Phase II study of BBR 3464 as treatment in patients with sensitive or refractory small cell lung cancer

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BBR 3464 is a novel triplatinum compound that has exhibited anti-tumor activity in both cisplatin-sensitive and cisplatin-resistant, as well as in p53 mutant tumor models. In phase I testing, the dose-limiting toxicities have included myelosuppression and diarrhea. Both an intermittent (day 1 every 21–28 days) and a continuous (daily × 5 days) schedule have been studied, and the intermittent schedule has been chosen for further development. The primary objective of this study was to assess the efficacy of BBR 3464 administered at a dose of 0.9 mg/m^2 i.v. over 1 h every 21 days in patients with small cell lung cancer who have progressed after first-line therapy. Pharmacokinetic analysis was also performed and will be reported. Patients were stratified based on prior response into resistant and sensitive (response duration 3 months or longer) subgroups. Thirty-seven patients were enrolled onto this multicenter study. The median number of cycles delivered was 2 in the resistant subgroup (range 1–12) and 3 in the sensitive subgroup (range 1–8). Most common grade 3/4 hematological toxicities included neutropenia (62%), febrile neutropenia (16%), anemia (10%), fatigue (5%) and hypokalemia (5%). Although no objective responses were seen in 34 evaluable patients, 11 patients (32%) had disease stabilization (four resistant/seven sensitive) with 23 patients (68%) experiencing continued disease progression (12 resistant/11 sensitive). Median time to progression was 53 days in the resistant subgroup [95% confidence interval (CI) 37–63] and 66 days in the sensitive subgroup (95% CI 51–136). The median and 1-year survival rate based on subgroup was 78 (resistant) (95% CI 56–165) versus 209 days (sensitive) (95% CI 83–296) and 6 (resistant) (95% CI 0–17) versus 20% (95% CI 2–38%), respectively. We conclude that the toxicity profile of BBR 3464 in this phase II trial is consistent with the phase I experience. The lack of activity in either patient subgroup, however, does not support further evaluation of this drug as a single agent in this disease. *Anti-Cancer Drugs* 17:697–704 © 2006 Lippincott Williams & Wilkins.

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Introduction

An estimated 171 900 new cases of lung cancer were diagnosed in the US in 2005 [1]. Between 15 and 20% of these patients will present with small cell disease. Although this percentage has dropped recently in the US, this still translates into an estimated 25 000–35 000 new cases annually. The majority of patients with small cell lung cancer will present with extensive-stage disease and will not be candidates for curative therapy. In recent studies of front-line cisplatin-based doublets, the median progression-free survival for this patient population has ranged from 4.8 to 8.0 months, with median, and 1- and 2-year survival rates of 8.9–12.8 months, and 25–58 and 10–20%, respectively [2,5]. Attempts to improve these outcomes by increasing dose intensity or adding a third drug have largely been unsuccessful [3,4]. For patients with limited-stage disease, there are more long-term survivors with 5-year survival rates of up to 26% reported with combined modality therapy [6]. The majority of these patients, however, will still progress within 2 years of completing therapy, with a median survival of 19–23 months [6,7].

Several drugs have been shown to have activity in the second-line setting in phase II trials, including topotecan, irinotecan, paclitaxel and gemcitabine [8,10]. In the US, topotecan is the only drug that is approved for this indication based on data from a randomized trial that compared topotecan to CAV (cyclophosphamide, doxorubicin and vincristine) in patients with sensitive disease who had relapsed greater than 60 days after first-line treatment [9]. Topotecan was associated with non-significant improvements in response rate (24.3 versus 18.3%, $P = 0.285$) and median time to progression (13.3 versus 12.3 weeks, $P = 0.552$) over CAV, with a similar toxicity profile to the combination regimen. The median

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survival for both groups was 25 weeks ($P = 0.795$). There were significant improvements in several disease-related symptoms, including dyspnea, hoarseness, fatigue and interference with daily activity with topotecan over CAV, however, suggesting that second-line therapy can have a palliative impact for this patient population.

Despite the increasing acceptance of the role of second-line therapy, there clearly remains a need to identify novel agents with activity in this disease. BBR 3464 is a novel trinuclear platinum (triplatinum) that has been shown to have activity against several tumor types in preclinical models, including lung cancer, and has been shown to be able to overcome cisplatin resistance [11,13]. Two schedules of this agent have been studied in phase I trials, including an intermittent schedule (day 1 every 28 days) and a continuous schedule (daily × 5) [14,15]. The dose-limiting toxicities for both schedules have been neutropenia and diarrhea [14,15]. In general, unlike cisplatin, nausea and vomiting, as well as renal or neurological toxicity have not been commonly reported with this compound. For convenience issues, the intermittent schedule was chosen for further development. As toxicity was mostly resolved by day 21, a subsequent trial was initiated studying two dose levels, i.e. 0.9 and 1.1 mg/m^2, administered every 21 days [15]. There was a higher proportion of patients at 1.1 mg/m^2 who required a dose reduction or delay; therefore, 0.9 mg/m^2 every 21 days was recommended for phase II testing.

In light of the preclinical activity in cisplatin-resistant tumors, as well as the manageable toxicity profile noted in the phase I trials, a multicenter open-label phase II trial of BBR 3464 at this dose and schedule was initiated for patients with relapsed small cell lung cancer. The specific objectives of the trial were to determine the efficacy of BBR 3464 in this patient population, as defined by response rate (primary objective), time to progression and survival, to determine the incidence and severity of toxic effects, and to further characterize the pharmacokinetics of this compound using this dosing schedule.

Patients and methods

Patient selection

Adult patients with histological or cytological evidence of small cell lung cancer and clinical evidence of metastatic disease that had progressed after first-line chemotherapy were enrolled onto this multicenter study. Patients with refractory (progressive disease on first-line therapy or relapsing ≤ 3 months after discontinuing first-line chemotherapy) and sensitive (relapse following response that lasted ≥ 3 months following last dose of chemotherapy) disease were included in the study population. Additional inclusion criteria included: at least 4 weeks since last major surgery, hormonal or immunotherapy and/or chemotherapy, and at least 6 weeks from carboplatin at a dose ≥ 500 mg/m^2 or AUC > 7 mg/ml/min; at least 2 weeks since last radiation treatment; at least one measurable lesion that had not been previously irradiated; ECOG performance status (PS) 0 or 1; adequate organ function as defined by neutrophil count $\geq 1.5 \times 10^9$/l, hemoglobin ≥ 9 g/dl, platelets $\geq 100 \times 10^9$/l, total serum bilirubin $\leq 1.5 \times$ upper normal limit (ULN), alkaline phosphatase $\leq 2.5 \times$ ULN, ALT or AST $\leq 2.5 \times$ ULN, albumin ≥ 2.5 g/dl, creatinine ≤ 1.5 mg/dl or calculated creatinine clearance ≥ 40 mg/min or 60 ml/min if there was a prior history of cisplatin therapy.

Patients were not eligible for enrollment onto the study if they had one of the following: more than one previous regimen of chemotherapy; non-measurable disease only; presence of serious illness or medical conditions (congestive heart failure or angina pectoris, myocardial infarction within 1 year prior to study entry, uncontrolled hypertension, or arrhythmia); history of significant neurological disorder other than metastatic disease or psychiatric disorder; symptomatic brain metastases or leptomeningeal disease; prior malignancies, except for curatively treated non-melanoma skin cancer or carcinoma *in situ* of the cervix, or other cancer cured by surgery alone with a disease-free survival longer than 5 years; pregnancy, lactation or refusal to use effective contraception.

All study candidates were required to provide written informed consent as approved by local institutional review boards before initiation of study procedures.

Treatment plan and response assessment

BBR 3464 was provided by the sponsor as a freeze-dried formulation in a Type 1 clear glass vial with each vial containing 1.5 mg of BBR 3464 with 150 mg of mannitol. BBR 3464 was reconstituted in 3 ml of 0.2% sodium chloride that was provided separately and additional 0.9% sodium chloride was added for a total volume of 500 ml. The dose of 0.9 mg/m^2 was given as an i.v. infusion over 1 h every 21 days. Based on the phase I experience, routine anti-emetics were not required, but were allowed to be given at the discretion of the Investigator. All patients received at least 3 cycles unless there was unacceptable toxicity, progressive disease or patients withdrew consent. Patients with a complete response, partial response or stable disease as established by computed tomography scan after 3 cycles were treated with an additional 3 cycles for a total of 6 cycles of therapy. Patients without progressive disease were allowed to continue treatment at the discretion of the investigator.

Dose modifications

Subsequent cycles were held until all drug-related toxicity recovered to at least National Cancer Institute

Common Toxicity Criteria (NCI-CTC) grade 1 (except hemoglobin and alopecia) and patients had a serum creatinine value of ≤ 2.0 mg/dl. If drug-related toxicities did not recover to NCI-CTC grade 1 or the serum creatinine did not recover to ≤ 2.0 mg/dl within 2 weeks (day 36), then patients were withdrawn from the study. In the case of grade 4 neutropenia that lasted > 5 days and was associated with complications (i.e. grade 2 fever), treatment was held for at least 1 week until recovery to at least NCI-CTC grade 1 and subsequent doses of BBR 3464 were reduced to 0.75 mg/m^2. If grade 4 neutropenia recurred, then prophylactic treatment with colony-stimulating factors was administered in subsequent cycles, but the dose was maintained at 0.75 mg/m^2. In the case of grade ≥ 3 diarrhea or other toxicities during a cycle judged by the investigator to warrant dose reduction, the dose of BBR 3464 was also reduced to 0.75 mg/m^2 for subsequent cycles. If grade ≥ 3 diarrhea recurred at the reduced dose despite the use of loperamide, the patient was withdrawn from the study.

Statistical design

The trial used a two-stage design to calculate the number of patients required for each category based on response to first-line therapy (refractory and sensitive). With a target response level of 20% and a lower response level of 5%, the first stage of enrollment was planned to be 12 evaluable patients for each group (i.e. 12 refractory patients and 12 sensitive patients). Patients were considered evaluable if they completed at least 3 cycles of treatment and performed at least one post-treatment disease assessment or if early progression occurred. If there were no responses in the first 12 evaluable patients for either group, then the trial was closed to enrollment for that patient population. If there was at least one response in a patient group, then an additional 25 patients were to be enrolled in the second stage for a total of 37 evaluable patients per response category.

The primary endpoint was response rate, which was evaluated according to the RECIST criteria [16]. Secondary endpoints included time to progression, overall survival and toxicity. All patients who met eligibility criteria and were assessable for response were included in the efficacy analysis. All patients who were registered and received BBR 3464 were included in the toxicity analysis. Toxicity was graded based on NCI-CTC version 2. After completion of study treatment, patients whose disease had not progressed were followed every 9 weeks until progression or next treatment. All patients were followed every 9 weeks for survival for 3 years after completion of study treatment. Time to progression and survival were measured from the date of enrollment until disease progression or death, respectively. Time to progression and survival were estimated by using Kaplan–Meier methods.

Pharmacokinetic analysis

Clinical pharmacokinetic studies were performed in all patients in cycle 1 of treatment. Plasma was collected prior to dose administration, and at 0.5, 7 and 23 h after the end of drug administration. The blood samples were collected in heparinized tubes and immediately centrifuged at 4000 *g* for 15 min to separate the plasma. When immediate centrifugation was not possible, the test tubes containing the blood samples were placed in an ice bath at 0–4°C for a maximum of 30 min. The plasma fraction was immediately separated and divided into two aliquots. One plasma aliquot of 2 ml was placed in a polypropylene tube and stored at –20°C or colder for platinum analysis. The second plasma aliquot was used to prepare an ultrafiltrate sample: using Millipore (Bedford, Massachusetts, USA) Ultrafree filters (10 000 molecular weight cut-off) the aliquot was centrifuged at 4000 *g* for 15 min and the ultrafiltrate frozen at –20°C or colder.

Total platinum concentrations in plasma were assessed by a Good Laboratory Practice validated inductively coupled plasma-mass spectrometry method and expressed as BBR 3464 equivalent concentrations. Additionally, partial validation for plasma ultrafiltrate [inter-assay accuracy and precision plus five replicates at the lower limit of quantification (LLOQ)] as well as for lithium heparinized plasma (intra-assay accuracy and precision plus six replicates at the LLOQ) was performed. The method and the validation data are reported in detail elsewhere [17].

Prior to measurement, the samples were diluted up to 4 ml with diluted nitric acid to obtain homogeneous samples in the appropriate concentration range. The monitored isotopes were ^{194}Pt (analyte) and ^{175}Lu (internal standard). The results demonstrated that the assay was selective with good accuracy and precision, and showed good linearity of the standard curves (from 2.5 to 250 ng/ml in whole plasma and from 0.3 to 30 ng/ml in plasma ultrafiltrate). The method was validated down to 2.5 ng/ml of platinum content (corresponding to 4.27 nmol/l BBR 3464 equivalents) in whole plasma and 0.3 ng/ml in plasma ultrafiltrate (corresponding to 0.51 nmol/l BBR 3464 equivalents). Inter-day accuracy accounted for 7.2 (% bias) and inter-run precision accounted for 2.5 (CV%). Furthermore the results proved the stability of the analyte in the plasma samples, prepared for measurement, as well as in plasma samples at different conditions. The method was validated according to international standards [18].

A limited sampling model (LSM) for the prediction of BBR 3464 area under the plasma concentration–time curve from 0 to 24 h (AUC_{0-24}) after i.v. administration was developed and validated. A multiple regression analysis was performed on a training data set of 10 patients participating in the phase I studies TPT-I-01

and TPT-I-02, receiving i.v. doses ranging from 0.2 to 1.1 mg/m^2 [15,16]. The equations describing the model are:

$$AUC_{0-24} = 44.1312 + 2.2610C_{0.5h} + 19.0924C_{7h} \quad (1)$$

$$AUC_{0-24} = -12.8749 + 6.6080C_{0.5h} + 17.3126C_{23h} \quad (2)$$

where $C_{0.5h}$, C_{7h} and C_{23h} represent the plasma platinum concentrations at 0.5, 7 and 23 h from the end of the infusion, respectively. The AUC values and the platinum concentrations are expressed as ng·h/ml and ng/ml, respectively. The model was validated on a second data set from patients who participated in the initial phase I trials, receiving i.v. BBR3464 at doses ranging from 0.12 to 1.1 mg/m^2. The model based on the points at 0.5 and 7 h gave a relative mean predictive error of 0.6% (range = −3.57–7.08%) and a relative root mean square error of 3.5%. The model based on the points 0.5 and 23 h gave a relative mean predictive error of 0.2% (range = −9.8–10.7%) and a relative root mean square error of 4.3% [8]. The predicted exposures, AUC_{0-24} values, were calculated for each patient using either (1) or (2) according to the availability of plasma samples at 7 or 23 h from the infusion end.

Results

Patient demographics

A total of 37 patients, 17 with refractory disease and 20 with sensitive disease, were enrolled from 12 centers and the data cut-off date was set as November of 2002. Their characteristics are listed in Table 1. The median age for the refractory patients and sensitive patients was 62 (range 39–74) and 64 (range 44–73), respectively. Of the 37 patients, the majority were male (70%) and most patients had a PS of 1 (76%).

Treatment administration summary

Tables 2 and 3 outline the treatment administration and reasons for treatment discontinuation. The median number of treatment cycles for refractory and sensitive patients was 2 (range 1–12) and 3 (range 1–8), respectively. Of the 37 patients enrolled on the trial, 24 patients went off-study due to progressive disease (73%), four patients by patient request (11%), three patients for unacceptable toxicity (8%), three patients by decision of the investigator (8%) and three patients who died on therapy (8%). The majority of patients with refractory disease at study entry went off-trial due to progressive disease (13 patients), followed by patient request (three patients) and death (one patient). The majority of patients with sensitive disease at study entry also went off-trial due to progressive disease (11 patients), followed by unacceptable toxicity (three patients), investigator's decision (three patients), death (two patients) and patient request (one patient).

Table 1 Patient demographics

	Refractory patients (n=17)	Sensitive patients (n=20)
Gender [n (%)]		
female	4 (24)	7 (35)
male	13 (76)	13 (65)
Race [n (%)]		
Black	1 (6)	0 (0)
Caucasian	16 (94)	20 (100)
Median age [years (range)]	62 (39–74)	64 (44–73)
PS [n (%)]		
0	3 (18)	6 (30)
1	14 (82)	14 (70)

Table 2 Treatment administration

	Refractory patients (n=17)	Sensitive patients (n=20)
No. of treatment cycles		
mean	2.9	3.4
median	2	3
range	1–12	1–8
Average dose per cycle (mg/m^2)	0.90	0.88
Patients requiring dose reduction or delay [n (%)]	4 (24)	10 (50)

Table 3 Reasons for treatment discontinuation [n (%)]

	Refractory patients (n=17)	Sensitive patients (n=20)
Progressive disease	13 (77)	11 (55)
Toxicity	0 (0)	3 (15)
Patient request	3 (17)	1 (5)
Investigator decision	0 (0)	3 (15)
Death	1 (6)	2 (10)

All 37 patients enrolled onto the trial received at least 1 cycle of chemotherapy. A total of 14 patients had their treatment held or the dose of their drug reduced (four patients with refractory disease and 10 patients with sensitive disease). The most common reason for dose reduction or delay was toxicity (71%), followed by 'other' (19%) and non-compliance (10%). There was no difference in the average dose per cycle (0.9 and 0.88 mg/m^2, refractory and sensitive, respectively) or average time between administration of the study drug (22 and 22.8 days, refractory and sensitive, respectively) between the two patient groups.

Toxicity

All 37 patients were evaluable for toxicity. Drug-related adverse events that occurred in more than 10% of patients are listed in Table 4. Although not formally compared, the rates of hematological or non-hematological toxicity were similar for both groups of patients. The majority of patients experienced significant myelosuppression. Grade 3 or 4 neutropenia occurred in 24 patients (62%), including nine patients in the refractory group (53%) and 15 patients in the sensitive group (75%). Overall, nine patients (16%) experienced febrile neutro-

Table 4 Drug-related adverse events occurring in more than 10% of patients

	Grade	All patients		Refractory patients ($n=17$)		Sensitive patients ($n=20$)	
		n	%	*n*	%	*n*	%
Hematological							
neutropenia	all grades	24	65	9	53	15	75
	grade 3/4	23	62	9	53	14	70
leukopenia	all grades	19	51	7	41	12	60
	grade 3/4	18	49	6	35	12	60
anemia	all grades	12	32	6	35	6	30
	grade 3/4	4	11	1	6	3	15
febrile neutropenia	all grades	6	16	2	12	4	20
	grade 3/4	6	16	2	12	4	20
thrombocytopenia	all grades	5	14	2	12	3	15
	grade 3/4	2	5	2	12	0	0
Gastrointestinal							
nausea	all grades	26	70	12	71	14	70
	grade 3/4	12	32	2	12	10	50
diarrhea	all grades	22	59	10	60	12	60
	grade 3/4	4	11	0	0	4	20
vomiting	all grades	17	46	7	41	10	50
	grade 3/4	6	16	1	6	5	25
abdominal pain	all grades	4	11	1	6	3	15
	grade 3/4	1	3	0	0	1	5
constipation	all grades	4	11	2	12	2	10
	grade 3/4	0	0	0	0	0	0
stomatitis	all grades	4	11	2	12	2	10
	grade 3/4	0	0	0	0	0	0
dehydration	all grades	6	16	2	12	6	30
	grade 3/4	5	14	1	6	4	20
Constitutional							
fatigue	all grades	19	51	5	29	14	70
	grade 3/4	2	5	0	0	2	10
anorexia	all grades	15	41	7	41	8	40
	grade 3/4	0	0	0	0	0	0
weight loss	all grades	6	16	2	12	4	20
	grade 3/4	0	0	0	0	0	0
Neurological							
dizziness	all grades	5	14	3	18	2	10
	grade 3/4	1	3	1	6	0	0
Infection							
candidal infection	all grades	4	11	2	12	2	10
	grade 3/4	0	0	0	0	0	0
Metabolic							
hypomagnesemia	all grades	4	11	1	6	3	15
	grade 3/4	0	0	0	0	0	0

penia. There were 18 patients (49%) who experienced grade 3 or 4 leukopenia. No significant opportunistic infections were reported, however. Four patients did experience fungal infections (*Candida*), but two of these cases were oral thrush and all were low grade.

The most common non-hematological toxicities included nausea (70%), diarrhea (59%), fatigue (51%) and vomiting (46%). There were 12 patients (32%) who experienced grade 3 or 4 nausea. For the non-hematological toxicities listed in Table 4, most were low grade. Overall, three patients died while on study, including one patient in the refractory group who died from respiratory failure that was felt to be unrelated to the study medication. Of the two patients in the sensitive group, one patient died after a suicide attempt and the other died from progressive disease.

Response and survival

Of the 37 patients enrolled onto the study, three were not evaluable for response, including one patient with refractory disease and two patients with sensitive disease. All three received less than 3 cycles of chemotherapy and did not have an additional post-treatment disease assessment. All patients were included in the efficacy analysis, however, on an intent-to-treat basis. As this was a multicenter trial and there was initial uncertainty about the number of evaluable patients enrolled, accrual did exceed the target for both subgroups (17 refractory and 20 sensitive). Table 5 outlines the response, time to progression and survival outcomes. No objective responses were seen in 34 evaluable patients. There were 11 patients (32%) who had disease stabilization, including three of the patients with refractory disease and seven of the patients with sensitive disease. The median time to progression was 53 days (range 1–247) for the patients with refractory disease at study entry and 66 days (1–136) for the patients with sensitive disease at study entry. The median survival was also longer for the patients with sensitive disease at study entry (209 days, range 21–414 +) compared with refractory patients (78 days, range 9 – 408 +), with 1-year survival rates of

20 (2–38) and 6% (95% CI 0–17%), sensitive and refractory patients, respectively (Fig. 1).

Pharmacokinetic analysis

All the patients were pre-treated with other platinum complexes and showed residual platinum concentrations in the basal samples. As a general rule, when basal concentrations were greater than 10% of the platinum concentration measured at the first observation time after BBR 3464 administration, data sets were not considered for the AUC calculation. Differently, when basal platinum concentrations were lower than 10%, the AUC values were calculated after subtraction of the basal platinum values from all the concentrations. The AUC was estimated in 10 patients and the calculation of the percentage of unbound platinum versus total platinum was performed in nine patients. The average BBR 3464 equivalent AUC_{0-24} value accounted for 1954 ± 381.7 nmol/l·h. The decrease in the neutrophil counts observed during the treatment did not correlate with the systemic exposures calculated (Fig. 2). The mean unbound fraction was 3.6 (SD 1.2) and 1.3% at the 0.5- and 23-h time points, respectively. Data for this calculation was available in all nine patients at the early time point and in four of nine patients at the later time point.

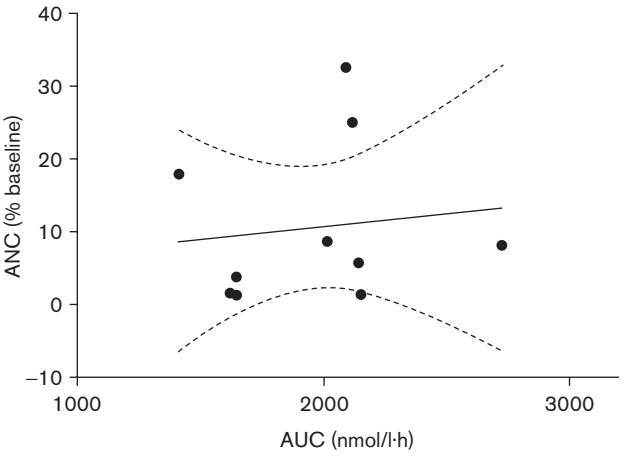
Table 5 Distribution of the best overall response rate, median survival (days) and time to progression (days)

	Refractory patients ($n=17$)	Sensitive patients ($n=20$)
Overall response rate [*n* (%)]	0	0
not evaluable	1 (6)	2 (10)
stable disease	4 (24)	7 (35)
progressive disease	12 (71)	11 (55)
Median survival [days (range)]	78 (9–408+)	209 (21–414+)
Median time to progression [days (range)]	53 (1–247)	66 (1–136)

Discussion

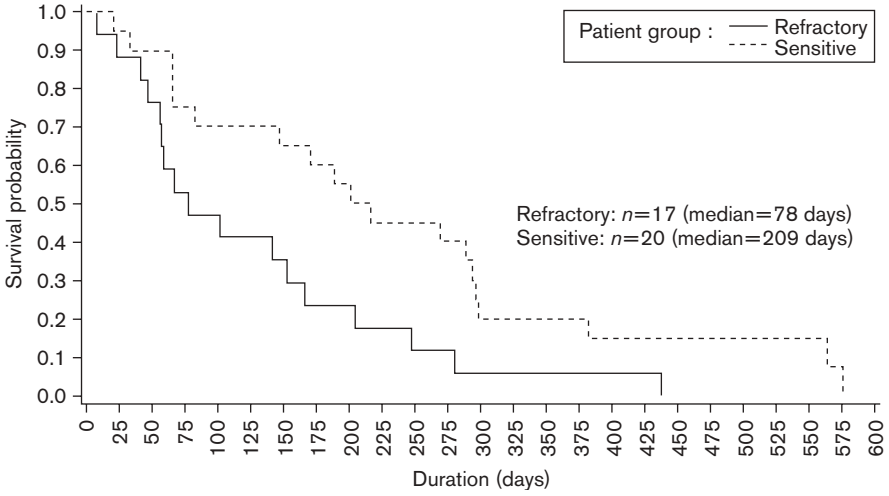
Treatment options for patients with relapsed small cell lung cancer remain suboptimal. The likelihood of response depends on whether patients have sensitive or refractory disease. For patients with sensitive disease, topotecan has been shown in a randomized trial to have comparable activity to CAV with an overall response rate

Fig. 2



Linear regression between absolute neutrophil count and total platinum BBR 3464 equivalent.

Fig. 1



Overall survival by patient subgroup.

of 24% [9]. In this trial, there was a higher proportion of patients treated with topotecan who experienced improvement in several disease-related symptoms (dyspnea, hoarseness, fatigue and anorexia), which is clearly appealing given the palliative intent of this therapy. However, the time to progression (13 weeks) and overall survival (25 weeks) remained short. In earlier phase II testing of topotecan, the response rates for patients with refractory disease has consistently been less than 10% (range 2–11%) [19]. A number of other single-agent and combination regimens have also been tested in the second-line setting [10,20,23]. The most active single-agents include gemcitabine, the taxanes (paclitaxel and docetaxel), irinotecan and ifosfamide [10,21,24].

As most patients are treated with platinum-based chemotherapy at diagnosis, newer drugs that are tested in the second-line setting need to able to overcome platinum resistance to be effective, particularly in those patients with refractory disease. BBR 3464 is a novel triplatinum that has been shown in preclinical testing to have a different mechanism of action than cisplatin with a broad spectrum of anti-tumor activity [11]. In addition, BBR 3464 has demonstrated the ability to overcome cisplatin resistance in preclinical models, making it a rational drug to study in patients with relapsed small cell lung cancer [11,13]. However, in this phase II trial, there were no responses seen in 37 patients. There were 11 patients who achieved disease stability (32%), including three patients who had refractory disease and seven patients who had sensitive disease, and 23 patients (62%) progressed on study (12 patients and 11 patients, refractory and sensitive, respectively). Despite the lack of responses, the median overall survival seen in this phase II study was similar to the median survival reported on both arms in the randomized trial of topotecan and CAV [9].

The toxicity associated with this agent in this phase II trial was significant. Like the phase I experience, both neutropenia and diarrhea were commonly reported. Neutropenia was frequently high grade (62% grade 3 or 4) and it was associated with a fever in 16% of patients. Although diarrhea was predominantly low grade, a significant number of patients experienced abdominal pain (11%) and dehydration (16%). Also, unlike the phase I experience [14,15], nausea and vomiting were common. Overall, 38% of patients required a dose reduction or a delay in drug delivery. The median number of cycles delivered for both subgroups was low (2 and 3, refractory and sensitive, respectively). Although most patients stopped treatment due to progressive disease, 15% of patients with sensitive disease discontinued treatment because of toxicity.

The pharmacokinetic profile of BBR 3464 has been evaluated in two phase I trials [14,15]. The total and free platinum concentrations have been shown to have a similar disposition profile with a distribution phase followed by a prolonged elimination phase. Both C_{max} and AUC increased proportionally with dose escalation, indicating linear kinetics. The unbound fraction of BBR 3464 in these trials was generally constant throughout the observation interval, ranging from 2 to 4%, which is consistent with the unbound fraction at the early time point in this trial. The data on the unbound fraction at late sampling times, however, were not sufficient to derive any conclusion relative to circulating unbound fraction over the entire observation interval. Also, although no relationship between the systemic exposure to BBR 3464 and absolute neutrophil count was identified, the small number of patients included in the AUC estimation limits the ability to draw a firm conclusion from this observation. Furthermore, prolonged presence of total platinum in the systemic circulation after administration of BBR 3464 has been observed in phase I trials [14,15]. Therefore, the exposure evaluated within 24 h of administration is likely to be of limited value in establishing a correlation between systemic exposure and toxicity with this agent.

In conclusion, BBR 3464 was not associated with significant clinical activity in this group of patients with relapsed small cell lung cancer. While the overall survival of the sensitive patients in this phase II trial was similar to what has been reported with other single agents in this group of patients, the lack of significant responses does not support further evaluation of this drug as a single agent in this disease. As patients progressed quickly on this study, particularly those patients with refractory disease, the number of treatment cycles that were delivered in this trial was low. Therefore, conclusions about the long-term effects of this drug cannot be drawn from this study and will need to wait for data from other ongoing phase II trials in other tumor types.

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