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ORIGINAL ARTICLE

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A phase I study of the trinuclear platinum compound, BBR 3464, in combination with protracted venous infusional 5-fluorouracil in patients with advanced cancer

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Abstract *Purpose*: BBR 3464 is a novel trinuclear platinum anticancer agent with a broad spectrum of preclinical antitumour activity. A phase I, open-label dose-escalating study was performed to determine the maximum tolerated dose (MTD) of BBR 3464 administered in combination with protracted venous infusional (PVI) 5-fluorouracil (5-FU) for up to six courses in patients with locally advanced and/or metastatic cancer. *Methods*: Dose escalation was based on observation of toxicity at each dose level. BBR 3464 (0.6 mg/m^2 escalated to 0.75 mg/m^2) was studied in combination with PVI 5-FU (200 mg/m^2 per day). *Results*: Entered into the study were 14 patients. The most frequent toxicities were nausea, neutropenia, fatigue and diarrhoea. The protocol-defined MTD was not determined as 11/14 patients experienced grade 3 or 4 neutropenia that interrupted the planned administration of PVI 5-FU on day 15 (of 21). Although these events were not dose-limiting, as defined in the protocol, they imposed limitations on the dose of PVI 5-FU administered. Antitumour activity was observed: a partial response in one patient (7%) with invasive breast cancer. Stable disease was confirmed in three patients (21%). These four patients all completed the planned six courses of combined therapy. *Conclusions*: In light of the lack of septic events associated with the recorded neutropenia, it may be possible to safely continue PVI 5-FU despite the grade 3 or 4 neutropenia or modify the PVI schedule and administer therapy on days 1–15 of the 21-day cycle, but these modifications were not considered in this study.

Keywords BBR 3464 · Infusional 5FU · Phase I

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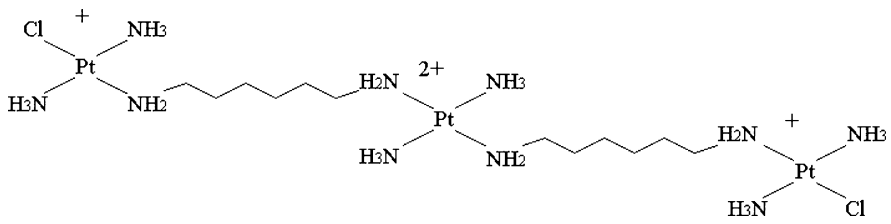
Introduction

BBR 3464 is a novel trinuclear platinum anticancer agent (Fig. 1) that has been developed based on the hypothesis that new, clinically useful platinum-based anticancer agents should have novel structures unrelated to those currently used in the clinic such as cisplatin and carboplatin. The novel structure may have new modes of DNA binding [8] leading to a different spectrum of antitumour activity, including the ability to overcome resistance to other platinum agents that is displayed by tumour lines [4, 5, 10, 12]. Preclinical data indicated that the spectrum of antitumour activity of BBR 3464 is broad, including activity against tumours such as lung and gastric carcinoma. The data also suggested the consistent ability of BBR 3464 to overcome acquired resistance to cisplatin in human xenografts [10] and that the antitumour activity of BBR 3464 is independent of the p53 status of the tumour [13].

In phase I studies, the administration of BBR 3464 as a single agent on day 1 of 28- and 21-day cycles as well as five daily fractions given on days 1–5 of a 28-day cycle was investigated. When given once every 28 days, the main dose-limiting toxicities (DLT) were neutropenia and diarrhoea encountered at a dose level of 1.1 mg/m^2 [11]. The recommended dose for 3-weekly administration was 0.9 mg/m^2 because 1.1 mg/m^2 induced a relatively high number of dose reductions and delays in subsequent administrations, suggesting that a longer recovery period

Fig. 1 Structure of BBR 3464



is advisable for this dose level [2, 11]. In the fractionated daily ×5 schedule, diarrhoea and neutropenia were again the main toxicities and 0.12 mg/m^2 per day for 5 days was defined as the maximum tolerated dose (MTD) [14].

5-Fluorouracil (5-FU) is a fluorinated analogue of uracil and is used in the treatment of many tumours. Infusional regimens have been shown to be superior to bolus schedules in the treatment of patients with colorectal cancer [3], and 5-FU is often combined with cisplatin due to their non-overlapping toxicity profiles and potential synergy. Synergy between BBR 3464 and 5-FU was suggested in preclinical in vivo studies using the human gastric tumour model MKN45 [11]. It was decided to administer 5-FU as a protracted venous infusion (PVI) due to its improved efficacy in gastrointestinal tumours and the low risk of diarrhoea (compared to bolus schedules), which was an anticipated side effect of BBR 3464.

The primary aim of this study was to determine the MTD of BBR 3464 administered intravenously on day 1 of a 21-day course and PVI 5-FU (continuous days 1–21) when administered in combination. The study was also designed to establish the dose levels of both drugs to be recommended for phase II studies and to observe any possible antitumour effects.

Material and methods

Patients

This was an open-label phase I study of BBR 3464 in combination with PVI 5-FU at increasing dose levels in patients with locally advanced and/or metastatic cancer.

Before entry into the study, all patients had a histologically confirmed diagnosis of locally advanced and/or metastatic cancer deemed to be unresponsive to or untreatable by standard therapies. All patients were required to give written informed consent. Before commencing the study, ethical approval was obtained from the Local Research Ethics Committee (LREC) for each site and the study was conducted in accordance with the principles of the Declaration of Helsinki (1996).

Patients were eligible for inclusion in this study if they were aged ≥18 years, of adequate performance status (≤ 1 on the WHO scale) and had a life expectancy of > 3 months. Patients must have recovered from all acute toxicities from prior therapy except alopecia and grade 1 or less peripheral neuropathy. Adequate bone marrow, hepatic and renal function was required (haemoglobin > 9 g/dl, neutrophil count > 1.5×10^9/l, platelet count > 100×10^9/l, serum bilirubin less than 1.5 times the upper normal limit (UNL), aspartate transaminase (AST) or alanine transaminase (ALT) and alkaline phosphatase (ALP) less than twice UNL (or less than five times UNL in the presence of liver metastases) and calculated creatinine clearance > 50 ml/min. Patients with primary brain tumours or brain metastases were eligible provided they had stable symptoms and had received a stable dose of steroids for 1 month prior to receiving study drug and were able to give informed consent.

Patients were ineligible in the event of: pregnancy or lactation; previous chemotherapy with BBR 3464; previous treatment with PVI 5-FU in the 6 months prior to study enrolment; radiotherapy, nitrosoureas, mitomycin C or melphalan within 6 weeks of the start of treatment; other cytotoxic chemotherapy within 4 weeks of the start of treatment; full anticoagulation therapy with warfarin (eligible if an alternative anticoagulant could be used). Patients were also excluded if they had clinically significant cardiovascular disease (including myocardial infarction within the prior 6 months, severe arrhythmia or uncontrolled hypertension); symptomatic motor or sensory neurotoxicity NCI CTC (National Cancer Institute Common Toxicity Criteria) grade 2 or more; psychiatric disabilities, seizures or CNS disorders thought to be clinically significant; known chronic obstructive airways disease or interstitial lung disease (dyspnoea NCI CTC grade 3 or more); carbon monoxide diffusion capacity < 50% of predicted value; prior disposition to diarrhoea (e.g. inflammatory bowel disease).

Initially, unless contraindicated, patients were treated with warfarin 1 mg/day to prevent Hickman line thrombosis. After commencement of this trial, other studies identified a potential interaction between BBR 3464 and warfarin, so patients no longer received warfarin prophylaxis.

Drug supply and administration

BBR 3464 was provided as a freeze-dried formulation in clear glass vials each containing 1.5 mg BBR 3464 and 150 mg mannitol. The contents of each vial were reconstituted with 3.0 ml of special diluent (0.2% sodium chloride). The appropriate volume of the resulting solution was then made up with 0.9% sodium chloride to a total volume of 500 ml. One course of therapy was 21 days and patients received up to six courses of therapy during this study. For each course BBR 3464 was administered as an intravenous infusion via a skin-tunnelled catheter over 1 h on day 1 followed by a 21-day observation period. As nausea and vomiting had not been a major feature in the intermittent schedule phase I trial of single-agent BBR 3464, no regimen of prophylactic antiemetics were stipulated in the protocol, although for some patients who had suffered nausea and vomiting with previous chemotherapy, oral dexamethasone 10 mg and oral granisetron 1 mg were administered prior to BBR 3464 infusion.

5-FU was presented in clear glass vials containing fluorouracil as the sodium salt, in Water for Injection BP as 25 mg/ml and 50 mg/ml solutions in different presentations. Fluorouracil was administered at a dose based on the patient's body surface area diluted in 5% glucose or 0.9% NaCl and was given continuously by PVI via a skin-tunnelled catheter 24 h per day for all 21 days of the 21-day cycle.

The start dose (level 1) of BBR 3464 was 0.6 mg/m^2 and of PVI 5-FU was 200 mg/m^2 per day. Initially, three patients were treated at each dose level outlined in the escalation schedule (Table 1). Level 5 would have represented full doses of both agents when administered as single agents. Dose escalation was based on observation of DLT. The first patient enrolled at each given dose level was monitored for 2 weeks before additional patients were entered at that dose level. If the initial patient was able to tolerate the combination of BBR 3464 and PVI 5-FU without experiencing

Table 1 Intended dose escalation schedule

Dose level	BBR 3464 (mg/m^2)	PVI 5-FU (mg/m^2/day)	Number of patients
1	0.60	200	3–6
2	0.75	200	3–6
3	0.75	250	3–6
4	0.90	250	3–6
5	0.90	300	3–6

serious unexpected toxicity, two additional patients were enrolled at the same dose level. At dose levels where none of the patients experienced DLT a maximum of three patients were treated. If a DLT was documented in the first three patients, an additional three patients were entered at that dose level. If no further DLTs were observed, dose escalation was to continue. If any DLT was observed in two or more patients at a given dose level (which would thus define the MTD), dose escalation was stopped.

The intention was to expand this patient cohort to ten patients and this dose level would represent the doses of BBR 3464 and 5-FU recommended for subsequent phase II studies. The doses were not escalated within a single patient during subsequent courses. Dose modifications based on toxicity were based on the NCI CTC version 2.0, and were discussed between the sponsor's medical representatives, investigators and Theradex (Europe) Ltd.

DLTs were defined as occurring in courses 1 and 2 only. DLTs were defined as: CTC grade 4 neutropenia lasting more than 5 days or febrile neutropenia, regardless of duration; CTC grade 4 thrombocytopenia; CTC grade 3 nonhaematological toxicity excluding alopecia, nausea and vomiting, but including diarrhoea despite loperamide treatment.

Before study entry a medical history and complete physical examination were performed. Prior to the study an audiogram, an electrocardiogram (ECG) and pulmonary function tests were performed. Audiogram and ECG were repeated during the study if clinically indicated. Pulmonary function tests were repeated after the second course of treatment and after completion of treatment (if more than two courses were administered). Disease status was evaluated with a baseline chest radiograph and appropriate radiological investigations. These were repeated after two cycles of treatment. Response Evaluation Criteria in Solid Tumours (RECIST) were used to assess tumour responses.

Results

Patient characteristics

The study group comprised 14 patients, 8 (57%) male and 6 (43%) female, with a median age was 56.5 years (range 35–74 years). The baseline WHO performance status was 0 in five patients (36%) and was 1 in nine patients (64%). The most frequently observed tumour site was the rectum (29%) and all of these tumours were characterized as adenocarcinomas. Histopathological tumour types for other primary sites were adenocarcinoma (small bowel, colon, oesophagus, breast, cervix and unknown site), glioblastoma (brain), poorly differentiated serous carcinoma (ovary), leiomyosarcoma (pelvis) and transitional cell carcinoma (bladder). The primary tumour site was unknown for one patient. The exposure of patients to prior antitumour therapy is presented in Table 2. All 14 patients had prior surgery, 13 patients (93%) had undergone previous chemotherapy, 3 patients (21%) had received prior hormone therapy, 1 patient (7%) had received prior immunotherapy and 9 patients (64%) had previously been treated with radiation therapy.

Table 2 Prior antitumor therapy: all enrolled patients

Therapy	Yes		No	
	n	%	*n*	%
Chemotherapy	13	93	1	7
Hormone therapy	3	21	11	79
Immunotherapy	1	7	13	93
Radiation therapy	9	64	5	36
Surgery	14	100	0	0

Dose escalation

No DLT was encountered in the first three patients entered at dose level 1 (0.6/200) and therefore the BBR 3464 dose was increased to 0.75 mg/m^2. (It was noted that although not a DLT, one patient had his 5-FU infusion discontinued for 5 days because of grade 3 neutropenia.) At dose level 2 (0.75/200), one of the first three patients experienced DLT (grade 4 fatigue and grade 3 diarrhoea) and therefore this dose level was expanded to six patients. No further patients experienced DLT as defined in the protocol, but in 10 out of 19 completed cycles the patients did not receive the intended dose intensity of the combination as a result of day 15 grade 3 or 4 neutropenia (resulting in discontinuation of PVI 5-FU as per protocol). The neutrophil count had recovered by day 22 in all of these cases. Therefore, following discussions between the sponsor, investigators and Theradex (Europe) Ltd, the BBR 3464 dose was de-escalated and further patients were enrolled at an intermediate dose of 0.68 mg/m^2 while keeping the dose of PVI 5-FU unchanged at 200 mg/m^2 per day. Of two patients enrolled at this dose, one experienced grade 4 neutropenia, and the other experienced grade 3 sepsis, grade 2 dyspnoea and grade 3 hypoxia. In these patients the 3rd week of PVI 5-FU was omitted in six out of six completed cycles because of neutropenia.

Following further discussion between the sponsor, investigators and Theradex (Europe) Ltd, it was decided to expand dose level 1 to six patients. These three additional patients required PVI 5-FU to be discontinued on day 15 in 11 out of 11 completed courses because of grade 3 or 4 neutropenia. Again, in all ten patients for whom a day-22 neutrophil count was available, there had been a full recovery (no day-22 neutrophil count available for one cycle in one patient). We would not have anticipated this on the basis of the first three patients entered into the trial, as only one required a 5-day discontinuation of PVI 5-FU whilst an inpatient because of documented grade 3 neutropenia, but this was not dose-limiting as defined in the protocol and had recovered by day 15.

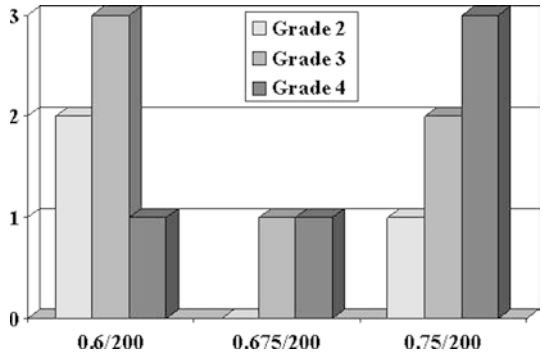


Fig. 2 Grade of neutropenia according to dose level

Of the 14 patients treated at all dose levels studied, 9 missed the 3rd week of infusional 5-FU due to grade 3 or 4 neutropenia, from which they subsequently recovered. Although these events were not dose-limiting according to the protocol definition, they imposed limitations on the dose of PVI 5-FU administered. Therefore, following discussion between the sponsor, investigators and Theradex (Europe) Ltd, it was concluded that using this combination it was not possible to deliver the desired dose and schedule of PVI 5-FU and that further dose de-escalation would lead to a dose of BBR 3464 below that expected to have a therapeutic effect, so it was agreed to stop recruitment to the trial.

Toxicities related to the BBR 3464/PVI 5-FU combination

Haematological

Neutropenia occurred in 11 out of 14 patients (79%) and was a feature at all dose levels (see Fig. 2) but with a tendency for more profound neutropenia with higher dose of BBR 3464. There were two episodes of neutropenic sepsis throughout the course of the study, both occurring at the highest dose level of BBR 3464 (0.75 mg/m^2). Leucopenia occurred in nine patients (64%), lymphopenia in four patients (29%), thrombocytopenia in two patients (14%) and anaemia in one patient (7%).

Importantly, the level of neutropenia was compromising the use of the combination as it prevented the safe administration of the day-15 to 22 PVI 5-FU.

Nonhaematological

The most notable nonhaematological toxicities were nausea, fatigue and diarrhoea (see Tables 3, 4 and 5). Nausea occurred in 13 patients (93%) and did not particularly increase in severity with increased dose of BBR 3464. With the exception of one patient, (CTC grade 3) nausea was CTC grade 2 or less. Nausea immediately following administration of BBR 3464 was never greater than grade 1 and was unrelated to antiemetic prophylaxis used (some patients received no antiemetic prophylaxis, some received granisetron only and some received granisetron and dexamethasone, depending on nausea or vomiting experienced with previous chemotherapy). Most nausea (including all grade 2 or 3 nausea) occurred 3 days or more after the administration of BBR 3464 and particularly affected the middle week of the 21-day cycle. Fatigue affected 11 patients (79%), was a major cause of morbidity and was more severe as the dose of BBR 3464 was increased. Fatigue was CTC grade 3 in three patients and CTC grade 4 in two patients. All of these patients described at least grade 1 fatigue at baseline. Diarrhoea (extent restricted by administration of loperamide) occurred in ten patients (71.4%), but only two had CTC grade 3 diarrhoea (no grade 4 diarrhoea).

Abdominal pain was a problem in eight patients (57%), in four of whom it was felt to be related to treatment and in two of whom it was associated with diarrhoea. The following toxicities occurred at CTC grade 2 or less: anorexia (six patients); taste disturbance (seven patients); alopecia (five patients); and stomatitis (four patients). No palmar-plantar erythema was encountered at the PVI 5-FU dose administered. There was one skin-tunnelled catheter-associated infection and

Table 3 Incidence of nausea at each dose level (number of patients at each CTC grade)

Dose level	Grade				
	0	1	2	3	4
1 + 4 (0.6/200)		3	3		
3 (0.675/200)	1		1		
2 (0.75/200)		4	1	1	

Table 4 Incidence of fatigue at each dose level (number of patients at each CTC grade)

Dose level	Grade				
	0	1	2	3	4
1 + 4 (0.6/200)	2		2	1 (1 at baseline)	1 (1 at baseline)
3 (0.675/200)			1	1 (1 at baseline)	
2 (0.75/200)	1	1	3		1 (1 at baseline)

Table 5 Incidence of diarrhoea at each dose level (number of patients at each CTC grade)

Dose level	Grade				
	0	1	2	3	4
1 + 4 (0.6/200)	2	2		2 (1 at baseline)	
3 (0.675/200)	1	1			
2 (0.75/200)	1	1	3	1	

one catheter-related thrombosis in a femoral vein that occurred in a patient already receiving tinzaparin for thromboembolic disease.

ALP, gamma glutamyltransferase (GGT) and transaminases were monitored throughout the study. Sporadic grade 1 or 2 abnormalities in transaminases were noted throughout the study in 12 of the 14 patients. All ALT levels had returned to normal by the off-study assessment in 9 of 12 patients. Five patients had AST abnormalities at the off-study assessment but none was more than grade 1. ALP levels were elevated at baseline in seven patients, were elevated during study in ten patients (grade 1 in seven, grade 2 in three) and had not returned to normal by the off-study assessment in any patients, making it difficult to assign causality. GGT levels were elevated at baseline in eight patients, were elevated during study in 11 patients (grade 1 in two, grade 2 in three, grade 3 in six) and eight of these had not returned to normal by the off-study assessment.

The derangement in liver function tests in one patient was reported as a serious adverse event. The patient, who had metastatic adenocarcinoma of the cervix without liver involvement had normal liver function tests at baseline. There was no evidence of bony metastases. Throughout her treatment her bilirubin and AST levels were normal. She suffered a progressive deterioration in her ALP and GGT levels to grade 2 and grade 3 levels, respectively, at which time she was removed from trial therapy. These indices both reached maximal levels 18 to 21 days after her last dose of BBR 3464 before progressively falling, although not back to within the normal range. Hepatitis screen was negative. Ultrasound and CT of the liver and porta hepatis revealed no cause for the derangement in liver function tests. Therefore a liver biopsy was performed and revealed normal liver architecture with no fibrosis. There was a focal mild ductular reaction around a few portal areas but no lobulitis. It was considered that this patient's blood chemistry abnormality was probably related to the study drug.

Antitumour activity following administration of BBR 3464

Of the 14 patients entered into the study, one patient achieved a partial response, three patients stable disease and seven patients had progressive disease. Three patients were not evaluable for efficacy: two were removed from the study due to serious adverse events (deep vein thrombosis and infection), and one was removed from the study on day 13 due to disease progression. The patient who achieved a partial response and the three patients with stable disease were the only patients to complete the planned six courses of combined therapy.

The partial response was noted in a 53-year-old female with invasive carcinoma of the right breast. This patient had been heavily pretreated: hormonal therapies (tamoxifen, Arimidex, Zoladex); CMF (cyclophosphamide, methotrexate and 5-FU); Adriamycin and cyclophosphamide; capecitabine and docetaxel; vinorelbine; Herceptin. She received six courses of therapy, beginning at BBR 3464 dose level 2 (0.75 mg/m^2) and 200 mg/m^2 per day PVI 5-FU, although after course 1 the doses were reduced to 0.60 mg/m^2 BBR 3464 (20% reduction to the previous dose level) and 150 mg/m^2 per day PVI 5-FU (25% dose reduction as already at the starting dose level for PVI 5-FU). The partial response was documented during course 3 of therapy and confirmed 9 weeks later on completion of course 6 (see Figs 3 and 4). The patient's disease progressed 2.5 months after the completion of therapy.

The first patient with stable disease was a 59-year-old female with adenocarcinoma of the rectum, previously treated with 5-FU and irinotecan. The patient received six courses of therapy, at BBR 3464 dose level 2 (0.75 mg/m^2) and 200 mg/m^2 per day PVI 5-FU. The patient was found to have stable disease during course 3, which was confirmed 9 weeks later at the end of course 6. This patient's disease progressed 5 months after finishing her last cycle of treatment. The second patient with stable disease was a 61-year-old Caucasian male with primary site of disease unknown. Previously

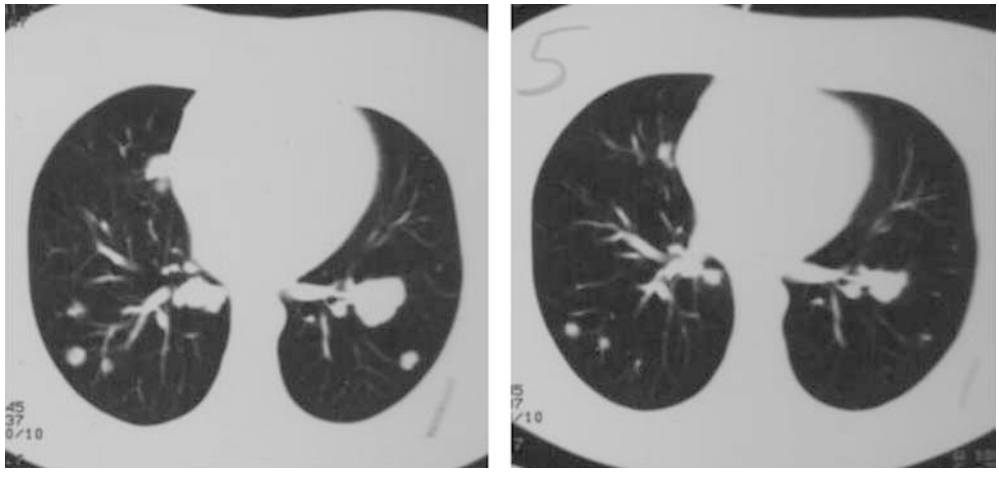


Fig. 3 Patient 05: lesion 1 before and after treatment with BBR 3464 and PVI 5-FU

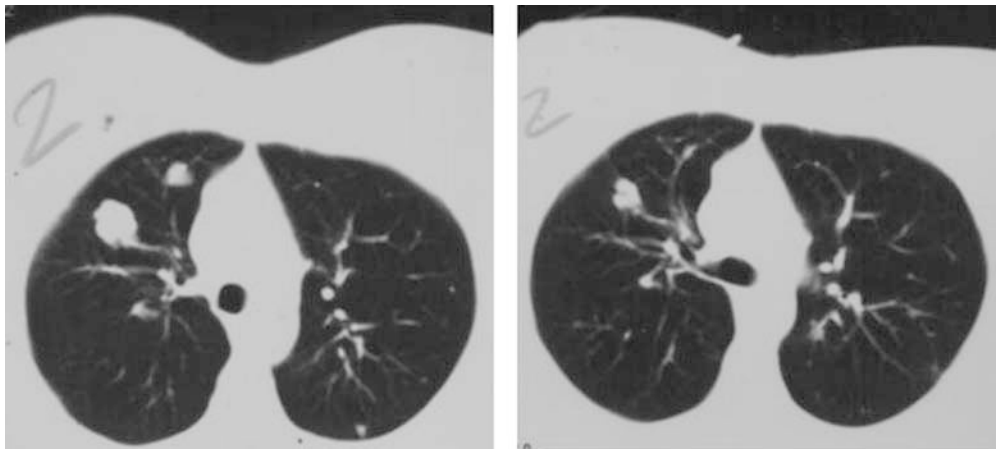


Fig. 4 Patient 05: lesion 2 before and after treatment with BBR 3464 and PVI 5-FU

untreated with cytotoxic agents, the patient received six courses of therapy, beginning at the intermediate BBR 3464 dose level (0.68 mg/m^2), which was reduced to 0.60 mg/m^2 (25% dose reduction) for courses 3 through 6. PVI 5-FU was maintained at 200 mg/m^2 per day. Stable disease was recorded during course 3 and was confirmed 11 weeks later after completion of course 6. This patient's disease progressed 2 months after his last cycle of BBR 3464/PVI 5-FU. The third patient with stable disease was a 65-year-old male with transitional cell cancer of the bladder who had previously received four cycles of CMV (cisplatin, methotrexate, vinblastine) chemotherapy. The patient received six courses of therapy, beginning at BBR 3464 dose level 1 (0.60 mg/m^2), which was reduced to 0.45 mg/m^2 (25% dose reduction) for courses 3 through 6. PVI 5-FU remained at 200 mg/m^2 per day. The patient was found to have stable disease during course 3, which was confirmed 10 weeks later at the end of course 6. This patient's disease progressed 2 months after completing his last cycle of BBR 3464/PVI 5-FU.

Discussion

This study was designed to evaluate the combination of BBR 3464 administered 3-weekly with PVI (continuous for 21 days) 5-FU. The major toxicities encountered were myelosuppression and diarrhoea, as would have been predicted from the phase I studies of single-agent BBR 3464 (Fig. 3, Tables 3 and 5) [11, 14]. Fatigue was also a major factor following administration of BBR 3464/PVI 5-FU (Table 4).

However, in this study the MTD (as defined in the protocol) was not encountered. Dose escalation was stopped and dose de-escalation commenced because the intended PVI 5-FU dose intensity could not be delivered as a result of neutropenia on day 15, leading to discontinuation of PVI 5-FU. This degree of neutropenia could have been predicted from the single-agent phase I studies of BBR 3464. In the intermittent schedule (TPT-I-01 protocol), patients received BBR 3464 on day 1 of a 28-day cycle. The main DLTs were neutropenia and diarrhoea, the former being a feature even at the 0.2 mg/m^2 dose level (although not dose-limiting at this dose level). The median nadir was day 14 and the median recovery of the neutrophil count was by day 21. In the intermittent 3-weekly schedule (TPT-I-01/21 days schedule protocol) when BBR 3464 was administered every 21 days instead of every 28 days, grade 3 or 4 neutropenia occurred in 13 out of 21 courses at 0.9 mg/m^2. Similar toxicity was observed in the fractionated daily ×5 schedule (TPT-I-02 protocol) [14]. In the present study there was a high incidence of grade 3 or 4 neutropenia (resulting in discontinuation of PVI 5-FU as per protocol) but recovery of neutrophil count was always achieved by day 22.

The frequency of grade 3 or 4 neutropenia encountered with BBR 3464 /PVI 5-FU in this study was high (79%) compared to that found in various studies using epirubicin, cisplatin and PVI 5-FU (ECF) in locally advanced and metastatic oesophagogastric and breast carcinoma where the rate of grade 3 or 4 neutropenia/leucopenia varied from 2% to 42% [1, 7, 15]. In these studies, PVI 5-FU was not discontinued for neutropenia or leucopenia, although in some the dose of PVI 5-FU was decreased if administration of cisplatin and epirubicin had to be delayed because of myelosuppression [7, 15]. In our unit and other units in the UK, it has been routine practice when administering ECF to omit PVI 5-FU for grade 3 or 4 neutropenia. This is most frequently performed during the 3rd week of the 21-day cycle. It was on the basis of this that the protocol was written to include PVI omission if the neutrophil count fell below 1.0×10^9/l, but it could be argued that in view of the low incidence of myelosuppression when 5-FU is given in a continuous infusion [9] we could have continued the PVI 5-FU despite neutropenia, thus administering the desired dose intensity of the regimen without compromising patient safety. This argument is supported by the fact that the neutrophil count had always recovered by day 22 (as in the single-agent phase I studies). There is no evidence that the PVI 5-FU contributed to the myelosuppression encountered in this study.

A skin-tunnelled catheter-related thrombosis was noted in one patient who interestingly was on treatment dose tinzaparin for thromboembolic disease. Initially, it had been intended to administer prophylactic minidose warfarin (1 mg/day) in the patients entered into this study. However, a potential interaction between warfarin and BBR 3464 was noted in a separate study and therefore this practice was discontinued. However, serial international normalized ratio (INR) monitoring in the first two patients entered who received minidose warfarin showed no rise in INR associated with the administration of BBR 3464 (data not shown).

Despite dose reductions and omission of PVI 5-FU compromising dose intensity severely, one patient (7%) responded to the regimen and three others (21%) had stable disease. This partial response occurred despite the fact that the patient had previously been treated with both 5-FU (in two different regimens) and capecitabine, suggesting that BBR 3464 may have contributed to the response.

In this study, the MTD was not defined using the criteria outlined in the protocol. The decision not to modify the protocol either to allow treatment with PVI 5-FU on day 15 despite grade 3 or 4 neutropenia was made for safety reasons. Also the potential to modify the protocol to electively discontinue PVI 5-FU on day 15 or combine BBR 3464 with capecitabine was made, as preliminary data from phase II studies being performed in gastric cancer had demonstrated insufficient single-agent activity of BBR 3464 to merit combination studies in this disease [6]—a major rationale for the combination tested. The clinical results obtained in those trials were not consistent with the efficacy identified in preclinical studies. The reason for this discrepancy is as yet unclear. One hypothesis that has been suggested is a species difference in pharmacokinetics as higher amounts of BBR 3464 are bound to plasma protein in humans than in mice, and the degradation of BBR 3464 to inactive species is more rapid in human plasma than in mouse plasma (Novuspharma, 2001, data on file). Whether novel formulations associated with a better pharmacokinetic profile (e.g. targeted delivery technologies) could improve the clinical efficacy of BBR 3464 remains to be clarified.

In summary, BBR 3464 could not be combined safely with PVI 5-FU at a dose sufficient to be associated with antitumour activity and simultaneously allow the maintenance of 5-FU dose intensity throughout the complete 21-day cycle.

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