	0 36	0.41	4.7	6.6	1.4
7	0.14	10.2	28.7	210	502	2.2	0.45	0.48	7.6	7.5	1.0
8	0.17	11.1	23.0	200	465	2.3	0 40	0.56	3.5	5.5	1.6
9	0.17	11.2	25.2	212	489	2.3	0.43	0.59	3.2	5.2	1.6

[a] Ratio AUC day 5/AUC day 1.

hours. The planned sampling times, limited in many cases to 24 and 72 hours after the end of the fifth administration, did not allow a reliable evaluation of the terminal half-life of total and free Pt. However, in 5 patients sampled longer than 72 hours, Pt levels were still detectable on day 15, with concentrations of about half the Cmax of both Pt species.

Table 5 reports Cmax, $AUC_{(0-24)}$ and the ratio of the $AUC_{(0-24)}$ on days 5 and one for both the total and free Pt species. At all dose levels, the values of Cmax and $AUC_{(0-24)}$ of total Pt on day 5 were twice as high as those on day 1. The Cmax and AUC of free Pt increased 1.5 times, and did so only at the highest dose level.

As shown in Figure 3 Cmax and AUC of total Pt appeared to be linearly related to the dose ($r = 0.950$). A similar relationship was also observed for free Pt (data not shown).

Approximatively 10% of the dose administered was recovered in the 24-hour urine fraction on day 1.

The Pt content was assessed in several tissues from one patient with ovarian and breast tumors, who died 28 days after the first cycle at 0.14 mg/m^2. Measurable Pt levels were still present in tumor, ascites and several other tissues, mainly kidney and lung (Table 6).

Discussion

The novel triplatinum complex BBR3464 was selected for clinical development because of a promising preclinical profile. In comparison with cisplatin, the different interaction with DNA, the good antitumor activity in several xenograft models irrespective of their pattern of sensitivity/resistance to CDDP, and the forty-fold higher potency of BBR3464 supports the concept that this new drug may play an important role in humans.

Based on the observation that lung toxicity in mice and dogs was more extensive after i.v. bolus than slow infusion, we selected to evaluate a daily × 5 schedule in humans, while other investigators performed an assessment of the conventional single intermittent regimen [8]. An accelerated titration design version 4B could be applied taking into account the toxicity information provided by the already ongoing single intermittent study.

The starting dose of 0.03 mg/m^2/daily, corresponding to 1/10 MEMTD and to a total dose of 0.15 mg/m^2 per cycle, could be doubled based on the absence of toxicity in only one patient because the doses of 0.2 mg/m^2 and 0.4 mg/m^2 had already been tested and proven safe in the ongoing trial adopting the single intermittent schedule.

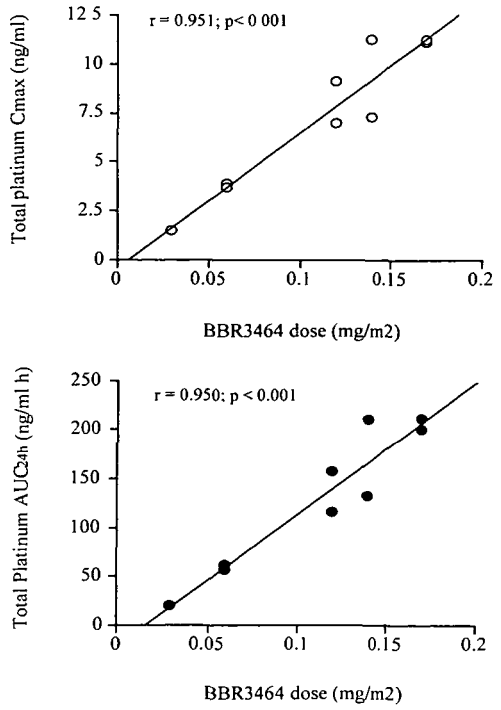

Figure 3. Correlation between dose and both Cmax and AUC of total platinum on day 1.

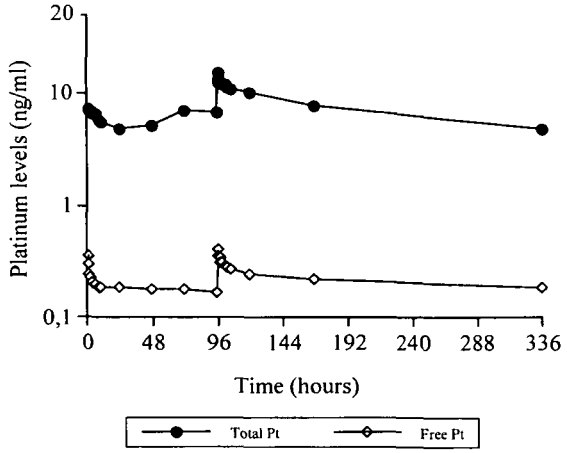

Figure 4. Plasma levels of total and free platinum in a patient who received 0.14 mg/m2 of BBR3464 given daily for five consecutive days.

An intensive regimen of hydration and close assessment of renal function was maintained in the study based on the concern that the repeated administration could cause cumulative renal effects. To rule out lung toxicity, CMDC had to be checked after cycles 1 and 2.

The accelerated titration design version 4B proved successful in speeding completion of the study and reducing the number of patients treated at potentially sub-therapeutic doses [4]. In fact, 5 dose levels were assessed in a total of 14 patients over 25 evaluable cycles. Overall, 12 patients and 18 cycles were evaluable at doses corresponding to the MTD or higher, and only two patients received non toxic, and potentially subtherapeutic doses.

As observed for other platinum compounds [9], at all dose levels of BBR3464 the clinical results qualitatively

Table 6. Pt levels in tissues and in plasma 28 days after treatment with BBR3464 (0.14 mg/m^2/day).

Tissue	Pt (ng/g)
Lung	16
Kidney	32
Brain	<0.01
Liver	10
Heart	16
Intestine	8.5
Breast ca.	3.4
Ovarian ca.	3.7
Lymphnode	8.5
Ascite	3.1[a]
Plasma (ultrafiltrate)	2.0[a] (0.09)[a]

[a] ng/ml.

confirmed the toxicology data, so that dose-limiting toxicities were neutropenia and GI effects, and the reduced emetic potential and neurotoxicity were confirmed, while no renal toxicity was observed. Based on these findings, we conclude that BBR3464 can be administered as an outpatient treatment, without hydration, and without routine antiemetic prophylaxis.

Of note, the clinical results did not confirm significant effects on the lung. The lack of significant alterations of CMDC may depend on a variety of reasons, including daily regimen, short duration of treatment and interspecies differences. In view of the clinical development of a single intermittent schedule and the potential role of BBR3464 in the treatment of lung cancer, however, it is recommended that the evaluation of lung function after repeated administrations and a careful selection of patients should be performed in phase II studies. Neutropenia, appearing one week after treatment and recovering in the following week, was the main DLT and defined the MTD at 0.12 mg/m^2/d. Late diarrhea, concomitant with neutropenia, was the other DLT; this toxicity appeared without identified risk-factors, and was responsive to an aggressive treatment with loperamide. Both DLTs showed a very steep dose-response curve, with a 0.06 mg/m^2/d dose interval between non toxic doses and the MTD.

The decision to apply only a 25% increase of the dose, from 0.12 mg/m^2 to 0.17 mg/m^2 even though toxicity did not reach the criteria of dose-limiting, was made on the basis of the toxicity profile of the compound. In fact, the occurrence of diarrhea increased significantly from 0.06 mg/m^2 to 0.12 mg/m^2 where it was reported in the first three patients treated, suggesting that a subsequent comparable increase of the dose might result in very severe toxicity. Neutropenia and diarrhea were dose-limiting also with the single intermittent schedule for which a higher recommended dose of 1.1 mg/m^2 was established (H. Calvert, personal communication). The intermittent dose schedule was selected for further development and is undergoing extensive phase II clinical evaluation.

Pharmacokinetic studies were performed by applying a very sensitive ICP-MS assay, with a high sensitivity

quantitation limit of 0.01 ng/ml, that allowed us to determine total and free Pt concentrations even in patients receiving submilligram doses of BBR3464.

The available pharmacokinetic data achieved in the whole range of the doses tested, from 0.03 to 0.17 mg/m^2, indicate that BBR3464 has linear kinetics. Both Cmax and $AUC_{(0-24)}$ increased proportionally with increasing doses. The linear relationship is present for both Pt species.

In this study, BBR3464 showed a slow elimination rate from the plasma compartment, with an apparent terminal half-life of several days. The prolonged terminal phase explains the cumulation of total, but also (at high dose) of ultrafiltered Pt, as shown by the increased $AUC_{(0\ 24)}$ d5/$AUC_{(0-24)}$ d1 ratio in plasma. Of note, the disposition of BBR3464 showed a quite limited interpatient variability.

The prolonged elimination half-life might explain the reduced tolerability of the daily regimen compared to the intermittent regimen and discourages its further clinical development.

Another distinctive and clinically relevant pharmacokinetic feature of BBR3464 is the reduced urinary excretion, accounting for only about 10% of the administered dose in the 24-hour following treatment. The low urinary excretion is in good agreement with the lack of clinical renal toxicity. Based on these findings, we conclude that BBR3464 can be administered as an outpatient treatment, without hydration, and without routine antiemetic prophylaxis.

In the present study, all patients had normal liver and renal function and information on pharmacokinetic behaviour in case of liver or renal impairment could not be provided. The reduced urinary excretion, however, suggests that full doses of BBR3464 could be administered also in instances of creatinine clearance in the range of of 40–60 ml/min.

Tissue distribution was studied in one patient who died 28 days after the first cycle at 0.14 mg/m^2. Measurable Pt levels were found in tumor, ascites and many other tissues, but most notably in lungs and kidneys.

In conclusion, the results of this study have confirmed the preclinical data that the trinuclear platinum complex BBR3464 is a new platinum analog with dose-limiting neutropenia, diarrhea, no renal or neurotoxicity, and decreased emetic potential.

The parallel pharmacokinetic study showed that the drug has a prolonged elimination half-life, that may partly explain the higher than expected toxicity of the d × 5 schedule.

The pharmacokinetic data in patients are consistent with preclinical observations in mice and dogs, where BBR3464 plasma concentrations declined in a multi-exponential fashion after i.v. administration, with a rapid, short decline related to the distribution phase followed by a slow and prolonged elimination phase, with half-life of 27 hours (mouse) to 58 hours (dog) [1].

The prolonged permanence of BBR3464 in the systemic circulation is likely due to low renal and hepatic drug extraction ratios, and a high protein binding. The unbound fraction of BBR3464 in patients approaches 2% over the entire observation interval. Differently from cisplatin and carboplatin, most drug is bound to plasma proteins at early times after the administration but the free drug is available in the circulation for a long time after dosing.

These human pharmacokinetics data have been and are of great value in guiding the clinical development of BBR3464.

The implementation of a 4B accelerated titration design, tailored to the clinical pattern of toxicity of the drug, resulted in the rapid but safe completion of the study with very few patients treated at doses below the MTD.

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