Phase I and Pharmacokinetic Study of Photodynamic Therapy for High-Grade Gliomas Using a Novel Boronated Porphyrin

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Purpose: **To determine the recommended dose, toxicity profile, and pharmacokinetics of a novel boronated porphyrin (BOPP) for photodynamic therapy (PDT) of intracranial tumors.**

Patients and Methods: **BOPP was administered alone in increasing doses (0.25, 0.5, 1.0, 2.0, 4.0, or 8.0 mg/kg) preoperatively in patients with intracranial tumors undergoing postresection PDT until dose-limiting toxicity (DLT) was observed.**

Results: **Twenty-nine assessable patients with intracranial tumors received BOPP intravenously 24 hours before surgery. The recommended dose was 4 mg/kg. Dose escalation was limited by thrombocytopenia. The most common nonhematologic toxicity was skin photosensitivity. Pharmacokinetic parameters showed increased area under the plasma concentration-time curve and maximum concentration with increased dose. Tumor BOPP concentrations also increased with increased dose.**

Conclusion: **BOPP at a dose of 4 mg/kg was well tolerated. DLT was thrombocytopenia, and photosensitivity was the only other toxicity of note. The efficacy of PDT using BOPP requires further exploration.**

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PRIMARY CEREBRAL tumors are responsible for approximately 2% of all cancer deaths, with about 13,000 persons dying each year in the United States.[1] The majority of these deaths are caused by high-grade gliomas, including glioblastoma multiforme (GBM) and anaplastic astrocytoma.[2] Current treatment of these tumors may include surgical resection,[3] postoperative whole-brain irradiation,[4] and adjuvant chemotherapy.[5] Improvements in progression-free survival and overall survival have not been achieved, most commonly, because of inadequate local control of disease.[6] Testing of novel local therapies is warranted in an attempt to improve local disease control and provide survival benefit.

Photodynamic therapy (PDT) has been extensively investigated in laboratory studies and has been used in clinical trials to treat a variety of tumors, including those of the esophagus, bladder, skin, lung, and brain, as well as nonmalignant conditions such as age-related macular degeneration of the eye and actinic keratoses of the skin.[6] PDT combines a photosensitizing drug and activating light, resulting in oxidative damage to tissues in which the drug is localized.[6]

The most extensively studied photosensitizer in oncologic indications is hematoporphyrin derivative (HpD) or its more purified form, Photofrin (QLT Phototherapeutics Inc, Canada).[6-9] We have previously reported a large series of patients (n = 160) treated with HpD, which resulted in a favorable median survival time for patients with newly diagnosed GBM of 26 months, with a 30% 2-year survival rate.[6,8] The median survival time of the patients with recurrent GBM was 9 months. No serious complications from the therapy were observed nor did there seem to be an increase in surgical- or radiation-related complications in this or other reported studies.[6-9]

Despite these promising results, PDT may be optimized by the use of more tumor selective and photoactive sensitizers. We previously identified a novel water-soluble amphiphilic boronated porphyrin (BOPP) as an excellent candidate for PDT studies.[10-12] BOPP has highly selective tumor uptake in xenograft models of glioma, is relatively nontoxic, and is identified in tumor cells infiltrating normal brain at a distance from the tumor mass.[10,11] BOPP is also a potent photosensitizer requiring significantly less light energy to mediate tumor kill than HpD.[12] Finally, BOPP localizes predominantly in tumor cell mitochondria, which are proposed to be the major site of phototoxic damage.[10-13]

This first in-man study investigated the toxicity of BOPP in patients with cerebral tumors and identified the dose-

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Table 1. Dose Escalation Schema

Dose Level	No. of Patients	BOPP Dose (mg/kg)	Light Dose (J/cm^2)
1	3	0.25	25
2	3	0.5	25
3	3	1.0	25
4	4	2.0	25
5	6	4.0	25
6	3	8.0	25
7	3	4.0	50
8	4	4.0	100

limiting toxicity (DLT) and maximum-tolerated dose (MTD) of the drug. In addition, we performed a pharmacokinetic and tissue biodistribution analysis after BOPP administration in this patient population.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients had high-grade gliomas (GBM or anaplastic astrocytoma), either newly diagnosed or recurrent, or solitary nonmelanotic metastatic cerebral tumors. Gliomas could be provisionally diagnosed by magnetic resonance imaging scan but required histologic confirmation. Patients may have received prior chemotherapy or radiotherapy more than 30 days before enrollment. Other eligibility criteria included the following: Karnofsky performance status of 60 or greater, age older than 18 years, neutrophil count greater than 1.5×10^9/L, platelet count greater than 100×10^9/L, bilirubin level and liver enzyme levels less than two times the upper limit of normal, creatinine level less than 0.15 mmol/L, and the patients must be geographically accessible and have no prior history of porphyria and no other major coexisting medical problems. The Royal Melbourne Hospital Institutional Ethics Committee approved the protocol, and written informed consent was obtained from all patients.

Study Design

The study was a single-center, open-label, noncomparative, nonrandomized, phase I dose escalation study. The dose escalation was in two parts (Table 1). First, the dose of BOPP was escalated until the DLT was identified. The second part was an escalation of the light dose at the MTD of BOPP. The objectives were to define the recommended dose, DLT, and pharmacokinetics of BOPP-mediated PDT when the drug was administered as a short intravenous infusion 24 hours before surgical resection and with postresection 630-nm laser light irradiation. Cohorts of three patients were treated with increasing doses of BOPP, starting at a dose of 0.25 mg/kg with a light dose of 25 J/cm^2 delivered by optical fiber to the residual tumor bed area after surgical debulking. The dose was escalated in increments as follows: 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, and 8.0 mg/kg (Table 1).

DLT was defined as World Health Organization grade 3 or 4 toxicities or postoperative raised intracranial pressure not controlled by pharmacologic means and considered because of the therapy. If a DLT occurred, then the cohort was expanded to six patients and, if two or more patients had a DLT, then the cohort before this was deemed the MTD. Once the MTD was defined, the light dose was escalated to 50 J/cm^2 and then 100 J/cm^2 at the MTD (Table 1). Neurologic monitoring was performed using the Glasgow Coma scale. Patients remained on study for 6 weeks with additional follow-up and therapy according to standard clinical practice.

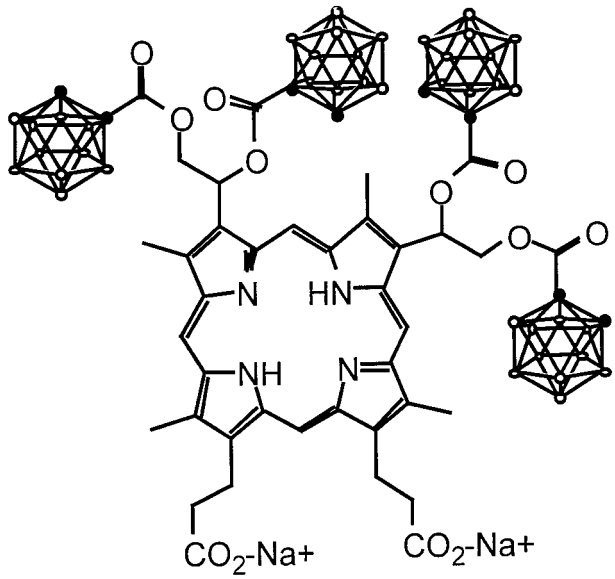

Fig 1. Chemical structure of BOPP.

In addition to standard follow-up, patients underwent regular review for skin and ocular phototoxicity before study, at day 6, day 14, at 6 weeks, and as necessary up to 90 days after treatment if there was residual phototoxicity at 6 weeks. Ocular tests were performed by an ophthalmologist assessing evidence of phototoxic damage, such as corneal and conjunctival inflammation and irritation. Ocular pressure and physical examination of the retina were also performed. Skin photosensitivity testing to ultraviolet A and ultraviolet B light was performed according to standard methods by a dermatologist.

Treatment

BOPP [tetrakiscarborane carboxylate ester of 2,4-Bis(α,β-dihydroxyethyl) deuteroporphyrin IX disodium salt] was supplied by the Institute of Drug Technology, Victoria, Australia (Fig 1) and was manufactured by minor modification of a previously published method.[14] Each 20-mL vial contained 100 mg of lyophilized BOPP that was reconstituted with 10 mL of normal saline. The solution was made up to 100 mL of normal saline and infused intravenously through a peripheral vein over 30 minutes, 24 hours before surgical resection. Care was taken to protect the solution and giving set from light exposure by wrapping the giving set and injection site in aluminum foil. After administration, the injection site was routinely bandaged for a period of 24 hours. Antiemetic premedication was not routinely given.

Anesthesia and surgical resection of the cerebral tumor were performed according to standard techniques. At the completion of resection, light of 630 ± 2 nm from a Laserscope KTP/Nd:YAG-PDT 630-nm dual laser system (Laserscope, United States) at a power output of between 2.0 to 3.2 W was delivered to the tumor bed. This was delivered using a cleaved, flat-cut tip quartz diffusing optical fiber of 400-μm inner core diameter with silica external cladding. The duration of irradiation was calculated according to the required energy density (J/cm^2) (Table 1) using measurements of the power from the fiber tip

and measurements of the irradiation area of the surgical cavity after resection of the tumor. As has been previously reported, during light delivery, the surgical cavity was filled with Intralipid (Baxter, Australia) (0.5% in isotonic saline), which acted as an isotropic diffuser of the laser light allowing even light delivery to the tissue and also prevented potential hyperthermia of the residual tumor bed.[6-8]

Pharmacokinetics

On the day of BOPP administration, blood samples for pharmacokinetic analysis were drawn at the following times: preinjection, and 30 minutes, 1, 2, 6, 24, 36, 48, 72, and 96 hours, and 14 days after injection. Additional samples were drawn in some patients at later time points during the period they were on study, generally at posttreatment follow-up, because of the relatively prolonged plasma elimination time. Blood was collected in heparinized tubes, and plasma was separated from blood cells centrifugally (1,200 g for 10 minutes) and stored at −20°C until analyzed.

BOPP levels in both tissue and plasma were determined relative to appropriate standard curves using a previously described method.[10] Briefly, plasma and tumor concentration of BOPP were assayed by fluorescence detection using a Perkin Elmer (Australia) LS30 Spectrofluorimeter fitted with a Hamamatsu (Japan) RS928 red sensitive photomultiplier. This method was validated for the complete extraction and measurement of BOPP in plasma and tissue. Tests were also undertaken to demonstrate that there was no interference in the extraction or assay by any concomitant medication administered to the patients during the time period over which plasma or tissue samples were taken. As previously reported, the assay method allowed for correction of BOPP concentration in the samples caused by interference of coextracted hemoglobin.[10,15]

A biexponential disposition function was fitted to the plasma BOPP concentration-time data by unweighted nonlinear least squares regression analysis. The coefficients were adjusted for the infusion duration and the adjusted coefficients and exponents of the biexponential equation were used to calculate the area under the plasma concentration versus time curve (AUC). Volume of distribution and plasma clearance were calculated by standard noncompartmental methods; hypothetical peak plasma concentration corresponding to instantaneous injection (Cmax) was calculated as the sum of the polyexponential coefficients, and the initial dilutional volume was calculated as dose/Cmax.[16] Statistical analysis was performed with Prism for Windows (Graph Pad Software, United States). Comparisons between groups were performed by one-way analysis of variance. Results are reported as means with one SD.

RESULTS

Patient Characteristics and Dose Escalation

Twenty-nine patients with newly diagnosed or recurrent brain tumors were enrolled onto the study. Patient characteristics are listed in Table 2. DLT was seen at 8 mg/kg. No DLT was seen at 4 mg/kg, and the light dose was escalated at this dose to 50 J/cm^2 (three patients) and 100 J/cm^2 (four patients) without additional toxicity. The recommended dose for future studies is 4 mg/kg, with a light dose of at least 50 to 100 J/cm^2.

Table 2. Patient Characteristics

Characteristic	No. of Patients
Total	29
Age, years	
Median	51
Range	30-75
Sex	
Male	20
Female	9
Karnofsky performance status	
Median	80
Range	70-100
Tumor type	
GBM	15
Anaplastic astrocytoma	12
Ganglioglioma	1
Metastatic tumor	1
Newly diagnosed	9
Recurrent disease	20
Prior chemotherapy	0
Prior radiotherapy	16

Toxicity

The toxicities of BOPP are listed in Table 3. Overall, BOPP PDT was very well tolerated. Thrombocytopenia was the DLT at 8 mg/kg. Two of three patients at this dose level developed significant thrombocytopenia (grade 3 and 4, one patient each). Both patients suffered intracerebral hemorrhage requiring re-operation and evacuation of hemorrhage. Both patients made full neurologic recoveries after this procedure. Three patients receiving 4 mg/kg developed grade 1 thrombocytopenia with no bleeding complications. No thrombocytopenia was noted at other dose levels nor in the remaining 10 patients treated at the 4 mg/kg dose.

One patient developed grade 3 nausea and vomiting. However, there were no other grade 3 or 4 toxicities, and no patient required readmission to hospital because of BOPP-related toxicity. The major nonhematologic clinical toxicity was prolonged skin photosensitivity as detected by skin sensitivity testing. Careful attention to skin protection from direct sunlight minimized this problem. One patient developed grade 2 erythema, and five patients developed grade 1 erythema. There was no evidence of phototoxic eye damage. Postoperative monitoring of neurologic function did not suggest any evidence of raised intracranial pressure in the treated patients. There was no apparent increase in intraoperative, postoperative, or postirradiation complications.

Pharmacokinetic Study

The major pharmacokinetic parameters are listed in Table 4 according to dose level. An interim pharmacokinetic analysis was performed on the first 14 patients, revealing an

Table 3. World Health Organization Toxicity Associated With BOPP Therapy

	Patients							
	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Thrombocytopenia	3	10	0	0	1	3	1	3
Anemia	4	14	1	3	0	0	0	0
Erythema	5	17	1	3	0	0	0	0
Local reaction	4	14	0	0	0	0	0	0
Raised LFTs	1	3	1	3	0	0	0	0
Nausea	2	7	1	3	0	0	0	0
Vomiting	0	0	1	3	1	3	0	0
Fever	0	0	1	3	0	0	0	0

Abbreviation: LFT, liver function test.

unexpectedly prolonged elimination time. In retrospect, insufficient sampling at later time points had been used in these patients so that the calculated half-life was considered to be an underestimation. These values are still included in Table 4 but should be considered in this light. Subsequently, additional sampling points beyond 14 days allowed more complete plasma sampling in the remaining patients. One patient had inadequate sampling because of complications associated with grade 4 thrombocytopenia and was not included in the analysis.

Both AUC and Cmax increased with the dose of BOPP (one-way analysis of variance, $P < .0001$ and $P < .0001$, respectively). In patients receiving 4 mg/kg, the mean total systemic clearance was 0.351 ± 0.089 mL/h/kg, mean elimination half-life was 402.4 ± 135.0 hours, mean volume of distribution was 0.181 ± 0.045 L/kg, mean Cmax was 90.51 ± 17.14 mcg/mL, and mean AUC was 12,100 ± 3,035 mcg·hr/mL.

Tumor BOPP concentration was measured in 22 patients (Table 5). The remaining seven patients did not have tumor BOPP concentrations assayed because of technical difficulties either in obtaining a tumor sample at surgery or in the processing of the sample during the extraction/measurement protocol. The mean tumor concentration of BOPP increased with the dose of BOPP. The mean tumor concentration in 10 patients receiving the 4 mg/kg dose was 8.17 ± 3.66 mcg/g of tumor. Table 5 also shows the ratio between BOPP tumor concentration and plasma concentration with the plasma concentration taken at approximately 24 hours after infusion and at the time of resection. The tumor:plasma concentration ratio after a dose of 4 mg/kg was 0.21 and was consistent across the dose ranges.

DISCUSSION

Local tumor recurrence remains the major determinant of progression-free survival and overall survival in patients with high-grade brain tumors. Despite multimodality approaches, including surgery, radiotherapy, and chemotherapy, the median overall survival for a patient with a GBM is only 12 months. Novel approaches to local disease control are necessary to improve the outlook for these patients.

PDT for malignant brain tumors also has a strong rationale because selective uptake of photosensitising drugs into the tumor bulk and peritumoral zone has been demonstrated in both experimental models of glioma and in human tumors.[6-12,15,17,18] The selective photodynamic destruction of tumor, with sparing of normal brain, has also been demonstrated in animal models of glioma,[12,19] and results of phase I and II studies of PDT as an adjuvant therapy for

Table 4. Pharmacokinetic Parameters of BOPP According to Dose Administered*

Dose BOPP (mg/kg)	No. of Patients	$t_{1/2}$ (hours)	CL (mL/hr/kg)	AUC (mcg · hr/mL)	C_{max} (mcg/mL)
0.25	3	292 ± 177.6†	0.531 ± 0.129	487.7 ± 104.9	3.87 ± 0.99
0.5	3	202.5 ± 79.9†	0.545 ± 0.08	927.5 ± 137.9	9.63 ± 2.21
1.0	3	219.3 ± 94.9†	0.549 ± 0.211	2,009 ± 754.6	21.53 ± 1.05
2.0	4	359.3 ± 193.3†	0.613 ± 0.316	3905 ± 1746	33.38 ± 15.94
4.0	13	402.4 ± 135.0	0.351 ± 0.089	12,100 ± 3035	90.51 ± 17.14
8.0	2	1493.0	0.213	4,2170	175.95

Abbreviations: $t_{1/2}$, half-life; CL, plasma clearance.

* Values expressed as mean ± SD (SD not included if no. of patients = 2).

† Values are likely to underestimate $t_{1/2}$ because of inadequate plasma sampling (see text).

Table 5. BOPP Concentrations According to Dose at Surgery

Dose (mg/kg)	No. of Tumors Assayed	Tumor BOPP Concentration (mcg/g)	Plasma BOPP Concentration (mcg/mL)	Tumor:Plasma Ratio
0.25	1	1.31	2.1	0.62
0.5	2	1.24	4.8	0.26
1	3	1.84 ± 1.30	9.30 ± 1.87	0.20
2	3	2.49 ± 1.61	15.2 ± 4.85	0.16
4	10	8.17 ± 3.66	38.35 ± 8.06	0.21
8	3	15.33 ± 4.02	95.03 ± 25.95	0.16

NOTE. Values expressed as mean ± SD (SD not included if no. of tumors assayed < three).

cerebral glioma have been promising,[6-9] although to date no definitive phase III studies have been completed.

BOPP, a novel boronated porphyrin, has highly selective tumor uptake in xenograft models with ratios of BOPP uptake into tumor relative to normal brain as high as 400:1.[10] Fluorescence laser scanning confocal microscopy confirmed the intracellular localization of BOPP in glioma cells in the tumor mass and also in tumor cells invading into normal brain parenchyma at a distance from the tumor mass. These studies also identified the tumor cell mitochondria as a site of localization and phototoxic damage of BOPP, which may in turn explain the efficacy of BOPP, given the sensitivity of this site to phototoxic damage.[10-13,20,21] In addition, studies of BOPP as a sensitizer for PDT in the experimental rat C6 glioma have shown that it requires approximately one tenth the amount of light to mediate the same degree of tumor kill as HpD.[12]

This study examined the safety and pharmacokinetics of the novel compound BOPP as a component of a photodynamic strategy in the treatment of malignant brain tumors. The recommended dose for future studies is 4.0 mg/kg, with a light dose of at least 50 to 100 J/cm^2. At this dose, BOPP was well tolerated and achieved substantial intratumor concentrations. Photosensitivity was a manageable toxicity with careful attention to skin protection from sunlight. There was no increase in intraoperative, postoperative, or postirradiation complications, with potential raised intracranial pressure controlled by pharmacologic means.

Thrombocytopenia was dose limiting at 8 mg/kg. Preclinical studies undertaken in canines and rats at relatively high BOPP doses had predicted that thrombocytopenia might be a significant toxicity in human studies.[22,23] The precise cause of thrombocytopenia is not known, but its onset within 3 to 4 days after infusion suggests a direct toxic effect on platelets by BOPP or its metabolites.[24-26]

The pharmacokinetic characteristics of BOPP were generally anticipated from preclinical studies. However, the elimination time was even more prolonged than expected, more so than animal studies, which suggested a relatively prolonged elimination time. This was confirmed clinically with skin photosensitivity testing, and this may have impacted on the accuracy of some pharmacokinetic parameters for the first 14 patients. Additional sampling at later time points for the remaining patients enabled complete plasma sampling and accurate pharmacokinetic calculations. In particular, complete sampling was possible at the 4 mg/kg dose level. Thus, Table 4 must be interpreted in the context that, for the dose levels of 0.25 to 2.0 mg/kg, the elimination time and AUC may be underestimates. Similarly, there was substantial interpatient variability between the two patients who received 8 mg/kg. Despite these caveats, there seemed to be a clear association between dose and AUC as well as peak plasma concentration. In contrast, clearance was independent of the BOPP dose administered.

Pre-clinical pharmacokinetic studies undertaken in canines demonstrated triexponential elimination kinetics, with half-life values for the α, β, and γ phases of 2.0 hours (SE, ± 0.3), 26.8 hours (SE, ± 1.2), and 558.9 hours (SE, ± 65.8), respectively.[22] In contrast, the data from the human subjects were best described by a bi-exponential equation. This difference may be because of the fewer number of blood samples drawn, particularly at early time points, and the improved sensitivity of the assay used to measure boron levels in this study.[22]

Importantly in this study, we were able to determine intratumor BOPP concentrations. This was measured in biopsy samples taken at surgery (approximately 24 hours after administration). The intratumor concentration was associated with dose, and at 4.0 mg/kg, significant intratumor concentrations of 8.17 ± 3.66 mcg BOPP/g tumor (wet weight) were achieved. These data compare favorably with our previous in vivo experiments in a rodent model, in which intratumor concentrations of BOPP ranged from 2 to 50 mcg/g, depending on administered dose.[10,11] Selective tumor kill with sparing of normal brain could be achieved in this rodent model after activation with 630-nm light,[12] even when the level of BOPP in the tumor was as low as 0.5 mcg/g.

A relatively consistent tumor:plasma BOPP concentration was achieved at this time point with a ratio of 0.21 at the 4.0 mg/kg dose level. In contrast, tumor:blood ratios at 24 hours in mice administered BOPP at doses of 10 and 100 mg/kg were 15 and 6.5, respectively, and in rats administered a dose of 35 mg/kg, the ratio was 6:1.[10,18] The much

lower value found in this study in humans undoubtedly reflects the much slower clearance of the drug from the blood and may suggest that future studies be designed with a longer time between drug administration and activation, which may allow more selective photosensitization of tumor tissue, while minimizing any potential normal brain phototoxicity mediated by elevated levels of BOPP in the bloodstream.

The elucidation of tumor BOPP levels is a critical finding. The substantial intratumor BOPP concentrations achieved at this dose suggests that an optimal biologic dose may be achieved at a lower BOPP dose than the MTD, thus further reducing the risk of toxicities such as thrombocytopenia and skin sensitivity. Furthermore, the detection of BOPP[10] in the invasive glioma cells is significant because these cells are the targets of PDT because they are not surgically resectable and are responsible for tumor recurrence.

In conclusion, this study has examined the tolerability and pharmacokinetic profile of BOPP, a novel boronated porphyrin, used as a component of PDT for high-grade gliomas. Thrombocytopenia is dose limiting, but at the recommended dose of 4 mg/kg, BOPP is very well tolerated with few side-effects. Furthermore, at the 4 mg/kg dose, significant intratumor concentrations of BOPP were achieved.

Previously published reports of HpD in the treatment of malignant brain tumors document excellent tolerability but lack compelling evidence of efficacy.[6-9] No randomized studies exist, and the published data has measured itself against historical controls. The apparent improvement in tumor selectivity and photoactivity associated with BOPP recommends additional PDT studies using this novel drug to examine its efficacy in the management of high-grade gliomas.

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