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A clinical phase I and pharmacokinetic study of BBR 2778, a novel anthracenedione analogue, administered intravenously, 3 weekly

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Abstract

The anthracenedione analogue, BBR 2778 is an active antitumour agent preclinically and has reduced potential for cardiotoxicity compared with other similar drugs in preclinical models. BBR 2778 was administered 3 weekly by a 1 h intravenous (i.v.) infusion to 24 patients and the dose escalated rapidly from 20 to 240 mg/m^2. The dose-limiting toxicity (DLT) was neutropenia, common toxicity criteria (CTC) grade 4 in 3/5 patients at 240 mg/m^2. Other toxicities $\geqslant$CTC grade 3 were: vomiting, lymphopenia, thrombocytopenia and lethargy. Blue discoloration of veins and urine was also noted. In 1 patient (120 mg/m^2, four cycles) left ventricular ejection reaction (LVEF) fell (CTC grade 2) but with no clinical sequelae. BBR 2778 plasma pharmacokinetics were biphasic (mean $t_{1/2}\beta$ at 180 mg/m^2 = 14.1 h) and the urinary elimination of the unchanged drug was $<10\%$. In a patient with previously treated small cell lung carcinoma (SCLC), a 49% reduction in measurable disease was noted with resolution of pericardial and pleural effusions (120 mg/m^2×eight cycles). From the results of this phase I study a dose of 180 mg/m^2 as a 1 h infusion every 3 weeks would be recommended for phase II trials.

Keywords: BBR 2778; Phase I; Pharmacokinetics

1. Introduction

BBR 2778 (6,9 [bis (2-aminoethyl)-amino]-benzo [g] isoquinolone-5,10-dione dimaleate salt) is a novel heteroanalogue of anthracenediones [1] (Fig. 1). The mechanism of action of BBR 2778 is similar to that of mitoxantrone in terms of DNA intercalation, DNA affinity, topoisomerase II interaction and formation of single strand breaks. BBR 2778 has shown cytotoxicity comparable with doxorubicin against murine lymphoma and leukaemia cell lines — YC-8 murine lymphoma, L1210 and YAC-1 murine leukaemia lines. BBR 2778 has partial cross-resistance with LoVo/Dox (doxorubicin-resistant LoVo cells) and HT29 MITOX (mitoxantrone-resistant HT29 cells). In *in vivo* studies with YC-8 murine lymphoma, ascitic and disseminated L1210 murine leukaemia, BBR 2778 showed a curative antitumour activity at the maximum tolerated dose with a number of long-term survivors and showed higher activity than mitoxantrone and doxorubicin. In disseminated P388 murine leukaemia, murine Lewis Lung Tumour and human ovarian carcinoma (IGROV-1), BBR 2778 showed antitumour activity, comparable with that of mitoxantrone and doxorubicin, and retained a high level of activity across a wide range (8–27 mg/kg) of doses. In human xenograft studies using MX-1 human mammary carcinoma, BBR 2778 demonstrated equivalent activity to mitoxantrone and in IGROV-1 human ovarian carcinoma, its activity was comparable with both mitoxantrone and doxorubicin. BBR 2778 has been shown to have a wide spectrum of activity comparable with that of mitoxantrone and doxorubicin [2,3].

Pharmacokinetic data from mice indicated a multi-exponential clearance with a rapid decline in drug concentrations during the distribution phase, followed by a slow and prolonged elimination phase lasting up to 192 h. The drug was widely distributed throughout the body

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with accumulation in some tissue compartments. In studies with radiolabelled BBR 2778 the highest percentages of the administered dose were found in the skeletal muscle, liver and kidneys of mice and rats. Less than 0.05% of the administered dose was found in the brain suggesting that the drug and its metabolites do not cross the blood–brain barrier. The efficiency of unchanged drug elimination from the systemic circulation was also shown to be high, but the metabolites were cleared more slowly with a greater volume of distribution. The main route of elimination appeared to be faecal excretion. The apparent terminal half-lives of BBR 2778 and total radioactivity derived from the plasma data were 2.9 h and 78.6 h in mice and 7.1 h and 81.9 h in rats, which suggested that BBR 2778 has a large volume of distribution with a relatively slow clearance of the drug and its metabolites [3].

Preclinical toxicology studies were performed in mice and rats. In mice, the maximum tolerated dose (MTD) was 65 mg/kg (195 mg/m^2). The dose-limiting toxicity (DLT) was bone marrow suppression. Blueing of the skin, plasma and urine was seen in mice and rats. In mice and rats BBR 2778 was devoid of any significant toxic effect on cardiac tissue after both single and multiple treatments. BBR 2778, at doses equiactive to mitoxantrone in preclinical *in vitro* and *in vivo* models induced a lesser overall myelosuppressive effect. Using Bertazzoli and colleagues' method [4], preclinical studies have shown no cardiotoxicity in mouse myocardium at doses equiactive to doxorubicin and mitoxantrone [5]. The presence of a dihydroxyanthraquinone system in the mitoxantrone and doxorubicin molecules, which is absent in the BBR 2778 molecule, seems to play a role in delayed cardiotoxicity. In fact, the presence of the adjacent hydroxyl and quinone groups may facilitate binding (e.g. with Fe^{3+}), and the drug–metal complex could thereby foster oxidation–reduction cycling by a metal-catalysed type of reaction [6]. In the case of BBR 2778, the replacement of a dihydroxy-phenylene group of mitoxantrone and doxorubicin with a pyridine ring, abolishes this mechanism and may prevent cardiotoxicity. BBR 2778, therefore, shows a reduced myelosuppressive potential and a very low potential for cardiotoxicity, making it an attractive agent for clinical use.

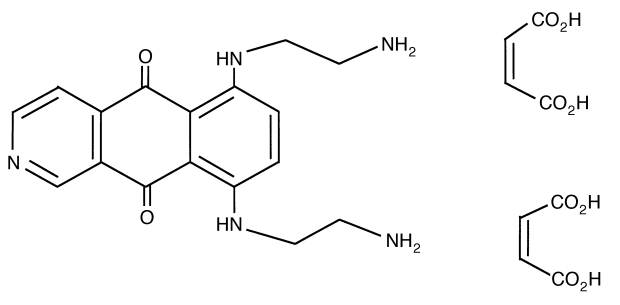

Fig. 1. Structures of BBR 2778 and mitoxantrone.

The aims of this phase I study were: (a) to determine the MTD of BBR 2778 when administered intravenously (i.v.) every 3 weeks to patients with cancer; (b) to establish the toxicity profile of BBR 2778; (c) to determine the pharmacokinetics of BBR 2778 at different dose levels; (d) to define a safe dose for subsequent phase II studies of antitumour activity; and (e) to observe and record any possible therapeutic efficacy of BBR 2778.

2. Patients and methods

This was an open non-randomised study with dose escalation that continued until the DLT was defined. A minimum of 3 patients were treated at each dose level. Before entry into the study, all patients had a histologically confirmed diagnosis of malignancy for which there was no alternative effective therapy. All patients were required to give written informed consent. Before commencing the study, ethical approval was obtained from the Medicine and Clinical Oncology Research Ethics Sub-Committee of Lothian Health Board (ref. LREC/1995/4/168) and the study was conducted according to the Helsinki Declaration.

Patients were eligible for inclusion in this study if they were aged 18–75 years, of adequate performance status ($\leqslant 2$ on the World Health Organization (WHO) scale) and had a life expectancy of >3 months. Adequate bone marrow, hepatic and renal function was required (white blood cell (WBC) $> 4.0\times10^9$/l, platelet count $> 100\times10^9$/l, calculated creatinine clearance >60 ml/min, bilirubin <17 μmol/l and alanine transaminase $< 1.25\times$ the upper limit of 40 u/l).

Patients were ineligible in the event of pregnancy, or previous chemotherapy with anthracyclines or mitoxantrone, or previous radiotherapy, nitrosoureas or mitomycin C within the preceding 6 weeks, or concurrent administration of another investigational drug or cytotoxic, hormonal or biological therapy. Patients were excluded from the study if they had brain metastases or primary brain tumours, or cardiovascular disease including cardiac arrhythmias, cardiac dysfunction, angina pectoris or previous myocardial infarction.

2.1. Drug supply and administration

BBR 2778 is a bis-maleate salt obtained in a crystalline form which is soluble in water. BBR 2778 was manufactured by Aston molecules (Aston Science Park, Birmingham, UK) and was formulated as a lyophilised product which was stored in vials at temperatures no higher than -20°C. It was diluted in 500 ml of 0.9% (w/v) sodium chloride and was administered into a peripheral vein as a 1 h infusion which was repeated at 21 day intervals provided there was recovery from

any drug-induced toxicity and no evidence of disease progression.

The starting dose for this phase I study was 20 mg/m^2 (1/10 of the mouse lethal dose (LD_{10})). It was planned to escalate doses depending on the incidence of toxicity. In the absence of DLT and significant toxicity (i.e. $\geqslant$ common toxicity criteria (CTC) grade 2) the doses were to be escalated rapidly by doubling. 3 patients were to be entered at each dose level, but if significant ($\geqslant$CTC grade 3) toxicity was identified, 3 additional patients were to be evaluated at that dose level. The MTD was defined as the dose level associated with the incidence of DLT in 2 or more out of 6 patients. The DLTs were defined as toxicities of CTC grade 3 non-haematological toxicity (excluding alopecia, nausea and vomiting), CTC grade 4 vomiting and CTC grade 4 haematological toxicity or CTC grade 3 haematological toxicity of more than 4 days duration and/or accompanied by neutropenic sepsis. A minimum of three courses were to be evaluated at each dose level before dose escalation. The recommended dose for phase II studies for evaluation of activity was defined as the dose level immediately prior to that associated with DLT. Before study entry a medical history, complete clinical examination including neurological examination and recording of the height and weight of the patients were performed. During the study a full blood count, urea and electrolytes and liver function tests were performed at weekly intervals. Prior to the study, cardiac status was assessed by means of a clinical history and examination including blood pressure measurements, an electrocardiogram to assess the cardiac rhythm and an echocardiogram (ECG) to obtain an estimate of the left ventricular ejection fraction (LVEF). These were repeated after each course of treatment. Disease status was evaluated with a baseline chest radiograph and appropriate radiological investigations. Standard International Union against Cancer (UICC) criteria were used to assess tumour responses [7].

2.2. Pharmacokinetics studies

The plasma pharmacokinetics of BBR 2778 were assessed in all of the patients who were entered into the phase I study. Blood samples were taken before drug administration, at 30, 55 and 60 min after the beginning of the infusion and at the following times after the 1 h infusion: 15 min, 30 min, 60 min, 90 min, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h. They were immediately centrifuged and the separated plasma was frozen and subsequently stored at −80°C until analysis using high performance liquid chromatography (HPLC) (see below). Individual basal urines and 24 h urines (as three fractions of 8 h each) were also collected, and, having accurately measured the total volume, 100 ml aliquots were stored at −80°C until analysed.

2.3. HPLC analysis of plasma and urine samples

A column-switching HPLC method using a Supelco ABZ column (250×2.1 mm, 5 μm) as an analytical column and a Supelco Supelguard ABZ column (20×4.6 mm, 5 μm) as an auxiliary column has been developed for the BBR 2778 assay in human plasma. Plasma samples (1 ml), spiked with the internal standard (BBR 2952, 6,9-bis[2-(1-pyrrolidinil) ethyl] aminobenzo[g]isoquinoline-5, 10-dione dimaleate) are brought to pH 9 with sodium acetate buffer and extracted with dichloromethane (8 ml). After centrifugation the organic phase is separated and 85% formic acid (100 μl) is added prior to drying under nitrogen stream at room temperature. The residue is redissolved in 50 mM potassium phosphate buffer pH 3 (300 μl). Aliquots ranging from 25 to 100 μl are injected onto the auxiliary column equilibrated with 0.05 M potassium buffer pH 5–acetonitrile–methanol (92/4/4, v/v/v). Having briefly (5 min) washed the auxiliary column, the drug and internal standard are eluted with 0.05 M potassium phosphate buffer pH 3–acetonitrile (93/7, v/v) and transferred to the analytical column, where chromatographic separation occurs. In plasma, the limit of quantitation of the method is 2 ng/ml, and the limit of detection 1 ng/ml. The method response is linear in the plasma concentration range from 2 to 250 ng/ml. Accuracy and precision are good: the accuracy varied from 98.4 to 100.0% and the precision from 5.0 to 10.3%. The method is applicable to urine samples with minor changes. In urine, the method response is linear in the concentration range from 50 to 5000 ng/ml. The limit of quantitation is 50 ng/ml, the accuracy and the precision vary respectively from 101.4 to 103.7% and from 2.0 to 3.7%.

2.4. Pharmacokinetic modelling

The individual plasma concentration–time profiles of BBR 2778 were analysed after the first administration of each treatment cycle by a model independent approach, using the pharmacokinetic software WinNonlin-Pro™ ver2.1 (Pharsight Corporation, Cary, NC, USA). Individual urinary excretion data were used to calculate the fractional and cumulative percentage of dose excreted via the renal route, and the renal clearance.

3. Results

3.1. Patient characteristics and dose escalation

24 patients, (10 (42%) male; 14 (58%) female), whose median age was 56 years (range: 27–66 years) entered the study. 17 patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. The

Table 1
Patient characteristics ($n = 24$)

Characteristic	
Gender	10 male 14 female
Median age	56 years (range: 27–66 years)
	n (%)
Tumour types	
Colorectal	9 (38)
Renal	5 (21)
Mesothelioma	2 (8)
Small cell lung cancer	2 (8)
Non-small cell lung cancer	2 (8)
Ovary	2 (8)
Cervix	1 (4)
Uterine	1 (4)
Previous treatment	
Surgery	16 (67)
Chemotherapy	19 (79)
Radiotherapy	12 (50)
Hormonal therapy	2 (8)
No previous treatment	1 (4)

most common tumour types entered were renal carcinoma (5 patients; 21%) and colorectal carcinoma (9 patients; 38%). 19 out of 24 patients (79%) had received prior chemotherapy (Table 1). The initial dose studied was 20 mg/m^2 on day 1 of a 21 day cycle and, after successful treatment of 3 patients, the dose was escalated with six dose levels being tested in this dose-finding study: 20, 40, 80, 120, 180 and 240 mg/m^2 (Table 2).

3.2. Toxicities related to BBR 2778

3.2.1. Haematological toxicities

There was no evidence of cumulative toxicity with BBR 2778. Neutropenia was the DLT occurring at CTC grade 4 in 3 of the 5 patients treated at the maximum dose tested (240 mg/m^2) (Table 3). In 2 of these 3 patients neutropenia persisted for $\geqslant 7$ days and both were admitted to hospital and received intravenous antibiotic therapy for febrile neutropenia.

One patient treated at the 80 mg/m^2 dose level and 5 of the 6 patients at 180 mg/m^2 dose level had grade 4 lymphopenia. However, all of these patients had grade 3–4 lymphopenia at baseline. Thrombocytopenia was only observed in 2 of 5 patients treated at the 240 mg/m^2 dose level. One patient had grade 4 thrombocytopenia while the other had drug-induced grade 3 thrombocytopenia complicated by ongoing rectal haemorrhage as a result of bowel infiltration by renal cancer.

Table 2
Dose escalation of BBR 2778

Dose level (mg/m^2)	*n* of patients (%)	*n* of cycles
20	3 (13)	11
40	4 (17)	16
80	3 (13)	9
120	3 (13)	13
180	6 (25)	9
240	5 (21)	11

3.2.2. Non-haematological toxicities

All of the patients who were treated had blue discoloration of the skin during the infusion of BBR 2778 which persisted after its completion. Virtually all had persistent blueing of the urine lasting several days and patients treated at higher doses had discoloration of the veins.

CTC grade 3 vomiting, lymphopenia, thrombocytopenia and lethargy were also observed (Table 4). One patient at the 120 mg/m^2 dose level had grade 3 vomiting and, thereafter, routine oral antiemetic prophylaxis was introduced, using ondansetron 8 mg or granisetron 1 mg with 10 mg of dexamethasone prior to administration of BBR 2778 and dexamethasone 4 mg twice daily and domperidone 20 mg four times daily for 3 days following treatment. With prophylactic antiemetics, 3 out of 11 patients at the 180 mg/m^2 and 240 mg/m^2 dose levels had CTC grade 1 or 2 vomiting, but no grade 3 vomiting was reported. Although stomatitis occurred in 8 patients, it was never dose limiting (i.e. $\leqslant$CTC grade 2). Alopecia, mainly CTC grade 1, was seen at all dose levels.

Prior to study entry all patients, as assessed by echocardiography, had normal cardiac function (mean LVEF = 60%, range: 41–77%), and of the 17 patients assessed at the end of their treatment, 16 had LVEFs within normal limits (mean = 58%, range: 46–74%). After four cycles of BBR 2778, representing a cumulative dose of 480 mg/m^2, 1 patient was noted to have a fall in ejection fraction from 67% to 46% which was not

Table 3
Haematological toxicities associated with the administration of BBR 2778 (the worst grade for the entire duration of treatment in each patient is given)

Dose (mg/m^2)	0	1	2	3	4
No. of patients at each CTC grade (neutropenia)					
20	3				
40	4				
80	2	1			
120	2				1
180	1	1	2	2	
240	1		1		3[a]
No. of patients at each CTC grade (thrombocytopenia)					
20	3				
40	4				
80	3				
120	3				
180	6				
240	3			1	1

CTC, common toxicity criteria.
[a] Grade 4 neutropenia lasted 3, 7 and 7 days at 240 mg/m^2.

Table 4
Non-haematological toxicities (the worst grade for the entire duration of treatment in each patient is given)

Dose (mg/m^2)	0	1	2	3	4
No. of patients at each CTC grade (nausea)					
20	2	1			
40	2	2			
80	2	1			
120			3		
180	5		1		
240	2	1	2		
No. of patients at each CTC grade (vomiting)					
20	3				
40	4				
80	3				
120			2	1	
180[a]	5	1			
240[a]	3	1	1		
No. of patients at each CTC grade (alopecia)					
20	2	1			
40	4				
80	2	1			
120		2	1		
180	2	3	1		
240	3	1	1		

CTC, Common toxicity criteria.
[a] With prophylactic antiemetics.

associated with any clinical sequelae. Although this patient was asymptomatic, the fall of over 20% in the resting ejection fraction is defined as a grade 2 toxicity using the CTC criteria. This patient had a history of viral myocarditis 14 years previously and reported ongoing dyspnoea on effort related to metastatic pulmonary disease.

3.3. Antitumour activity following administration of BBR 2778

There was definite evidence of antitumour activity in a patient with small cell lung cancer (SCLC), with a 49% reduction in measurable disease (computer tomography (CT) scan) and resolution of both pericardial and pleural effusions following five cycles of BBR 2778 at 120 mg/m^2 (Fig. 2). This patient had progressive disease shortly after discontinuing standard first-line therapy (cisplatin and etoposide). The time to disease progression was 21 weeks. A patient who had had prior radiotherapy and chemotherapy for non-small cell lung carcinoma (NSCLC) was treated at 40 mg/m^2 and reported a symptomatic improvement and had stable disease through nine cycles of treatment before progressing after 27 weeks of therapy.

3.4. Pharmacokinetic studies

BBR 2778 pharmacokinetics conformed to a two-compartment linear open model. HPLC assessment of plasma and urine concentrations of BBR 2778 showed that the drug has a large volume of distribution (21.4 l/kg at 180 m/mg^2) and a rapid clearance (1.15 l/h/kg at 180 mg/m^2). The terminal half-life of BBR 2778 was 14.1 h at 180 mg/m^2. Urinary elimination of BBR 2778 as unchanged drug was less than 10%.

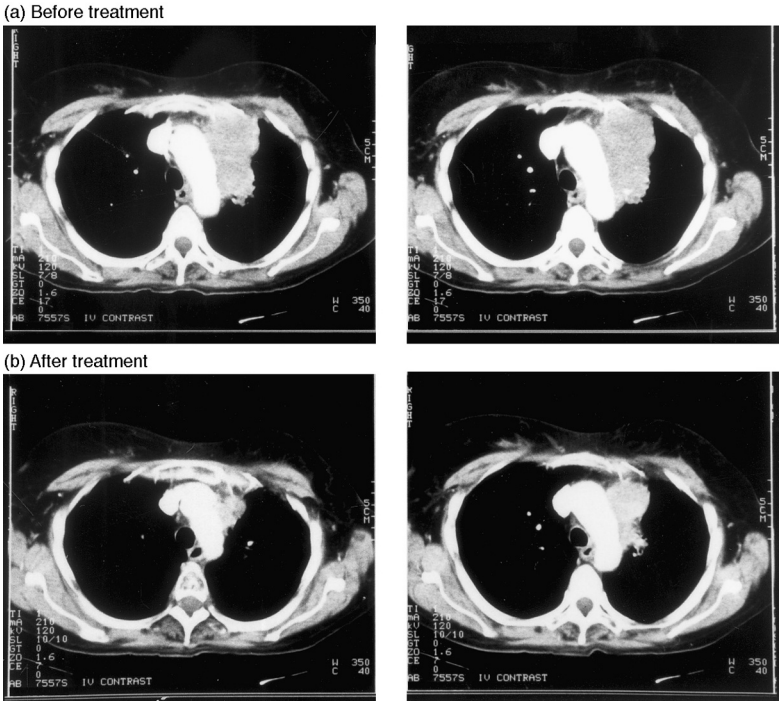

Fig. 2. Computer tomography (CT) scan demonstrating response to BBR 2778.

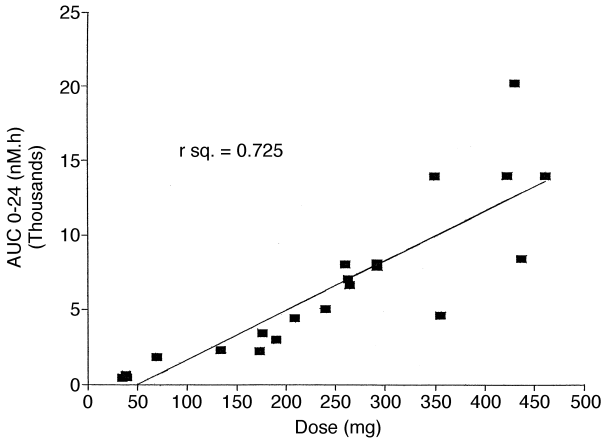

Fig. 3. Area under the concentration curve (AUC) compared with absolute dose (mg) of BBR 2778.

BBR 2778 pharmacokinetics are linear when the area under the concentration curve (AUC) is compared with the absolute dose (Fig. 3). Non-linear pharmacokinetics was suggested at doses greater than 180 mg/m^2 when the AUC was compared with the dose expressed as mg/unit of body surface area (Fig. 4), but this may represent an artefact of assuming a direct relationship between body surface area and clearance, as it is less clearly non-linear when AUC and absolute dose are compared. While calculating the dose of BBR 2778 in relation to body surface area is considered to be safe and, therefore, appropriate these data suggest that a more detailed population analysis with covariates should be performed, e.g. using NONMEM, to truly define relationships between drug clearance and physiological parameters.

Neutropenia has been shown to be related to both dose and the AUC of BBR 2778 (Fig. 5), which is not surprising in view of the close relationship between the dose and the AUC.

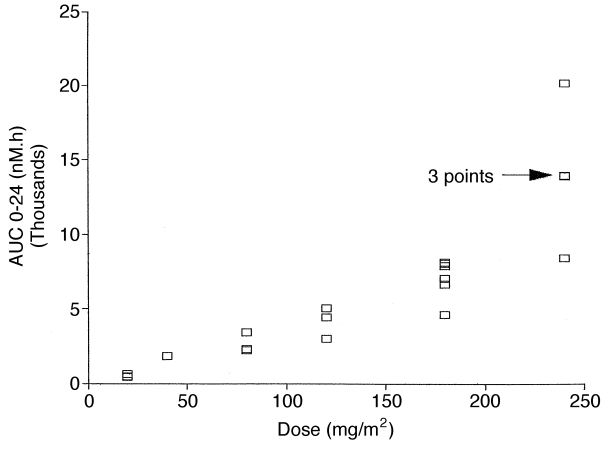

Fig. 4. Area under the concentration curve (AUC) compared with dose level (mg/m^2) of BBR 2778.

4. Discussion

These data represent a completed phase I and pharmacokinetic study of the novel anticancer drug BBR 2778. The DLT was prolonged neutropenia (CTC grade 4 or CTC grade 3 lasting >4 days) and this occurred at a dose of 240 mg/m^2 per day in 2 out of 5 patients. One case of grade 4 thrombocytopenia was also seen at this dose level. In 2 out of 6 patients treated at the 180 mg/m^2 dose level there was CTC grade 3 neutropenia, but no grade 4 neutropenia and no decrease in platelets was seen. This dose level would be recommended for phase II trials, although there may be scope for a dose escalation in patients with minimal myelosuppression in cycle 1.

BBR 2778 was generally well tolerated with a low incidence of other cytotoxic side-effects ($\geqslant$CTC grade 2) classified as probably/possibly drug-related. Other toxicities included blue discoloration of the skin and urine, alopecia, stomatitis, nausea and vomiting and lethargy.

Preclinical studies had shown a reduced potential for cardiotoxicity related to BBR 2778 compared with other drugs in this class. One patient treated at the 120 mg/m^2 dose level (four cycles) was noted to have a fall in LVEF (CTC grade 2) from an initial value of 67% to 51% and then to 46%, at which point it was felt unwise to proceed with further BBR 2778. Despite the fall in LVEF the patient was asymptomatic and had no clinical sequelae. Although BBR 2778 demonstrated reduced cardiotoxicity in preclinical studies, the findings of this phase I study suggest further cardiac monitoring would be prudent in phase II studies.

The pharmacokinetic data have indicated that BBR 2778 pharmacokinetics are linear when the AUC is compared with absolute dose and the mean terminal half-life is estimated to be 14.1 h at 180 mg/m^2. The linear association of AUC and absolute dose is relevant to the debate regarding the use of body surface area to individualise chemotherapy dosing and, in particular anthracycline dosing. It has been proposed that doses of the anthracycline, epirubicin, should be given as either

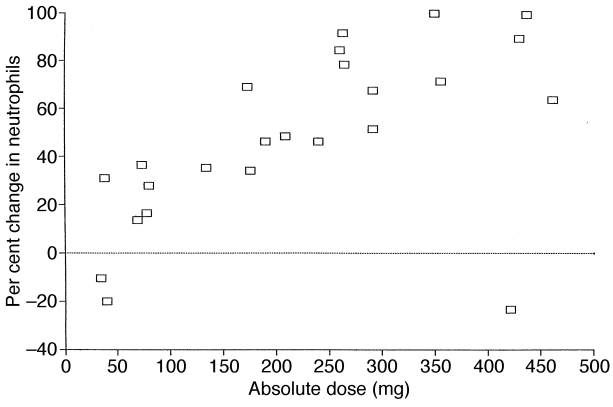

Fig. 5. Neutropenia compared with absolute dose of BBR 2778.

fixed doses or adjusted for quantitative assessments of liver function such as antipyrine clearance or coagulation tests which predict anthracycline clearance [8,9], rather than the more traditional body surface area adjustment. Urinary elimination of BBR 2778 is low, confirming preclinical studies which had suggested that the majority of drug is eliminated via faecal excretion. Mitoxantrone has a similarly low proportion of drug excreted in the urine (< 10%) and it is the intensity of the chromophore moiety within the molecule which accounts for the changes in urinary colour.

There was clear evidence of antitumour activity in 1 patient with SCLC, previously treated with platinum and etoposide, who achieved 49% reduction in measurable disease and resolution of pericardial and pleural effusions. In another patient with NSCLC a symptomatic improvement was noted with disease stabilisation throughout nine cycles (189 days).

Mitoxantrone and doxorubicin have also been shown to have activity in human SCLC lines. Mitoxantrone has *in vitro* antitumour activity against human adenocarcinoma of the lung, SCLC, melanoma and biliary tree cancer with some antitumour activity against breast cancer, ovarian cancer, non-Hodgkin's lymphoma, head and neck cancer, squamous cell lung cancer, soft tissue sarcoma, gastric cancer and hepatomas. It also has been demonstrated to have cytotoxic activity in SBC-3/ADM human SCLC cells which are 30-fold more resistant to doxorubicin than the parent cell line (SBC-3). The SBC-3/ADM cells were as sensitive to mitoxantrone as the parent cells [10].

However, mitoxantrone has little therapeutic activity in patients with SCLC. In a phase II study of 65 patients with progressive SCLC after conventional therapy, which included regimens containing doxorubicin, only two partial responses were seen with mitoxantrone [11]. 22 patients with SCLC, in a trial of 185 patients with lung cancer, had no responses to treatment with mitoxantrone at a dose of 5 mg/m^2 weekly [12]. Similarly, no responses were seen in a trial of 15 chemotherapy-näive patients with extensive SCLC who were treated with mitoxantrone on a 3-weekly schedule [13]. Doxorubicin as single-agent therapy for SCLC has a response rate of 25% [14]. When treated within a phase II trial of 31 patients with advanced lung cancer, 3 out of 6 patients with SCLC had a partial response to a 3-day schedule of doxorubicin. However, in this study 7 patients developed electrocardiogram changes and 5 developed congestive cardiac failure following the administration of chemotherapy [15]. Doxorubicin is administered commonly to patients with SCLC as part of the VAC (vincristine, doxorubicin, cyclophosphamide) [16] and ACE (doxorubicin, cyclophosphamide, etoposide) [17] regimens. Therefore, BBR 2778 may offer a potentially less cardiotoxic alternative to doxorubicin in the treatment of SCLC with evidence of activity in this disease being shown in this phase I study. BBR 2778 certainly merits phase II evaluation in this disease.

In summary, BBR 2778 is a well tolerated cytotoxic agent with neutropenia as its DLT. The recommended dose for phase II trials is 180 mg/m^2 as a 1-h infusion every 3 weeks and further testing of this agent in SCLC and other solid tumours is warranted.

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