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ORIGINAL ARTICLE

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Phase II trial of intravenous lobradimil and carboplatin in childhood brain tumors: a report from the Children's Oncology Group

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Abstract *Backround*: Lobradimil is a synthetic bradykinin analog that rapidly and transiently increases the permeability of the blood-brain barrier (BBB). The combination of lobradimil and carboplatin was studied in pediatric patients with primary brain tumors in a phase II trial, the primary endpoints of which were to estimate the response rate and time to disease progression. *Patients and methods*: Patients were stratified by histology into five cohorts: brainstem glioma, high-grade glioma, low-grade glioma, medullobastoma/primitive neuroectodermal tumor (PNET), and ependymoma. Patients received carboplatin adaptively dosed to achieve a target AUC of 3.5 mg min/ml per day (7 mg·min/ml/cycle) intravenously over 15 min on 2 consecutive days and lobradimil 600 ng/kg ideal body weight/day on 2 consecutive days each 28 day cycle. *Results*: Forty-one patients, age 2–19 years, were enrolled; 38 patients, including 1 patient ultimately determined to have atypical neurocytoma, were evaluable for response. No objective responses were observed in the brainstem glioma ($n=12$) and high-grade glioma ($n=9$) cohorts, although two patients with high-grade glioma had prolonged disease stabilization (>6 months). The study was closed for commercial reasons prior to achieving the accrual goals for the ependymoma ($n=8$), medulloblastoma/PNET ($n=6$) and low-grade glioma ($n=2$) cohorts, although responses were observed in 1 patient with PNET and 2 patients with ependymoma. *Conclusion*: The combination of lobradimil and carboplatin was inactive in childhood high-grade gliomas and brainstem gliomas.

Keywords Brain tumors · Lobradimil · Children · Ependymoma · Glioma · Medulloblastoma · Phase II · RMP-7

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Introduction

The blood-brain barrier (BBB) is a specialized layer of endothelial cells in brain capillaries that restricts the entry of most hydrophilic and large lipophilic compounds into the brain [11]. The synthetic bradykinin analog, lobradimil (Cereport®, RMP-7), is a potent and specific bradykinin B_2 receptor agonist. The interaction of bradykinin or lobradimil with the B_2 receptor rapidly and transiently increases the permeability of the BBB [2, 7, 9, 12]. In pre-clinical studies of rats with implanted RG-2 gliomas, intravenous lobradimil significantly increased the uptake of carboplatin into brain tumors and brain tissue surrounding the tumor [2]. Tumor-bearing animals that received the combination of lobradimil and carboplatin survived longer than animals that received carboplatin alone [9].

In the phase I study of lobradimil and carboplatin in adults with progressive malignant glioma, lobradimil

was tolerable when administered intravenously over 10 min at doses of up to 300 ng/kg [3]. The major side effects of lobradimil were immediate and transient, and included flushing, nausea, headache and tachycardia. A maximum tolerated dose (MTD) was not defined. A phase I study of lobradimil and adaptively dosed carboplatin was subsequently performed in pediatric patients with brain tumors. The combination was safe and tolerable with a similar transient toxicity profile for lobradimil at doses up to 600 ng/kg ideal body weight [14]. An MTD of lobradimil was not defined in this study, as the incidence and severity of toxic effects from lobradimil did not appear to increase in proportion to the dose over the dosage range studied.

We conducted a phase II trial of lobradimil and carboplatin in pediatric patients with recurrent or progressive brain tumors. Patients were stratified by diagnosis into the following strata: high-grade glioma, brainstem glioma, low-grade glioma, medulloblastoma/PNET, and ependymoma. The primary outcome measures were objective response rate and time to disease progression.

Patients and methods

Eligibility

Patients of age ≤ 21 years with histologically confirmed high-grade glioma, low-grade glioma, medulloblastoma/PNET, and ependymoma refractory to standard therapy were eligible for this trial. Histologic confirmation was not required for patients with radiographic evidence of a brainstem tumor. Measurable tumor and evidence of recurrent or progressive disease were required for eligibility. Patients were required to have a life expectancy of at least 8 weeks, have an ECOG performance score of ≤ 2, and have recovered from the toxic effects of all prior therapy. A bilirubin < 1.5 times the upper limit of normal and SGPT ≤ 2.5 times the upper limit of normal were also required. Normal renal function was not required for study entry because carboplatin was adaptively dosed based on renal function, but patients were required to have a serum creatinine of ≤ 1.2 mg/dl if under 5 years of age, ≤ 1.5 mg/dl for patients 5–10 years, ≤ 1.8 mg/dl for patients 10–15 years, and ≤ 2.4 mg/dl for patients over 15 years. Patients must have had an absolute granulocyte count $\geq 1{,}000/\mu l$, a hemoglobin ≥ 8.0 gm/dl, and a platelet count $\geq 100{,}000/\mu l$ at study entry.

Patients with medulloblastoma/PNET were eligible at the time of first or second recurrence of tumor (i.e., no more than two prior chemotherapy regimens). Patients with other diagnoses were eligible at the time of first recurrence of tumor. Patients were excluded if they had received prior treatment with carboplatin or lobradimil. Informed consent was obtained from the patient or his/her legal guardian in accordance with institutional guidelines.

Trial design

Radioisotopic GFR (^{99m}Tc-DTPA) was performed within 1 week prior to therapy for calculation of the carboplatin dose. Magnetic resonance imaging (MRI), with and without gadolinium, was performed on all patients within 2 weeks of the first dose of lobradimil and carboplatin.

Lobradimil was supplied by Alkermes, Inc. (Cambridge, MA, USA) as a sterile solution at a concentration of 0.02 mg/ml. The calculated dose was diluted in 0.9% sterile sodium chloride to a total infusion volume of 20 ml for all patients. Lobradimil was administered intravenously over 10 min at a dose of 600 ng/kg ideal body weight (IBW) per day on days 1 and 2 of each 28-day cycle, with each infusion beginning 5 min before the end of the carboplatin infusion. Carboplatin, which was infused intravenously over 15 min, was adaptively dosed based on the glomerular filtration rate (GFR) to achieve a target area under the concentration–time curve (AUC) of 3.5 mg·min/ml per dose (7.0 mg·min/ml per cycle). The adaptive dosing formula developed by Marina et al. [8] was used to determine the carboplatin dose:

$$\begin{aligned}&\text{Carboplatin daily dose } [\text{mg/m}^2]\\&\quad = \text{Target AUC } [\text{mg}\cdot\text{min/ml}]\\&\qquad \times (0.93 \times \text{GFR } [\text{ml/min/m}^2] + 15)\end{aligned}$$

Assessment of efficacy

MRI, with and without gadolinium, was performed at baseline (pretreatment), prior to cycles 3, 5, 7, 9, 11, and after cycle 12. Response (percent change in tumor size from baseline) was determined from bidimensional measurements on the follow-up scan with the best response compared to the tumor size in the pretreatment MRI scan. The response criteria are listed in Table 1. Time to progression was defined as the duration of time between the starting date of therapy (cycle 1, day 1) and the date that clinical or radiographic disease progression was first documented.

Statistical considerations in trial design

The trial used an optimal two-stage design [13] intended to rule out p_0, an uninteresting level of response, in favor of p_1, a targeted level of response. Because of expectations of varying response outcomes, patients were stratified into five disease categories: high-grade glioma (anaplastic astrocytoma and glioblastoma multiforme), low-grade glioma, brainstem glioma, medulloblastoma/PNET, and ependymoma. Based on a review of prior phase II trials of carboplatin alone in childhood brain tumors [1, 4, 5], we assumed that the response rate of medulloblastoma/PNET to carboplatin (p_0) alone was 20%, and the response rate for the remaining tumor

Table 1 Response criteria

Response	Definition
Complete response (CR)	≥95% reduction in the sum of the products of the two longest perpendicular diameters of all measurable tumors; no new lesions; stable or tapering dose of corticosteroids.
Partial response (PR)	From ≥50 to <95% reduction in the sum of the products of the two longest perpendicular diameters of all measurable tumors; no new lesions; stable or tapering dose of corticosteroids.
Minor response (MR)	From ≥25 to <50% reduction in the sum of the product of the two longest perpendicular diameters of all measurable tumors; no new lesions; stable or tapering dose of corticosteroids.
Stable disease (SD)	<25% increase or reduction in the sum of the product of the two longest perpendicular diameters of all measurable tumors; no new lesions or a ≥25% reduction in the sum of the products of the two longest perpendicular diameters of all measurable tumors; no appearance of new lesions; increased dose of corticosteroids compared to the pretreatment dose level.
Progressive disease (PD)	The appearance of new tumors or a >25% increase in the sum of the product of the two longest perpendicular diameters of all existing measurable tumors.

types to carboplatin alone was 5%. For all strata, we set both α (the probability of accepting the combination as active when it is inactive) and β (the probability of rejecting the combination as inactive when it is active) equal to 0.10.

For medulloblastomas/PNET with $p_0 = 0.20$ and $p_1 = 0.40$, the first stage of accrual targeted 17 patients evaluable for response, with plans to enroll a second stage of 20 patients, if 4 or more of the first 17 patients had an objective response, for a total of 37 patients, which included minor response (MR), partial response (PR), and complete response (CR). The combination of carboplatin and lobradimil would be considered inactive in medulloblastomas/PNET if 0–3 of the first 17 evaluable patients responded or 4–10 of 37 evaluable patients in both stages responded.

For brainstem gliomas, $p_0 = 0.05$ and $p_1 = 0.20$, the first stage of accrual targeted 12 patients, with a second stage of 25 patients, if there was an objective response in 1 or more of the first 12 patients, for a total of 37 patients. The combination of carboplatin and lobradimil would be considered inactive in brainstem glioma if 0 of the first 12 evaluable patients demonstrated a response or if 1–3 of 37 evaluable patients in both stages responded.

For remaining cohorts (ependymoma, low-grade glioma, and high-grade glioma), $p_0 = 0.05$, $p_1 = 0.25$, the first stage of accrual was designed to include 9 patients for each disease stratum. If an objective response was observed in 1 or more of the first 9 patients evaluable, accrual to that disease strata would include a second stage of 15 patients, for a total of 24 patients. The combination of carboplatin and lobradimil would be considered inactive for disease strata if 0 of the first 9 evaluable patients responded or if 1–2 of 24 evaluable patients in both stages demonstrated a response.

The study was discontinued prior to achieving accrual goals for the low-grade glioma, medulloblastoma/PNET and ependymoma cohorts for commercial reasons unrelated to patient safety or efficacy.

Results

A total of 41 patients were enrolled between July 1998 and September 2002, 40 received the combination of lobradimil and carboplatin, and 38 were evaluable for response. One patient developed symptoms of cord compression and did not receive treatment. Two patients did not have baseline MRI scans within the required time period. Of the 38 evaluable patients, 12 had brainstem glioma, 9 had high-grade glioma, 2 had low-grade glioma, 6 had medulloblastoma/PNET, and 8 had ependymoma. One patient initially diagnosed with ependymoma received treatment, but his diagnosis was later changed to atypical neurocytoma after extensive pathology review. Patient characteristics are listed in Table 2.

First stage accrual goals were met for the brainstem glioma ($n = 12$), and high-grade glioma ($n = 9$) strata. No objective responses (CR, PR, MR) were observed in these disease strata. All patients progressed; therefore, the time to progression could be calculated without using actuarial methods. The median time to disease progression for the brainstem glioma cohort was 84 days (range 7–139, mean 79). One patient with brainstem glioma had rapid disease progression and died 1 week after receiving his first cycle of therapy. The median time to disease progression for the high-grade glioma cohort was 78 days (range 29–302, mean 114). One patient with a high-grade thalamic tumor received 17 cycles of lobradimil and carboplatin before being removed from study due to an elevated serum creatinine. One patient with glioblastoma received 8 cycles of therapy prior to tumor progression.

First stage accrual goals were not met for the remaining tumor strata prior to study termination, although responses were observed. A partial response was observed in a patient with PNET (response rate = 1/6 (17%); exact 95% CI: 0–64%). This patient received 12 cycles of therapy and then underwent resection of her

Table 2 Characteristics of 40 patients treated with lobradimil and carboplatin

Median (range) age	9 (2–21) years
Gender (M/F)	20/20
Median (range) ECOG performance status	1 (0–2)
Prior XRT (yes/no)	38/2
Median #prior chemo regimens	1 (range 0–2)
Median baseline tumor size[a]	8.75 cm^2 (range 0.8–48.8, mean 12.2)

[a]Baseline tumor size was calculated using WHO two-dimensional criteria (the sum of the product of the longest diameter and its longest perpendicular diameter for each tumor)

residual disease, followed by high-dose chemotherapy with stem cell rescue. Partial responses were also observed in two patients with ependymoma (response rate = 2/8 (25%); exact 95% CI: 3–65%), one of whom had disease progression after 4 cycles, and the other completed 12 cycles of therapy.

Forty patients were fully evaluable for toxicity (i.e., evaluable at day 28). Lobradimil and carboplatin were generally well tolerated. The toxicities during cycle 1 are listed in Table 3. Myelosuppression was attributed to carboplatin. Grade 4 neutropenia occurred in 11 patients and persisted for a median of 9 days (range 1–23). Grade 4 thrombocytopenia occurred in 4 patients for a median of 1 day (range 1–4 days). Flushing, headache, nausea, and vomiting, which were frequent but generally low grade, were attributed to lobradimil. Two patients had a seizure during cycle 1, including one who had a seizure during the lobradimil infusion on day 1. This patient had a history of acute lymphoblastic leukemia with CNS disease, extensive medulloblastoma/PNET and a prior history of seizures. She was treated with carboplatin alone on day 2. One patient with low-grade glioma was removed from study after cycle 2 because of severe ototoxicity. The patient was a 4-year-old boy previously treated with thioguanine, procarbazine, CCNU, and vincristine, who had no prior history of hearing impairment, but was reported to have difficulty hearing after cycle 2 of lobradimil and carboplatin.

Table 3 Number of patients with toxicities (by grade) during cycle 1

Toxicity	Grade			
	1	2	3	4
Neutropenia			9	11
Thrombocytopenia			13	4
Anemia			5	
Headache	9	8	2	
Stomach pain	10	8	1	
Nausea	23	2	1	
Vomiting	16	3	1	
Flushing	24	9		
Hypotension		2		
Seizure			2	
Syncope			1	

Audiometry confirmed the moderate-severe bilateral sensorineural hearing loss. One patient with high-grade glioma was removed from the study due to an elevated serum creatinine.

Discussion

The combination of lobradimil and carboplatin was generally safe and well tolerated when administered on a 2-day schedule at doses of 600 ng/kg IBW for lobradimil and a carboplatin target AUC of 3.5 mg·min/ml per day. The toxicity profile in this study is similar to that observed in the phase I study of lobradimil and carboplatin in children with brain tumors [14]. The primary toxicity was myelosuppression, presumably from carboplatin. Headache, flushing, and gastrointestinal complaints were also commonly observed, although these were generally low grade and transient. Serious adverse events that occurred on this protocol included one episode of Grade 3 ototoxicity, likely related to the carboplatin, and two seizures in patients with pre-existing seizure disorders.

In children with high-grade and brainstem gliomas, the activity of carboplatin was not significantly enhanced by lobradimil. In a Phase II trial [6] in adult patients with high-grade gliomas (WHO Grade III/IV), 300 ng/kg lobradamil was infused over 10 min, starting 10 min after the initiation of a 15-min infusion of carboplatin, which was adaptively dosed to target an AUC of 5 to 7 mg min/ml. Seventy-nine percent of chemotherapy-naïve patients had stable disease or partial or complete responses, but in patients who had received prior chemotherapy, only 24% had stable disease. The lower response in previously treated patients is consistent with the outcome on our trial.

In a randomized, double-blind, placebo-controlled phase II trial [10] of carboplatin with or without lobradimil, the median time to progression in adults with recurrent high-grade gliomas was 9.7 weeks in the lobradimil plus carboplatin arm versus 8.0 weeks in the carboplatin plus placebo arm. Lobradimil, at a dose of 300 ng/kg on this trial, did not significantly improve the efficacy of carboplatin, but the investigators suggested that higher doses of lobradimil might be required to increase delivery of carboplatin to tumors. However, the twofold higher dose used in our study did not improve the antitumor activity of lobradimil and carboplatin in our patients with high-grade gliomas and brainstem gliomas.

Responses were observed in patients with PNET and ependymona, but there were too few patients accrued to these disease strata to conclude whether the response rates were above that expected with carboplatin alone. The trial was terminated prior to completing accrual to all disease strata for commercial reasons.

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