Phase I clinical and pharmacokinetic study of BBR 3576, a novel aza-anthrapyrazole, administered i.v. every 4 weeks in patients with advanced solid tumors: a phase I study group trial of the Central European Society of Anticancer-Drug Research (CESAR)

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BBR 3576 is a novel aza-anthrapyrazole with limited potential for cardiotoxicity in preclinical models. This phase I clinical and pharmacokinetic study was performed to determine the maximum tolerated dose, the dose-limiting toxicity (DLT) and the pharmacokinetic profile of BBR 3576 administered i.v. as a 1-h infusion repeated every 4 weeks. In total, 27 patients were treated at doses starting from 1 to 150 mg/m^2. The dose levels 1, 2, 4, 8, 16, 32, 64, 90, 125 and 150 mg/m^2 were investigated in one, three, one, three, two, one, three, four, three and six patients, respectively. The DLT was a grade 3 stomatitis at 150 mg/m^2. At this dose level as well as at 125 mg/m^2, neutropenia grade 3 and 4 were frequently seen, but not reaching the criteria for DLT. Time to neutrophil nadir was about 2 weeks and recovery took place within 1 week. Other bone marrow toxicities were mild; lymphopenia was also observed. No significant drug-induced cardiotoxicity was observed. The plasma concentration versus time curves of BBR 3576 showed a biexponential profile with a linear kinetic behavior. A very large volume of distribution, a high plasma clearance and long elimination half-lives were calculated. Renal unchanged drug excretion was less than 10% and therefore a minor excretion route. No objective antitumor responses were found. On the basis of this study, the recommended dose for phase II studies is 150 mg/m^2, although the maximum tolerated dose as per protocol definition was not reached. This trial showed that BBR 3576 has a manageable toxicity profile on a 4-week schedule. Phase II studies have started in patients with solid tumors, as suggested by preclinical data in different *in vivo* model systems. *Anti-Cancer Drugs* 15:15–22 © 2004 Lippincott Williams & Wilkins.

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Introduction

Anthracyclines are one of the most active antitumor drugs and are clinically efficacious against a wide range of tumors [1]. One major limitation of anthracyclines is the cumulative cardiotoxicity caused by the generation of free radicals during drug processing in cardiac cells [2]. The risk for developing a significant congestive heart failure exceeds 5% above a cumulative doxorubicin dose of 550 mg/m^2 (or about 900 mg/m^2 in case of epirubicin) [3,4]. The very effective drug combination doxorubicin–paclitaxel is hampered by the fact that this combination presents unacceptable cardiac risks when the doxorubicin dose exceeds 360 mg/m^2 (which means after six treatment cycles) [5]. Parallel to the development of cardioprotective agents such as dexrazoxone [6], development of new compounds with less cardiotoxicity potency is still the other strategy to overcome this problem.

BBR 3576 is a hetero-analog of the anthrapyrazole class of compounds (Fig. 1) [7]. The mechanism of action of BBR 3576 is similar to that of mitoxantrone in terms of DNA intercalation, DNA affinity, topoisomerase II interaction and formation of single-strand breaks. BBR 3576 showed curative antitumor activity at the maximum tolerated dose (MTD) with a number of long-term survivors, and showed greater activity than mitoxantrone and doxorubicin in preclinical studies. BBR 3576 retained a high level of activity across a wide range of doses. In human xenograft studies equivalent antitumor activity was

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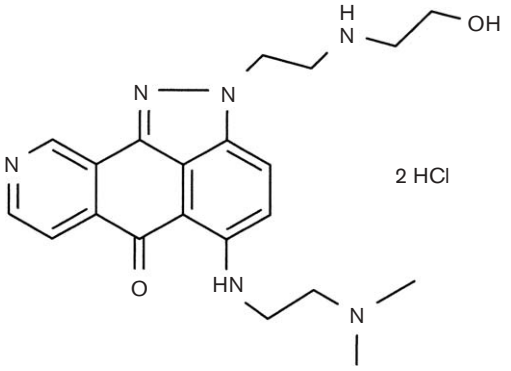
Fig. 1



Chemical structure of BBR 3576.

observed when compared with doxorubicin and mitoxantrone [8]. The compound showed reduced cardiotoxicity when repeatedly administered in rodent models [9].

Pharmacokinetic data from mice indicated a rapid decline in drug concentrations during the distribution phase, followed by a slower and prolonged elimination phase with a half-life of 17.2 h. The drug was widely distributed throughout the body, which suggested that BBR 3576 has a large volume of distribution (Novuspharma, data on file).

The aims of this phase I study were: (i) to determine the MTD when administered i.v. every 4 weeks to patients with cancer, (ii) to establish the toxicity profile of BBR 3576, (iii) to determine the pharmacokinetics at different dose levels, (iv) to define a safe dose for phase II evaluation, and (v) observe and record any therapeutic efficacy of BBR 3576.

Patients and methods

Eligibility

Patients with histologically proven, progressive malignant solid tumors were eligible for the study. Other eligibility criteria were: age ≥ 18 years; ECOG PS 0-2; no chemotherapy within 4 weeks preceding the study; adequate hematopoietic (WBC $\geq 4000/\mu l$, ANC $\geq 2000/\mu l$, thrombocytes $> 100/nl$), hepatic (bilirubin < 1.5 mg/dl, ALAT and ASAT < 2.5 times upper normal limit) and renal function (creatinine clearance ≥ 60 ml/min); absence of pregnancy; absence of acute infections; absence of heart disease; absence of brain metastasis and/or other neurological disorders; absence of persistent toxicity from prior therapy.

Study design

The study was performed according to German drug regulations. The protocol was approved by the ethics committees of all participating centers. Assessments performed prior to therapy included physical examination, vital signs, blood cell counts including differentiation of WBC, serum chemistry, electrocardiogram, evaluation of left ventricular function (LVF) by cardiac ultrasound, chest X-ray and tumor measurements by ultrasound or computed tomography scans. During treatment, patients had weekly assessments of blood counts, physical examination and evaluation of drug-related toxicity using the NCI-CTC grading system, version 2.0 March 1998. The evaluation of LVF was repeated every two treatment cycles or if clinically indicated. Response evaluation was performed after each two treatment cycles using the RECIST criteria [10]. Patients were withdrawn from the protocol in case of tumor progression, severe adverse events, incompliant patient or patient refusal.

Drug administration

BBR 3576 was supplied by Novuspharma (Bresso, Italy) in vials containing 50 mg of lyophilized sterile drug. Before infusion, the drug was diluted in 500 ml of physiological saline. BBR 3576 was administered as an i.v. infusion over 1 h on day 1, repeated every 4 weeks.

Dose escalation procedure, MTD and dose-limiting toxicity (DLT)

An accelerated titration design was used, followed by a standard phase design. The starting dose was 1 mg/m^2 and doubled until adverse events had been observed (DLT or grade ≥ 2 toxicity). After drug-related toxicity was observed and the accelerated phase ended, the dose escalation steps in the standard phase were of 40%. The decision to escalate the dose was based on toxicity observed in the first cycle. No intra-patient dose escalation was allowed. DLT main criteria were defined as any of the following events: grade III non-hematological toxicity (excluding alopecia, nausea and vomiting); grade IV nausea; grade IV hematological toxicity on platelets and hemoglobin; grade IV granulocyte toxicity of $\geq$ 7-day duration or febrile neutropenia. The MTD was defined as the dose where two or more out of six patients feature a DLT.

Once the MTD was reached, the recommended dose for phase II studies could be identified.

Pharmacokinetic study

Plasma and urine were sampled during the first treatment cycle in all patients included in this study to determine the BBR 3576 concentration. Blood samples (8 ml) were collected in heparinized tubes immediately before drug administration, and 0.5 and 0.95, 1 (end of infusion), 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 32 to 36, 48 and 72 h after start of infusion. The blood samples were immediately centrifuged (1500 *g*, 15 min) and plasma was frozen at -20°C for subsequent analysis. A urine sample collected

from a period before treatment was used as control. A fractional 72-h urine collection was performed every 4 h during the first 12-h period; thereafter at 12-h intervals. The total volume of each fraction was accurately measured and recorded. Aliquots were stored at –20°C till analysis.

HPLC analysis

BBR 3576 was determined in plasma and urine samples using a validated method (Novuspharma, data on file). The method involves a solid-phase extraction of BBR 3576 and the internal standard (BBR 3588) from the biological samples followed by reversed-phase HPLC at room temperature with fluorimetric detection (excitation wavelength 220 nm, emission wavelength 520 nm). The interday precision and accuracy ranged respectively from 2.9 to 4.9% (CV) and 94.6 to 97.6% in plasma, and from 2.3 to 8.6% and 96.2 to 104.0% in urine. The limit of quantitation (LOQ) was 5 ng/ml and the limit of detection (LOD) 2.5 ng/ml. All analyses were performed according to GLP.

Data analysis

Individual plasma concentration–time curves were analyzed by a model-independent approach (WinNonlin Pro 2.1;. Pharsight, Mountain View, CA). The following parameters were calculated for unchanged BBR 3576: maximum concentration (C_{max}); apparent terminal half-life ($t_{1/2,z}$), calculated from the rate constant associated to the apparent terminal phase, estimated by log-linear regression analysis; area under the plasma concentration time curve from time zero to t_f (the last sampling at which BBR 3576 was measurable, usually 72 h), $AUC_{(0-tf)}$, calculated by the linear trapezoidal rule, and to infinity (AUC); AUC normalized for the administered dose (AUC/D); mean residence time (MRT), calculated as the ratio between the area under the first moment curve (AUMC) and the AUC; systemic clearance (CL), calculated as CL = D/AUC, where D is the administered dose; volume of distribution at steady state, calculated as $V_{ss} = -CL \cdot MRT$.

The amount of drug excreted in urine in each time interval and cumulatively over 72 h, $A_{e(0-72)}$,was calculated by multiplying the drug concentration in each fraction by the corresponding total fraction volume. By dividing $A_{e(0-72)}$ for the administered dose, we estimated the fraction of dose excreted unchanged in urine, $f_{e(0-72)}$. The renal clearance was calculated as $CL_R = A_{e(0-t_f)}/AUC_{(0-t_f)}$ in which $A_{e(0-t_f)}$ is the amount of BBR 3576 excreted in urine in the time interval from 0 to t_f, often equal to 72 h.

Results

A total of 27 patients, whose characteristics are reported in Table 1, were treated with BBR 3576 over 10 dose levels and a total of 48 cycles. All of the patients were evaluable for toxicity. The following dose levels were studied: 1, 2, 4, 8, 16, 32, 64, 90, 125 and 150 mg/m^2.

Table 1 **Demographic data of the patients enrolled in the pharmacokinetic study with BBR 3576**

Patient no.	Patient ID	Gender	Age (years)	Dose (mg/m^2)	Body weight (kg)	BSA (m^2)	Serum creatinine (mg/dl)
101	HL	M	66	1	81.0	1.96	1.10
102	ES	F	55	2	62.0	1.60	0.80
103	KD	M	61	2	118.0	2.36	1.10
104	AR	M	64	2	102.0	2.14	0.90
301	ME	M	66	4	76.0	2.00	0.70
105	AF	M	52	8	74.0	1.96	1.00
106	NH	M	33	8	63.0	1.85	1.20
201	EK	M	75	8	83.0	2.00	0.85
107	HM	F	51	16	72.0	1.84	0.70
202	EG	F	64	16	90.0	2.00	0.69
302	GI	F	63	32	74.0	1.84	0.60
108	BM	M	53	64	73.0	1.89	0.80
203	GC	F	67	64	75.0	1.80	0.86
303	JG	M	53	64	64.0	1.74	1.10
109	GC	M	58	90	64.0	1.68	1.30
204	KK	F	56	90	72.1	1.70	0.65
205	SC	F	59	90	56.4	1.60	0.70
206	EO	M	72	90	74.0	1.90	0.92
110	GB	F	52	125	64.0	1.60	0.30
207	AP	F	53	125	82.2	1.95	0.80
208	AP	F	56	125	78.0	1.90	0.82
111	ES	M	70	150	69.2	1.74	0.80
112	BL	F	61	150	78.7	1.82	1.10
209	BR	M	69	150	82.3	2.00	0.80
210	HF	M	72	150	71.0	1.90	0.70
211	EB	F	39	150	105.0	2.00	0.68
212	KB	M	60	150	87.0	2.00	0.93
Mean			59.3		77.4	1.88	0.85
SD			9.7		13.9	0.17	0.21

A dose-dependent myelosuppression was the principal toxicity of this regimen.

Hematological toxicity

Myelotoxicity was the most common toxicity observed with BBR 3576. Neutropenia was the main myelotoxicity observed. Hematological toxicity is summarized in Table 2.

The WBC nadir was observed after approximately 2 weeks with a recovery time of about 1 week. At the doses of 90, 125 and 150 mg/m^2 the median ANC nadir was 1.05 (0.85–1.57), 0.7 (0.4–1.2) and 0.9 (0.4–2.7) $\times 10^9$/l, respectively. The ANC nadir occurred in approximately 2 weeks with a recovery time of 1 week. Platelet count and hemoglobin concentration occasionally decreased in patients treated with the highest doses, without reaching clinically significant low values.

Non-hematological toxicity

The most frequent toxicities were nausea, vomiting, pyrexia as well as fatigue. Non-hematological toxicities are listed in Table 3.

These toxicities were never dose limiting. Stomatitis grade 3 (dose limiting) was observed in one of six patients at 150 mg/m^3. Alopecia was not observed at a significant degree. Cardiotoxicity as drop from 65 to 45 and 50% of the ejection fraction and angina pectoris was observed in one patient at the 1 mg/m^2 dose level. This finding was most probably due to a pre-existing coronary heart disease. At all other (higher) dose levels no signs of cardiotoxicity (defined as ECG changes or functional changes of the LVF) were observed.

Because only five patients received more than 2 cycles, no clear judgment is possible on the cumulative toxicity induced by BBR 3576.

Pharmacokinetic and pharmacodynamic study

After administration of doses of 64 mg/m^2 and higher, it was possible to measure BBR 3576 up to the last scheduled sampling time (72 h) and correctly describe its pharmacokinetic behavior. In patients receiving lower doses, BBR 3576 concentrations reached the limit of quantitation (5 ng/ml) at earlier times. For these patients, a reliable quantitation of most pharmacokinetic parameters was unfeasible. Semilogarithmic plots of individual BBR 3576 plasma concentration–time curves displayed a multiexponential kinetic profile (Fig. 2).

This behavior reflects a rapid distribution process from the plasma compartment to peripheral tissue compartments within 4–8 h, followed by a prolonged elimination phase. The individual values of the terminal half-life averaged from 35.8 to 58.9 h over the dose range 64–150 mg/m^2. At 150 mg/m^2 the mean half-life in six patients was 41.8 h. The maximum concentrations were most often observed at the end of the infusion and increased linearly with the dose increase (Fig. 3).

After administration of 150 mg/m^2, the recommended dose for phase II studies (RDPH2), C_{max} averaged

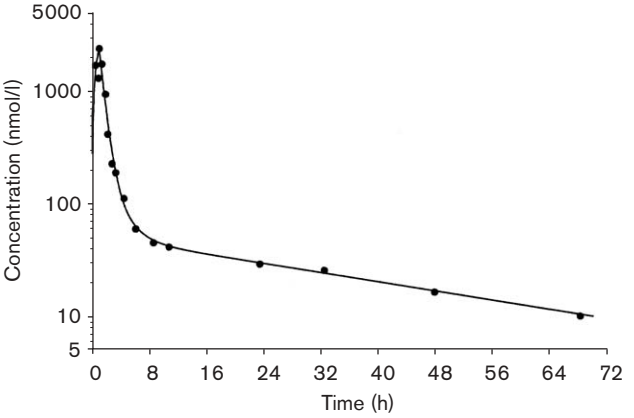
Table 2 Hematological toxicity: no. of patients with related hematological adverse events by worst grade for 90, 125 and 150 mg/m^2 dose levels (all cycles)

Adverse event (MedDRA code)	Grade			
	1	2	3	4
90 mg/m^2 (n=4)				
leukopenia		1	2	1
neutropenia		1	2	1
125 mg/m^2 (n=3)				
leukopenia		1	2	
neutropenia		1	1	1
150 mg/m^2 (n=6)				
leukopenia	2	3	1	
neutropenia		1	2	1

Table 3 Non-hematological toxicity: no. of patients with related non-hematological adverse events by worst grade for 90, 125 and 150 mg/m^2 dose levels (all cycles)

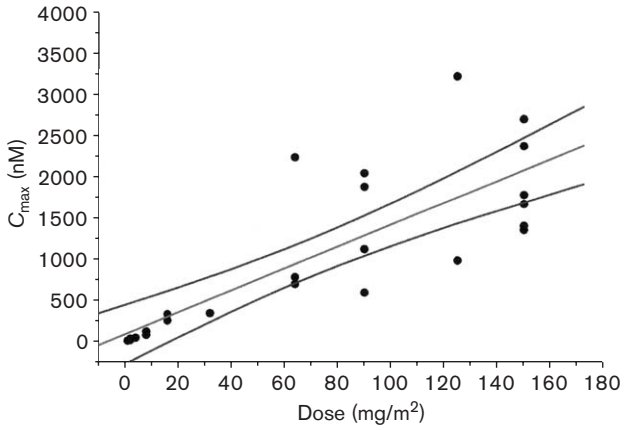
Adverse event (MedDRA code)	Grade			
	1	2	3	4
90 mg/m^2 (n=4)				
dyspepsia	1			
dysphagia	1			
nausea	1			
stomatitis	1			
fatigue	1			
pyrexia			1	
anorexia	1	1		
alopecia	1			
125 mg/m^2 (n=3)				
abdominal pain lower	1			
diarrhea nos		1		
dysphagia	1			
nausea	2			
vomiting nos	1			
fatigue	1	1		
weight decreased			1	
anorexia		1		
anxiety nec	1			
dysuria	1			
breast pain	1			
pneumonia nos		1		
alopecia	1			
dry skin	1			
150 mg/m^2 (n=6)				
diarrhea nos	1	2		
dyspepsia	1			
nausea	2			
stomatitis			1	
vomiting nos	2			
fatigue	2	1		
peripheral swelling		1		
pyrexia	3	1		
headache nos	1			
lung infection nos	1			
alopecia	2			
pruritus nos	1			
epistaxis	1			
phlebitis nos		1		

Fig. 2



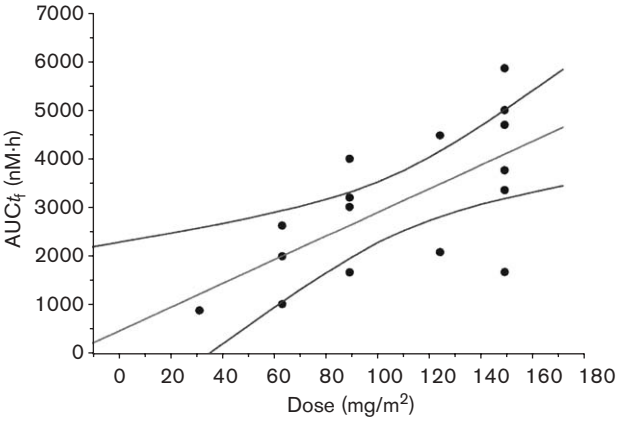
Concentrations of BBR 3576 in plasma of a representative patient after an i.v. infusion of 150 mg/m^2. The filled circles represent the experimental observations, the curve represents the fitting line (biexponential model, weighting factor $1/\ddot{y}^2$, in which $\ddot{y}$ is the predicted concentration).

Fig. 3



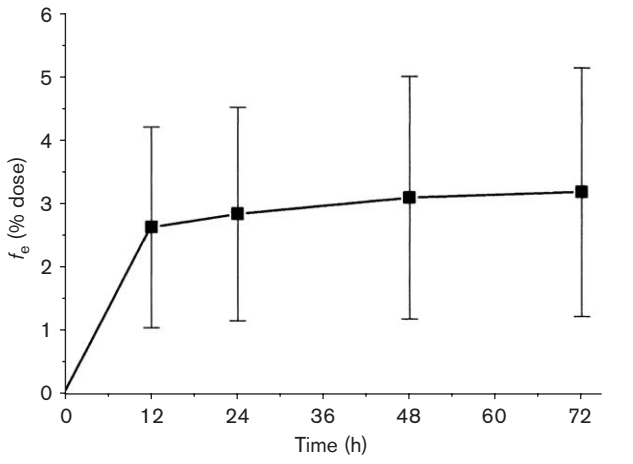
Correlation between C_{max} and administered dose. Regression line and 95% confidence interval. $Y = 90.14 + 13.26X$, $R^2 = 0.66566$, $p < 0.0001$.

Fig. 4



Correlation between AUC_{t_f} and administered dose. Regression line and 95% confidence interval. $Y = 472.05 + 24.43X$, $R^2 = 0.43554$, $p < 0.01$.

Fig. 5



Excretion of BBR 3576 in urine after administration of 150 mg/m^2. Mean values and SD ($n = 6$).

1877 nM.The $AUC_{(0-t_f)}$, which reflects the patient's systemic exposure to BBR 3576, correlated significantly with the administered dose (Fig. 4).

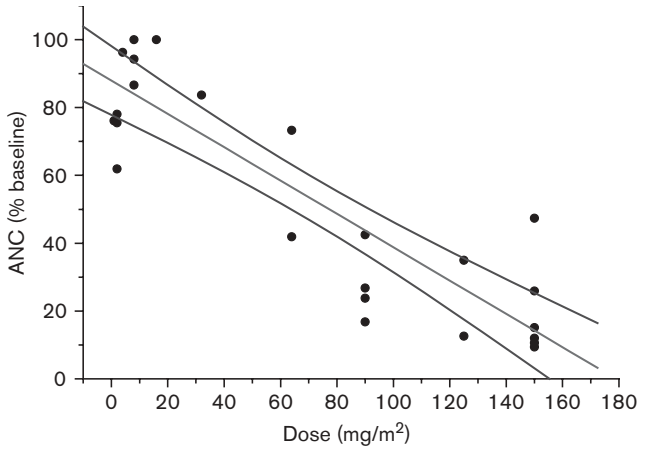
BBR 3576 has a high volume of distribution and a high systemic clearance; the values of these parameters are not affected by the dose increase from 64 to 150 mg/m^2, suggesting that BBR 3576 pharmacokinetics is linear. The amount of BBR 3576 in the plasma compartment is low when compared to the total amount in the body as deduced from the large volume of distribution; therefore, despite the high systemic clearance, the overall drug elimination from the body is prolonged. The calculated BBR 3576 total plasma clearance (1.86 l/h/kg at 150 mg/m^2) was greater than the sum of kidney and liver plasma flows (approximately 1.2 l/h/kg [11]). This observation suggests that further elimination routes, other than the kidneys and the liver, may exist that contribute to the overall drug elimination. Irreversible binding to organic macromolecules or accumulation in the red blood cells might contribute to the drug disappearance from the circulation. This observation is also consistent with the large volume of distribution ($V_{ss} = 44.3$ l/kg at 150 mg/m^2). The excretion of unchanged BBR 3576 in urine averaged 1.25–5.18%, with most of the excretion occurring in the first 12 h after administration (Fig. 5).

Table 4 Main pharmacokinetic parameters of BBR 3576 in patients after i.v. administration (1-h infusion)

	Dose (mg/m^2)							
	64 (n=3)		90 (n=4)		125 (n=2)		150 (n=6)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
C_{max} (nM)	1237.9	865.0	1407.7	676.9	2098.3	1579.8	1876.9	543.7
AUC_t (nM·h)	1914.3	815.5	3009.5	972.0	3314.4	1702.7	4096.5	1470.3
AUC (nM·h)	2614.8	1066.3	3832.3	1559.3	4351.0	1172.7	4933.1	1972.4
AUC/D (m^2·h/l)	0.019	0.008	0.020	0.008	0.016	0.004	0.015	0.006
$t_{1/2,z}$ (h)	42.1	20.9	35.8	10.6	58.9	21.5	41.8	25.0
V_{ss} (l/kg)	53.1	17.8	42.2	13.5	88.5	81.6	44.3	15.3
CL (l/h/kg)	1.56	0.80	1.48	0.62	1.53	0.38	1.86	1.05
MRT (h)	40.2	20.7	32.4	19.3	52.8	40.0	30.2	17.8
f_e (0–72) (%)	1.25	–[a]	3.15	2.82	2.45	–[a]	1.57	0.93
CLR (ml/h/kg)	30.2	–[a]	50.5	37.3	47.9	33.9	35.0	28.1
CLR/CL (%)	1.23	–[a]	3.53	3.00	2.94	1.48	3.71	1.19

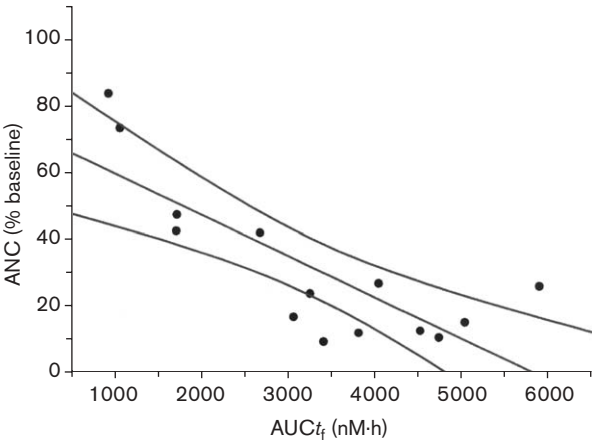
[a]SD was not calculated because data refer to one patient.

Fig. 6



Correlation between ANC at nadir (% decrease of baseline values) after the first cycle and the administered dose. Regression line and 95% confidence interval. $Y=87.96-0.4913X$, $R^2=0.78487$, $p<0.0001$.

Fig. 7



Correlation between ANC at nadir (% decrease of baseline values) after the first cycle and AUC_{t_f}. Regression line and 95% confidence interval. $Y=71.93-0.01235X$, $R^2=0.64279$, $p<0.001$.

After administration of 150 mg/m^2 the mean urine excretion was 3.2% (SD 2.0%) of the administered dose, indicating that renal excretion is a minor elimination route. The renal clearance was modest, ranging on average between 30.2 and 94.6 ml/h/kg, and far lower than the systemic clearance. The mean CL_R/CL ratio varied between 1.23 and 5.70%. The MRT at the highest dose averaged 30.2 h confirming the prolonged permanence of the drug in the systemic circulation. The mean values of pharmacokinetic parameters are listed in Table 4.

ANC values were measured in all patients at regular time intervals. The ANCs at nadir after the first administration, expressed as percentage of the baseline, were plotted against the administered dose and the exposure (AUC). The decrease of ANC correlates significantly with both dose and AUC (Figs 6 and 7).

Antitumor activity

No patient showed an objective response (partial or complete remission). Two patients received 4 cycles because they were stable after 2 cycles.

Discussion

The search for new compounds structurally related to anthracyclines or anthracenediones represents an ongoing challenge in the improvement of acute and long-term cardiac tolerance and efficacy for patients with highly anthracycline/anthracenedione-sensitive tumors like breast cancer, lymphomas and leukemias [12]. Anthracyclines like doxorubicin and epirubicin are the most often used drugs in adjuvant and palliative therapy protocols in breast cancer, and doxorubicin is the most often used drug in lymphoma, and daunorubicin and idarubicinan are the most often used drugs in leukemia. All four drugs feature a specific cumulative anthracycline-induced cardiomyotoxicity problem [1,3]. A second risk is up

through their potential to inhibit topoisomerase II. Topoisomerase II inhibitors can induce an acute leukemia which has to be kept in mind, especially in the adjuvant setting [13]. Mitoxantrone, the only drug from the anthracenedione class [14] with less cardiotoxicity, is used in palliative breast cancer treatments as well as in lymphoma and leukemia treatment protocols, but to a much lower degree because it is a general belief that mitoxantrone is less cardiotoxic, but less effective too. That is the reason why it is rarely used in curative therapy protocols. The pharmacokinetics of mitoxantrone has been described, and there are some similarities to BBR 3576 with respect the long terminal half-life, the extraordinary large volume of distribution and the rapid clearance [15].

More recently, a novel anthracenedione (BBR 2778) [16,17] and new aza-anthrapyrazole (BBR 3438 and BBR 3576) compounds were developed [18,19]. It was found that they induce modest or no histopathological alteration of cardiac tissues when repeatedly administered in rodent models [9,20]. Besides outstanding activities in hematological and solid tumors accompanied by a good tolerability profile, the reduced cardiotoxicity represented one of the major claims that supported the decision to carry on the clinical development of these compounds.

The most advance agent of this class, BBR 2778 [16,17,21], is now being explored in phase II and phase III clinical trials for hematological indications.

The present phase I study with BBR 3576, resulted in the recommended dose for phase II studies of 150 mg/m^2 q4w. Looking at the safety profile of the six patients enrolled at the 150 mg/m^2 dose level, it was noted that there was one DLT (stomatitis grade 3) in one patient and important toxicities on white blood cells in the other patients. Although the protocol stated that it was possible, having one DLT out of six patients, to expose patients to a higher dose, it was decided not to administer higher doses to further patients taking also into account the toxicity profile of the lower dose level of 125 mg/m^2. This lower dose showed a toxicity profile on hematology which was not relevantly different from the higher dose. However, no DLTs were observed.

Consequently, the recommended dose for phase II was set to be 150 mg/m^2 BBR 3576, considering also that the MTD, which required two DLTs in six patients, was not reached.

The drug exhibited no surprising toxicities, as was anticipated from the preclinical profile. The principal toxicity was a fully reversible myelotoxicity, mainly neutropenia. All other toxicities were less prominent and always reversible. Notably, alopecia and fatigue were never a problem, which is different from the anthracyclines, but more similar to the anthracediones mitoxantrone [22] and BBR 2778 [21], and to the aza-anthrapyrazole BBR 3438 [18]. The problem of cumulative cardiotoxicity, which is a drug-class problem, in general cannot be definitively answered for BBR 3576 because most of the patients went off study after only a few treatment cycles. During that time, no acute cardiotoxicity was observed. The cumulative cardiotoxicity has to be carefully evaluated within phase II studies, where patients who respond to this drug will receive a much higher drug dose. Comparisons with doxorubicin or epirubicin within phase III studies will give the final answer about a significant reduction of the cumulative cardiotoxicity problem.

The pharmacokinetics of BBR 3576 showed no real surprise. The plasma concentration versus time curves showed a rapid drug distribution within 4–8 h, followed by a long elimination half-life which is typical for this drug class. Over the dose range from 64 to 150 mg/m^2, in which the pharmacokinetic profile could be fully investigated, BBR 3576 showed a linear pharmacokinetics, as judged from the dose proportionality of C_{max} and AUC_{t_f}, and the constant values of clearance and volume of distribution. In other words, the distribution and elimination patterns do not appear to be affected by the dose increase from 64 to 150 mg/m^2. BBR 3576 is a high clearance drug. The main drug clearance appears to occur via the liver, the bile duct system and consequently the feces, whereas excretion via the kidney is a minor elimination route. Binding in deep tissue compartments explains the high volume of distribution of BBR 3576, a property observed in most anthracyclines and anthracenediones in clinical use. Most likely, excretion in the bile and metabolism accounts for most of the elimination of the administered drug, whereas renal excretion plays no significant role. The metabolic pathways were not studied within this clinical study.

Although clinical activity was not the primary end point of this study, patients were assessed for objective response whenever possible. No responses were seen. However, the patient recruitment was not optimized with respect to cancer types and pre-treatment conditions, and a reliable conclusion about drug antitumor efficacy cannot be reached based on these data. Anticancer activity will be determined within the running phase II studies. Preliminary signs of encouraging biological activity were seen in patients with prostate cancer [19].

This phase I trial demonstrated that BBR 3576 has a manageable toxicity profile on a q4w schedule and recommends the dose of 150 mg/m^2 for phase II trials.

On the other hand, as it is the major goal of a phase I trial to end up with a recommendation for a safe and potentially effective dose for use in phase II studies, it was the intention of the three participating cancer centers to reach this within the shortest period of time with the fewest number of patients possible using the accelerated titration design for phase I clinical trials [23]. Patient recruitment was fast and finished within less than 1 year, with phase II studies having started shortly after determining the recommended dose, leaving open the possibility of subsequent adjustments to the recommended dose and schedule in different types of patient populations.

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