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Short Communication

A Phase I Study of Intravenous RMP-7 with Carboplatin in Patients with Progression of Malignant Glioma

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RMP-7, a nine amino acid peptide bradykinin agonist, increases the delivery of hydrophilic compounds across the blood–tumour barrier. In this dose ranging study, 14 patients with progressing malignant glioma (9 glioblastoma multiforme, 4 anaplastic astrocytoma, 1 anaplastic oligodendroglioma; age range 31–68 years, baseline Karnofsky range 60–90%, 5 having had prior chemotherapy) were treated with intravenous RMP-7 and carboplatin to assess the safety, tolerability, and side-effect profile of increasing doses of this combination. Carboplatin dosing was by target area under the curve (AUC) according to the Calvert protocol. Patients were allocated to one of five treatment regimes: cohort A ($n = 2$) received 50 ng/kg RMP-7 and target AUC 5 mg/ml/min carboplatin; cohort B ($n = 3$) 100 ng/kg RMP-7 + AUC 5; cohort C ($n = 2$) 100 ng/kg RMP-7 + AUC 7; cohort D ($n = 2$) 200 ng/kg RMP-7 + AUC 7; cohort E ($n = 5$) 300 ng/kg RMP-7 + AUC 7. Treatment was given once every 4 weeks with magnetic resonance imaging scans every 2 months. Patients received 37 cycles in total (median 2, range 1–7). The drug combination, as a cancer treatment, was tolerated in all groups. Effects possibly related to RMP-7 included flushing, nausea, headache and mild increase in heart rate, all transient. 3 patients in cohort E experienced grade 3/4 neutropenia and thrombocytopenia. These toxicities are consistent with known effects of carboplatin at this dose range. In cohort E ($n = 5$) 1 patient improved and another remained stable for ≥ 6 months. In summary, the dose was escalated to the maximum dose of RMP-7 given to volunteers without additional related side-effects. The side-effects of the combination were consistent with giving the two drugs alone and would merit further study for efficacy. **© 1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE PROGNOSIS for patients with high grade malignant glioma (WHO grades III–IV) remains dismal. Radiotherapy significantly improves survival compared with supportive therapy or nitrosourea chemotherapy alone [1], but relapse is the outcome even with radiation dose escalation [2–4] or adjuvant chemotherapy [5, 6]. Chemotherapy for relapsed disease is unsatisfactory and more effective treatment is urgently needed [7], although some success has been reported for anaplastic oligodendroglioma [8].

In vitro tumour sensitivity to CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) and procarbazine is significantly related to an increased relapse-free interval with adjuvant procarbazine, CCNU and vincristine [9], but other drugs active *in vitro* (e.g. 5-FU (5-fluorouracil), cytosine arabinoside, carboplatin) have low clinical activity [10–12]. This difference between *in vitro* and *in vivo* response has been ascribed to the blood–brain barrier which limits access of water soluble agents to normal brain and tumour [13, 14]. Thus, a strategy for treatment should be to open the blood–brain barrier within and around the tumour at the time of administration of such active but water soluble chemotherapy. Carboplatin, which exhibits a dose–response relationship in terms of the percentage patients responding to treatment for a wide range of non-cerebral tumours, is among the most active agents *in vitro* and has less neurotoxicity and less renal toxicity than cisplatin [11, 15].

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RMP-7, a synthetic nonapeptide, is a B2 receptor agonist, but without the marked B1 effects and very short half-life of native bradykinin. Electron microscopy in animals has shown that intravenous RMP-7 increases blood–brain barrier permeability by a transient effect on the tight junctions between brain capillary endothelial cells [16]. Studies in animals and man have demonstrated that RMP-7 transiently increases the permeability of the tumour–blood barrier without adverse affects on the brain, in a dose-dependent manner [17–19]. Transient dose-related effects (flushing, warmth, paraesthesia, nausea and/or vomiting headache) were observed in normal volunteers receiving RMP-7 given as a 2 min bolus or 10 min infusion and demonstrated the safety of doses between 30 and 300 ng/kg [20]. However, no higher regimes have been tested at this time.

The present study was a phase I dose ranging study to assess the safety, tolerability and side-effect profile of the combination of intravenous RMP-7 and carboplatin in patients with progression of high grade glioma.

PATIENTS AND METHODS

This study was an open, single centre assessment of escalating doses of RMP-7 and carboplatin. The protocol was granted a Clinical Trial Exemption Certificate by the Medicines Control Agency and was approved by the Local Research Ethics Committee at Addenbrooke's Hospital, Cambridge, U.K. All patients provided written informed consent to their participation.

Patients

Male or female patients, aged 18–75 years, with histologically proven high grade glioma and progression of disease documented by clinical status or imaging, were recruited to the study. Tumours were enhancing on magnetic resonance imaging (MRI) scans. Patients were excluded if they had received chemotherapy for glioma in the previous 6 weeks or radiotherapy to the brain in the previous 2 months. They were also excluded if they had a WHO clinical status of 3 or greater and haematology or biochemistry parameters outside defined limits of clinical significance. Other exclusion criteria were a life expectancy of less than 8 weeks, markedly raised intracranial pressure, pregnancy, lactation or other clinically significant disease.

Treatment

Successive cohorts of patients were administered treatment according to the dose escalation protocol defined in Table 1. Patients received 4 weekly cycles of the combination of RMP-7 and carboplatin. When all the patients in a cohort had completed the first cycle without dose-limiting toxicity, new patients were recruited to the next cohort. Patients suffering marrow suppression could have subsequent cycles of chemotherapy delayed to allow recovery and cycles of chemotherapy could be continued until, in the opinion of the investigator, it was no longer in that patient's best interests.

Table 1. *Dose escalation protocol*

Cohort	Carboplatin dose (target AUC)	RMP-7 dose (ng/kg)
A	5	50
B	5	100
C	7	100
D	7	200
E	7	300

AUC, area under the curve.

Carboplatin (in 250 ml 5% dextrose) was administered as a 15 min infusion via an infusion pump. The carboplatin dose was calculated according to the Calvert formula [21] using glomerular filtration rate (GFR) by ^{51}Cr-ethylene diamine tetraacetic acid (EDTA) and the target area under the curve (AUC) for the cohort (Table 1). RMP-7 was provided as a sterile solution at a concentration of 0.02 mg/ml which was diluted to the required volume with 0.9% saline. Doses of 50 and 100 ng/kg were given as a 2 min bolus injection during the last 5 min of the carboplatin infusion, whilst 200 and 300 ng/kg doses were administered as a 10 min infusion commencing 10 min after the carboplatin infusion began. Anti-emetic therapy was given routinely; ondansetron (8 mg intravenously) was given 30 min prior to the start of the carboplatin infusion, dexamethasone (8 mg intravenously) was given 2 h post-treatment and oral ondansetron, 12 and 24 h post-treatment.

Assessments

Laboratory and clinical assessments were undertaken during each cycle of therapy. MRI scans were repeated at the end of cycle 2 and at the end of subsequent even numbered cycles or on clinical relapse if earlier. Tumour volume was assessed from the images by the reviewing consultant radiologist. Drug toxicity grading was undertaken during each cycle according to the NCI Common Toxicity Criteria (CTC); toxicity was assessed by history, physical examination and blood (FBC, urea, creatinine, electrolytes, CK and liver function) and urine (dipstick) testing on days -1 and 15 of each cycle. An electrocardiogram (ECG) was also performed at baseline and at the end of the study. Clinical assessments included neurological function and neurological impairment by the MRC Neurological Status Scale and clinical performance by the Karnofsky Index and the WHO clinical performance status rating scale. In addition, blood samples for carboplatin pharmacokinetic measurements were taken in cohort B onwards, at 0, 15, 20 and 30 min and 1, 2, 4, 6, 12 and 24 h after the infusion commenced.

4 of the 5 patients in cohort E also underwent computed tomography (CT) contrast imaging to assess the blood to brain transfer constant and, thus, to measure the permeability of the blood–brain barrier prior to treatment and during RMP-7 infusion. The results of these blood–brain barrier studies have been published separately [19].

RESULTS

14 patients received a total of 37 (median 2, range 1–7) cycles of treatment and remained in the study for between 41 and 226 days. The baseline characteristics of these patients are listed in Table 2. 12 patients were withdrawn from the study because of disease progression. 1 patient died during the study period and another was discontinued because of an adverse event (ECG changes). A patient who had been discontinued because of disease progression died 6 days after withdrawal.

Evidence of toxicity was noted for all patients, but cumulative toxicity was not seen. The numbers of patients experiencing grade 3 and 4 toxicity, either present at baseline or up to cycle 4 in the study are presented in Table 3. Grade 3/4 toxicities are also presented by cohort. Only 3 patients, all

Table 2. Baseline characteristics of the patients

Cohort	Age (gender) years	Tumour type	Previous radiation therapy	Previous chemotherapy	WHO clinical performance	Karnofsky score (%)
A	41 (M)	AO	Yes	None	1	80
A	54 (M)	GM	Yes	None	2	80
B	62 (F)	GM	No	None	2	70
B	49 (M)	GM	Yes	None	1	90
B	31 (F)	AA	Yes	PCV, temozolamide	2	70
C	35 (M)	AA	Yes	PCV	2	70
C	72 (M)	GM	No	None	1	80
D	56 (M)	GM	Yes	None	0	90
D	68 (F)	GM	No	None	2	70
E	33 (F)	GM	Yes	PCV	0	90
E	51 (M)	GM	Yes	PCV	0	90
E	45 (F)	AA	Yes	None	1	90
E	40 (M)	AA	Yes	None	0	90
E	53 (M)	GM	Yes	PCV	2	60

AO, anaplastic oligodendroglioma; GM, glioblastoma multiforme; AA, anaplastic astrocytoma; PCV, procarbazine + CCNU + vincristine.

receiving carboplatin AUC 7 and RMP-7 300 ng/kg (cohort E), experienced grade 3/4 thrombocytopenia and/or neutropenia and all 3 had received previous PCV chemotherapy. In 2 of these 3 patients myelosuppression resulted in treatment delay and dose reduction for two cycles—1 was admitted to hospital with neutropenic sepsis and 1 experienced grade 3 anaemia at cycle 4. 4 patients received transfusions, either whole blood or platelets. 2 patients in cohort E continued to receive chemotherapy beyond four cycles; 1 of these patients continued to experience haematological toxicity (white blood cells, platelets, granulocytes/bands and lymphocytes) in cycles 5, 6 and 7.

Grade 3 hyperglycaemia was seen in 1 patient at baseline and throughout the study and in a further 2 patients during the treatment phase of the study. All were receiving steroids.

Other relatively minor adverse events were reported in all patients; the most commonly reported events were vasodilation, headache, nausea and vomiting. 9 patients experienced a total of 21 episodes of vasodilation (flushing, feeling hot), 19 of which were considered either definitely or probably related to the associated RMP-7 administration. The majority of episodes of nausea and vomiting were primarily related to carboplatin, but events which were considered probably or possibly related to RMP-7 included headaches, nausea, vomiting, tiredness, mild tachycardia, mild rise in blood pressure (CTC grade 1 or less) and asymptomatic T wave changes on ECG (also CTC grade 1) in 2 cases. The majority of these events were mild in severity and resolved either spontaneously or following therapeutic intervention.

Other adverse events which were considered to be related to the patients' concomitant medication, primarily the steroids, included candida, proximal myopathy, weight gain, arthralgia, agitation, intermittent dyspepsia and abdominal pain. Raised transaminases were noted in 9 patients at baseline; there was no consistent change in transaminase on study treatment.

11 (79%) patients had at least one serious adverse event, defined as at least one of the following: fatal, life-threatening, resulting in or prolonging hospitalisation. Four events in 3 patients were considered possibly related to RMP-7. 1 patient experienced episodes of dizziness, headache and what were probably seizures requiring hospitalisation, but subsequent similar occurrences were attributed to tumour progression. Another patient experienced vomiting and associated headache the day after treatment in cycle 1, resulting in the period of hospitalisation being prolonged. The third patient demonstrated ECG changes (T wave inversion in I, II, AVL, V4-V6) without associated cardiac signs or symptoms, after two cycles of chemotherapy, resulting in prolongation of hospitalisation for investigation.

There were 3 patients in whom asymptomatic T wave ECG changes were seen, one in each of cohorts B, D and E. All 3 of these patients had disease progression at the time this occurred. The patient in cohort E died of tumour progression

Table 3. Summary of grade 3 and 4 toxicities by number of patients*

Parameter	Number of patients							By cohort†		
	Baseline ($n=14$)	Cycle 1 ($n=14$)	Cycle 2 ($n=11$)	Cycle 3 ($n=4$)	Cycle 4 ($n=3$)	Final ($n=12$)	Total no.	Cohort C ($n=2$)	Cohort D ($n=2$)	Cohort E ($n=2$)
WBC	1	3	1		1		3			2
Platelets		2			1		3			3
Haemoglobin					1		1			1
Granulocytes/bands	1	3	1		1		3			2
Lymphocytes	6	7	3	1	2	3	8	1		2
Infection		1					1			1
Hyperglycaemia	1	2	1	1	1	2	3		1	1

WBC, white blood cells. *WBC ≤ 1.9, platelets ≤ 49.9, haemoglobin ≤ 7.9 g/dl, granulocytes/bands ≤ 0.9, lymphocytes ≤ 0.9, hyperglycaemia ≥ 14.0 mmol/l, infection (severe or life threatening). † No grade 3 or 4 toxicities were seen in cohorts A and B after dosing.

Table 4. *Carboplatin pharmacokinetic (free platinum) results by cohort*

RMP-7 dose (ng/kg)	Mean C_{max} (μg/ml)	Mean $t_{1/2}$ (min)	Mean V_{dis} (1)	Mean CLR (ml/min)
100 ($n = 3$*)	71.3	29.1	32.7	122.0
200 ($n = 2$*)	105.0	29.0	27.5	123.0
300 ($n = 4$*)	91.7	66.6	19.5	111.8

*Number of PK assessments. C_{max}, maximum concentration; $t_{1/2}$, half-life; V_{dis}, volume of distribution; CLR, clearance.

shortly after discontinuation from the study. Subsequent cardiac histopathology revealed only mild atherosclerosis without any areas of significant stenosis, no inflammatory infiltrate and no significant degree of fibrosis.

Only 1 patient died during the study period. He had clinical tumour progression, had discontinued his steroids and died from intracranial hypertension. The event was not considered related to RMP-7.

There was no clinically apparent change in hearing, vision or peripheral nerve function during the study. 9 patients had serial audiograms, including those who had four, six and seven cycles of chemotherapy. 1 patient with poor audiology prior to treatment developed a possible further 20 DB high tone hearing loss after two cycles, but co-operation with the test was poor and he had received aminoglycoside antibiotics. 4 patients had areas of 10 DB loss and in 4 patients there was no change.

No clinically significant changes were observed in non-neurological routine physical examinations. All patients had normal renal function at baseline; a decrease in GFR was observed in the 8 patients, ranging from 7 to 36%, in whom repeat measurements were made, but the values remained within the normal range.

Carboplatin kinetics from the 7 patients studied at AUC 7 are detailed in Table 4, and are within the range previously reported for carboplatin alone.

In cohort E, 1 patient showed an improvement in neurological impairment according to an MRC score and was stable in terms of MRI tumour volume (change of less than 10%) on a reducing dose of steroid for 6 months. A further patient was stable both on imaging and neurological scoring (MRC neurological score and WHO performance status of 0) for 7 months. In this patient, although the overall size of the tumour did not change, the enhancing area showed significant reduction. 2 further patients demonstrated tumour progression by imaging (increases in volumes of 40 and 54%) over 2 months, but were neurologically stable and on a stable dose of steroids over that period. One of these patients underwent debulking surgery followed by PCV chemotherapy and was alive 10 months later. The fifth patient, previously treated with PCV (procarbazine, CCNU + vincristine) received only one cycle of RMP-7 and carboplatin and demonstrated rapid progression.

DISCUSSION

RMP-7 in combination with carboplatin is being developed for the treatment of malignant glioma and this was the initial administration of the intravenous RMP-7 and carboplatin combination in this indication. The objectives were to identify a maximum tolerated dose and to characterise the side-effect and toxicity profile.

The side-effect profile observed was consistent with the known side-effect profile of the two agents given alone. RMP-7 at a dose of 300 ng/kg and carboplatin at a dose of target AUC 7 was well tolerated. There was no evidence that RMP-7 modified the known toxicity of carboplatin. As previously reported, the side-effects considered possibly or probably related to RMP-7 were predominately vasodilatation, headache, nausea, vomiting, mild tachycardia and minimal hypertension. Typically, as previously described in normal volunteers, they arose early during the infusion, were mild and resolved within 5–20 min of completion of the infusion. The blood pressure in all patients remained within the normal range. Tiredness and fatigue were also considered as possibly related to RMP-7, but these are also known effects of chemotherapy.

There was no indication that RMP-7 modified other known effects of carboplatin, i.e. myelosuppression, delayed nausea and vomiting, or alterations in renal function and hearing. Modest falls in GFR occurred in the 8 patients where this was measured, but all except 1, which fell to 72 ml/min, remained in the normal range. Reductions in creatinine clearance were noted in a series of 1893 patients treated with carboplatin alone [15] with reduction to below 60 ml/min in 27% of that series. Clinically apparent hearing loss has been recorded in 1% of patients receiving carboplatin. Audiology changes in this study were minimal and there were no clinical changes in hearing.

Bronchospasm, urge to stool and piloerection have been reported with bradykinin administration. Such side-effects were not seen in this study and are presumably related to B1 agonism.

3 patients experienced at least one serious adverse event (seizures, delayed vomiting and ECG changes) that was contemporaneously considered possibly related to RMP-7. However, there is no substantial evidence for a newly identified serious adverse reaction to either RMP-7 or carboplatin. The seizures were consistent with tumour progression, whilst the delayed vomiting is consistent with the side-effect profile of carboplatin and has never been seen with RMP-7 alone. Changes in ECGs are not uncommon in patients with evolving intracranial lesions, having been noted in 10–20% of patients [22, 23]. No patient had symptoms, signs or radiological evidence of heart failure.

Assessment of efficacy was not an objective of this study. In the highest dose group ($n = 5$) and the regime subsequently selected for phase II studies, 1 patient showed neurological improvement on a reducing dose of steroids and another stabilisation, both for a reasonable period of time (6 and 7 months). There were insufficient numbers to estimate whether RMP-7 increases the limited response rate of carboplatin alone.

This approach using RMP-7 may be compared to osmotic disruption of the blood–brain barrier with intra-arterial mannitol. RMP-7 has been shown in animal tumour models [17, 24] and in the blood–brain barrier imaging studies undertaken as part of this protocol to reduce the blood–brain barrier within the tumour whilst sparing the normal brain [19]. This is important when potentially toxic chemotherapy agents are being administered. Conversely, experimental work suggests that mannitol disruption may have more effect on the blood–brain barrier in normal brain than in the tumour [25–27] and a high complication rate has been seen in clinical trials [28, 29].

The evidence from this study is that RMP-7 does not change the side-effect and safety profile of carboplatin, and vice versa, allowing both compounds to be administered without dose adjustment in patients with adequate bone marrow reserve. Reduction of carboplatin dose may be required in patients heavily pretreated with bone marrow ablative chemotherapy. With an adequate anti-emetic regime and in patients with adequate bone marrow reserves, carboplatin is a well tolerated chemotherapy drug. RMP-7 has shown no late side-effects. Side-effects during the infusion of the two drugs were mild and well tolerated and, thus, the combination of RMP-7 and carboplatin can be given in the out-patient setting. This combination is, therefore, suitable for use in future studies in this group of patients as an out-patient regime. If the combination is demonstrated to be at least as effective as nitrosourea-containing regimes, such as BCNU (bischloronitrosourea) or PCV, it will be advantageous as first-line therapy, because it does not cause persistent ablation of marrow reserve and does not have the complications of rash, prolonged nausea during oral therapy, and peripheral neuropathy which are associated with PCV. Clinical development of RMP-7 in combination with carboplatin in the treatment of brain tumours is now continuing.

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