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Phase II studies of BBR3464, a novel tri-nuclear platinum complex, in patients with gastric or gastro-oesophageal adenocarcinoma

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Abstract

BBR3464, a novel tri-nuclear platinum complex, forms long-range DNA adducts and is highly potent when compared with cisplatin *in vitro*. Preclinical studies demonstrated activity in cisplatin-resistant tumours and tumours with mutated *p*53 status. Phase I & II clinical studies gave preliminary indications of activity in melanoma, pancreatic, lung and ovarian cancers. The aim of this study was to determine the efficacy and confirm the toxicity of BBR3464 when given either as first- or second-line treatment for advanced disease in patients with gastric and gastro-oesphageal adenocarcinoma. Two multicentre, open label, Gehan design studies were conducted; one study used BBR3464 as first-line and the other as second-line treatment for metastatic or locally advanced disease. Nineteen first-line and 26 second-line patients were enrolled receiving a total of 74 and 53 infusions, respectively. Initially, seven patients in the second-line study received BBR3464 using the planned schedule of 1.1 mg/m^2 every 4 weeks; however, 5 of these patients experienced dose-limiting grade 3 or 4 febrile neutropenia; subsequent patients in both studies were treated using the modified schedule of 0.9 mg/m^2, every 21 days. In 1 of 17 evaluable, previously untreated patients, regression of multiple skin lesions was noted with stabilisation of lung metastases and maxillary sinus mass, lasting 155 days. In the first-line study, the median time to progression was 85 days [95% Confidence Interval (CI): 42, 127] (2.8 months) and in the second-line study, the median time to progression was 71 days [95% CI: 42, 109] and 38 days [95% CI: 32, 73] in the 1.1 and 0.9 mg/m^2 dose level groups, respectively. Toxicity data were available for 45 patients. Neutropenia was the main toxicity seen (G3: 40%, G4: 40%). Febrile neutropenia was observed in six patients (15%) treated with 0.9 mg/m^2 compared with five patients (71%) treated with 1.1 mg/m^2 BBR3464. Other drug-related toxicities (G3/4) included: anaemia, thrombocytopenia, nausea, vomiting, diarrhoea, mucositis and fatigue. Diarrhoea and nausea/ vomiting were adequately controlled by the use of loperamide and antiemetics, respectively. Recruitment to the second-line study was closed early due to the poor response rate (1/17 evaluable, 6%; 95% CI: 1%, 27%) and short time to progression noted in the first-line study. Further studies with BBR3464 in this tumour type are not recommended.

Keywords: BBR3464; Gastric cancer; Phase II; Platinum complex

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1. Introduction

BBR3464 is a charged (+4), triplatinum complex, with a novel mechanism of DNA interaction (Fig. 1): the principal conformational change induced by BBR3464 is a change from a right-handed (B) to a left-handed (Z) DNA double helix. Unlike other agents, this induction of Z-DNA is irreversible [4]. Bifunctional long-range DNA adducts are formed (both inter- and intra-strand cross-links). In contrast to cisplatin, DNA intra-strand adducts induced by BBR3464 do not lead to DNA bending and are not recognised by high mobility group-proteins, which recognise cisplatin-damaged DNA. These features could be a critical reason for the ability of BBR3464 to overcome resistance to cisplatin. BBR3464 is approximately 40-fold more potent than cisplatin on a molar basis and is active both in cisplatin-sensitive and cisplatin-resistant tumour models, as well as in tumours with mutated *p*53 status [5,6].

In a Phase I study patients were treated with BBR3464 at dose levels of 0.2, 0.4, 0.8 and 1.1 mg/m^2, once every 28 days [1]. Significant toxicity (diarrhoea and neutropenia) was confined to the 1.1 mg/m^2 dose level. There was no significant nephrotoxicity, neurotoxicity or pulmonary toxicity. An encouraging confirmed partial response (PR), measured using computerised tomography (CT) imaging, was seen in a patient with metastatic pancreatic cancer. The dose-limiting toxicities (DLT) were neutropenia and diarrhoea. The white cell nadir occurred around Day 14; spontaneous recovery was prompt and usually complete by Day 21. Grade 4 diarrhoea was seen in one patient at the dose level of 1.1 mg/m^2. Diarrhoea was preceded by cramping abdominal pain and was sometimes accompanied by mucositis, dehydration, hypotension and electrolyte imbalance. Symptoms of diarrhoea began a few days after BBR3464 administration, with the worst grade being reached around Day 14 (range 7–14 days). A reduced dosing interval of 21 days was also evaluated and a dose of 1.1 mg/m^2 every 28 days, or 0.9 mg/m^2 every 21 days was recommended for Phase II evaluation.

The use of platinum-containing combination chemotherapy in patients with advanced gastric and gastro-oesophageal cancer is associated with high response rates [3], but the median survival for patients with metastatic disease remains poor [8]. Therefore, we considered it appropriate to undertake studies to determine the anti-tumour activity of BBR3464 as first-line treatment, and in order to fully assess its potential, its utility as second-line therapy was studied, in light of its apparent activity in cisplatin-resistant tumour models, in patients with metastatic or locally advanced inoperable gastric or gastro-oesophageal adenocarcinoma.

2. Patients and methods

2.1. Study design and plan

These were multi-centre, open label, uncontrolled, two-step, non-randomised Phase II studies. Eight centres participated in the studies: 6 in the United Kingdom (UK), 2 in Italy. The protocols were approved by the Ethics Committee of each participating centre and all patients were required to give written informed consent prior to treatment. The Gehan two-step method was used to calculate the number of patients required in each study based on *a priori* minimum expectation of response rates of 20% for first-line and 15% for second-line treatment [2]. According to this method, 14 and 19 evaluable patients (first-line and second-line, respectively) with metastatic or locally advanced inoperable gastric or gastro-oesophageal adenocarcinoma were required to complete the first phase of the studies. Patients were considered evaluable for response if two cycles of treatment were received or treatment was stopped after only one cycle because of documented disease progression. If one or more responses were seen, additional patients up to a maximum of 11 would be recruited for the second phase. Patients failing to complete two evaluable cycles for reasons other than disease progression were replaced. Accrual to the trial continued pending the evaluation of response in the initial cohort of 14 or 19 patients, respectively.

2.2. Selection of study population

Patients were eligible for the first-line study if they had histologically-or cytologically-proven, inoperable, locally advanced or metastatic gastric or gastro-oesophageal adenocarcinoma and had not received prior chemotherapy for metastatic disease. Prior adjuvant or neo-adjuvant chemotherapy was allowed if patients had relapsed $\geqslant 6$ months from the end of treatment.

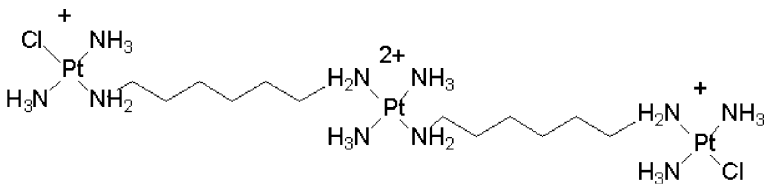

Fig. 1. Structure of BBR3464.

Patients were eligible for the second-line study if they had failed first-line treatment for metastatic disease and had not received adjuvant or neo-adjuvant treatment.

Entry criteria specific to this agent were that the Carbon Monoxide Diffusion Capacity (CMDC) must have been at least 50% of the predicted value. In addition, prior disposition to diarrhoea, e.g. Crohn's Disease or ulcerative colitis, or a poor nutritional status that could be further compromised by severe diarrhoea was considered an exclusion criterion, in view of the experience in late pre-clinical and Phase I clinical trials. Other entry criteria were standard for a Phase II trial undertaken by Cancer Research UK and/or the South European New Drugs Organisation (SENDO).

2.3. Pre-treatment procedures and observations

Standard pre-treatment evaluations were performed within seven days and audiometric measurements, and pulmonary function tests (by CMDC), were performed within two weeks of the start of BBR3464 treatment. All patients had a CT or magnetic resonance imaging (MRI) scan of the pelvis and abdomen (or other sites as appropriate) to measure disease within four weeks and clinical evaluation of marker lesions within 1 week prior of the start of the study. Haematology and biochemistry evaluations were performed weekly during treatment. Tumour response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) [7]. Toxicity was assessed using National Cancer Institute (NCI)–Common Toxicity Criteria (CTC) Version 2.0.

2.4. Dose and treatment schedule

The dosing regimen of 1.1 mg/m^2 BBR3464 every 28 days, was chosen for these studies. However, based on early results from the study (see Section 3) in patients receiving second-line therapy, the protocol was amended, for safety reasons, to BBR3464, 0.9 mg/m^2 every 21 days. The drug was administered by a 1 h intravenous (i.v.) infusion into a peripheral vein, without pre- or post-hydration. BBR3464 was manufactured by Bigmar SA, 24 Cadepiano St, Barbengo CH-6917, Switzerland for Novuspharma S.p.A. Italy. In the UK, it was distributed by the Cancer Research UK Formulation Unit and Propharma, Department of Pharmaceutical Sciences, University of Strathclyde, Royal College Building, 204 George Street, Glasgow G1 1XW, Scotland. In Italy, it was distributed by Bigmar SA.

Treatment continued for six cycles, unless there was evidence of disease progression, unacceptable toxicity or it was discontinued at the patient's request. Further cycles could be given at the discretion of the investigator responsible for the patient concerned. Dose adjustments were based upon the worst haematological or non-haematological toxicity occurring in the previous cycle.

3. Results

3.1. Patient characteristics

Forty five patients (19 first-line, 26 second-line) entered the studies between May 2000 and 2001 at 8 centres (UK; 6, Italy; 2). Patient characteristics are shown in Table 1.

3.2. Prior chemotherapy

In the first-line study, no patients had received prior treatment for metastatic disease. Five of the 19 patients enrolled (26%) had received prior adjuvant or neo-adjuvant chemotherapy. In the second-line study, all 26 patients were pre-treated. Twenty (77%) had received prior chemotherapy regimens containing platinum (Table 2). Eighteen patients started their first cycle of study drug treatment less than six months (<26 weeks) after stopping platinum chemotherapy, four patients within six months to one year ($\geqslant$26 weeks to $\leqslant$52 weeks), and two patients after more than one year (>52 weeks); for two patients no accurate stop date of prior chemotherapy was recorded. The mean time between the last platinum chemotherapy end date and the first cycle start date was 21.2 weeks and the median was 11.3 weeks (range 4.9–88 weeks).

3.3. Tumour response evaluation

Seventeen of nineteen (90%) patients in the first-line study and 18 (69%) patients in the second-line study

Table 1

Characteristics	First-line ($n = 19$)	Second-line ($n = 26$)
Age, median (range) (in years)	62 (38–75)	63 (42–77)
Male	15	24
Female	4	2
PS	0 = 13	0 = 6
	1 = 6	1 = 20
Primary site	Gastric = 16	Gastric = 16
	G-O Junction = 3	G-O junction = 10
Previous chemotherapy	5 patients	26 patients (protocol requirement)

PS, performance status; G-O, gastro-oesophageal.

Table 2
Prior chemotherapy in second-line patients

Regimen received	Number of patients (%)
Platinum based chemotherapy	20(77)
ECF (1 & FAM)	13(50)
MCF	5(19)
CAM	1(4)
EP (& Raltitrexed)	1(4)
Other chemotherapy	6(23)
FAM	4(15)
5-FU	1(4)
5-FU/FA	1(4)

ECF, epirubicin/cisplatin/5-FU; MCF, mitomycin C/carboplatin/5-FU.

CAM, carboplatin/doxorubicin/mitomycin C; EP, epirubicin/platinum drug.

FAM, 5FU/doxorubicin/mitomycin C; FA (folinic acid); 5-FU, 5-fluorouracil.

One patient had potential neo-adjuvant treatment with ECF (three cycles), but the tumour was inoperable and so it was decided to continue chemotherapy with FAM (three cycles), as this regimen was easier to administer to the patient. One patient had treatment with ECF followed by treatment with 5-FU; radiotherapy was also given at the time of 5-fluorouracil.

were evaluable. Response data for the second-line study have been split to show data for the seven patients entered at 1.1 mg/m^2, 4 weekly and the 19 patients entered at 0.9 mg/m^2, 3 weekly (Table 3). Five patients showed early progression and came off-study after one cycle. Ten patients (22%) were not evaluable as they were deemed "off-study" after one cycle for reasons other than early progression.

The Gehan two-step, method used in the first-line study, required the entry of 15 evaluable patients (based on 1 response) and therefore this study was completed according to protocol. To exclude a response rate of 15% in the second-line patient cohort, 19 evaluable patients were to be treated at 0.9 mg/m^2, 3 weekly, but the study was terminated early, in light of the disappointing response rate (1/17 evaluable: 6%; 94% Confidence Interval (CI): 1%, 27%) and short time to progression identified in the first-line study.

The PR occurred in a patient with multiple skin lesions, histologically confirmed as adenocarcinoma consistent with a gastric primary, who received 9 cycles (6 cycles at 0.9 mg/m^2 and 3 cycles at 0.7 mg/m^2). The duration of the response was 155 days. In this patient, bidimensional measurements of 7 of 31 skin lesions were recorded and 24 lesions disappeared completely. This patient also had a measurable lesion in the maxillary sinus, which remained stable throughout treatment.

In the first-line study, the median time to progression was only 85 days [95% CI: 42, 127] (2.8 months). In the second-line study, the median time to progression was 71 days [95% CI: 42, 109] and 38 days [95% CI: 32, 73] in the 1.1 and 0.9 mg/m^2 dose level groups, respectively.

3.4. Toxicity and dose modification

The toxicity profile, predicted from Phase I trials, included myelosuppression, diarrhoea, nausea and vomiting. Dose delays and modification occurred frequently in both studies, usually secondary to haematological toxicity. In particular, in the second-line study a safety review was performed on the first 6 patients, of whom 5 (83%) experienced grade 3 or 4 febrile neutropenia following the first cycle of BBR3464 at the 1.1 mg/m^2 dose level. This incidence of febrile neutropenia was thought unacceptable and therefore a dose reduction to 0.9 mg/m^2 was instigated for all patients treated in the first-line study and subsequent patients in the second-line study. In patients treated at 0.9 mg/m^2, grade 4 neutropenia was noted in 47% (first-line) and 52% (second-line) of patients. Febrile neutropenia was experienced by 16% (first-line) and 5% (second-line) patients treated at 0.9 mg/m^2. Grade 2/3 thrombocytopenia was only seen in previously treated patients (21%, second-line) and there was no grade 4 thrombocytopenia.

3.5. Non-haematological toxicity associated with the administration of BBR3464

Patients were not routinely premedicated with antiemetics. However, in the first-line study, 11/19 (58%) patients received prophylactic antiemetics at some point during treatment and 8/19 (42%) received medication for nausea/vomiting. In the second-line study, 20/26 (77%) received prophylactic antiemetics or medication for nausea/vomiting. Drug-related grade 3 diarrhoea was experienced by 8 patients. Grade 3 abdominal pain/abdominal cramps occurred in 3 patients.

Table 3
Best response to BBR3464

Best response	First-line ($n = 19$) no. of patients (%)	Second-line (1.1 mg/m^2, $n = 7$) no. of patients	Second-line (0.9 mg/m^2, $n = 19$) no. of patients (%)
Complete response	0	0	0
Partial response	1(5)	0	0
No change	9(47)	1	4(21)
Progressive disease	6(32)	3	6(32)
Early progression	1(5)	0	4(21)
Not evaluable	2(11)	3	5(26)

One patient experienced grade 2, drug-related renal impairment and drug-related hypokalaemia (grade 3/4) was noted in 4 patients. Alopecia was experienced by 12 patients overall. Four patients experienced minor reductions in CMDC and these episodes were considered as possibly related to the study drug. There was no clinically apparent ototoxicity or neurological toxicity. Five patients demonstrated minor changes of sensory-neural loss from baseline determined by an audiogram. One patient had two episodes of grade 1 paraesthesia of the face, after cycles 1 and 2 (both at 0.9 mg/m^2), which were considered related to the study drug. One patient in these studies experienced drug-related grade 2 sensory neuropathy.

4. Discussion

This report describes the Phase II (activity) trials of BBR3464 in patients with gastro-oesophageal cancer performed as a collaboration between the SENDO and the Cancer Research UK Phase I/II Committee. Pre-clinical studies had demonstrated the activity of BBR3464 in models of cisplatin resistance and models expressing mutant *p*53 activity. Gastric cancer models were included in these pre-clinical studies (HS746T, cisplatin-sensitive and GXF 214, cisplatin-resistant) and encouraging activity was demonstrated, making this an appropriate patient group in whom to test BBR3464. Cisplatin is already used extensively in this disease.

In patients receiving BBR3464 as second-line therapy for advanced disease, haematological toxicity was common, occurring in 25/26 patients (96%). Febrile neutropenia was unexpectedly frequent (5/6 patients, 83%) at the initial dose level (1.1 mg/m^2) leading to a safety review and dose reduction to 0.9 mg/m^2. The unexpectedly poor tolerance of BBR3464 in the initial group of patients treated at 1.1 mg/m^2, 4 weekly, may have been related to the poor functional reserve associated with metastatic gastric cancer, as evidenced by a high proportion of patients with anorexia and hypoalbuminaemia (13/26, 50%) at baseline.

Nineteen patients, previously untreated for metastatic disease (of whom 17 were evaluable for response) received BBR3464 as first-line therapy at a dose of 0.9 mg/m^2, administered i.v., every 21 days. There was one documented PR, in a patient with a measurable lesion in the maxillary sinus and 31 skin lesions. Seven of these lesions were considered measurable and all reduced in size on treatment leading to a confirmed PR lasting 155 days. Unfortunately, time to progression was short in this group of patients, the median time to progression being only 85 days [95% CI: 42, 127].

Haematological toxicity was common in previously untreated patients. Three patients (16%) had grade 3 febrile neutropenia and six patients (32%) had grade 4 neutropenia without fever. Gastrointestinal toxicity, particularly diarrhoea (drug-related in 32/45 patients, 71%) was also frequent. The likelihood of diarrhoea had been anticipated and was generally controlled by loperamide. Nausea and vomiting was controlled by antiemetics, although 11/19 patients (58%) received antiemetics prophylactically at some point in the first-line study. Fatigue was also common (24/45 patients, 53%). In studies of this kind, it is often difficult to assign the causality of fatigue, but in 20 patients it was interpreted, by the investigator, to be drug-related.

In patients receiving BBR3464 as second-line therapy, 26 patients (18 evaluable) were entered at two dose levels (1.1 mg/m^2 every 28 days and 0.9 mg/m^2 every 21 days). There were no documented partial responses and, although the study design had stated 19 evaluable patients should be entered in the initial phase of this trial, the study was closed early due to lack of activity seen in the first-line study.

Metabolic abnormalities were noted (hypokalaemia, hypomagnesaemia) and elevations of urea and creatinine. However, it was difficult to assign causality in patients with diarrhoea and/or disease progression. Renal toxicity was not thought to be a feature in the Phase I trials of this agent [9]. However, further monitoring of organ function is recommended in patients receiving more prolonged treatment with BBR3464.

The clinical results obtained in these trials are at variance with the pre-clinical studies with BBR3464 and the reason for this is unclear. Plasma protein binding of BBR3464 is higher in man than in mice and also the degradation of BBR3464 to an inactive species is more rapid in human plasma than in mouse plasma (Novuspharma 2001, data not shown). Species-specific differences in toxicity have also been noted, supporting these hypotheses.

In summary, although the toxicities encountered in these Phase II trials had been predicted from Phase I testing, the degree of haematological toxicity encountered in patients treated at 1.1 mg/m^2 had not been anticipated and a dose reduction was implemented. In patients in this study receiving BBR3464 at a dose of 0.9 mg/m^2, every 21 days, the side-effects were generally tolerable. However, only minimal anti-tumour activity was identified (response rate in evaluable patients = 6% [95% CI: 1%, 27%]) and therefore the use of BBR3464 in this disease setting is not recommended.

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