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Clinical Study

Evaluation of photodynamic therapy near functional brain tissue in patients with recurrent brain tumors

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Summary

Introduction: Photodynamic therapy (PDT) involves the selective retention of a photosensitizer that upon activation with light mediates tumor cell destruction via the production of singlet oxygen. This study evaluates the toxicity of PDT and a new light-delivery device based on light-emitting diode (LED) technology in selected patients with brain tumors.

Methods: Twenty patients with recurrent malignant brain tumors received 22 treatments with PDT. Sixteen tumors were supratentorial and four tumors were infratentorial. Patients received IV Photofrin® 24 h prior to light exposure starting at 0.75 mg kg^{-1}. Laser and LED arrays were used to deliver 100 J cm^{-2} of light to the sensitized tumors. Fourteen patients received PDT with a laser-balloon adapter, two via interstitial optical fibers and five patients had LED based PDT. At the maximum Photofrin® dose of 2.0 mg kg^{-1} five patients received laser-balloon adapter light and five patients received LED light. In addition, three patients received LED light with 0.25 mg kg^{-1} of Visudine®, a benzoporphyrin derivative (BPD). Quantitative analysis of toxicity and time to progression was performed.

Results: Two patients had toxicity consisting of ataxia and facial weakness after treatment with interstitial fibers. Escalating doses of Photofrin® were tolerated to the maximum dose of 2.0 mg kg^{-1}. BPD did not result in additional toxicity. PDT in the posterior fossa or near eloquent brain was tolerated using the LED or laser-balloon adapter. All patients had tumor responses as documented by MRI scan and the mean time to tumor progression after PDT was 67 weeks.

Conclusion: PDT with LED balloon adapters (also tunable dye laser) has acceptable toxicity in brain tumor patients. Future studies using more effective photosensitizers could improve local recurrence control.

Introduction

Photodynamic therapy (PDT) is a novel local treatment for recurrent brain tumors. The cytotoxic photodynamic effect on tumor cells depends on the interaction of localized photosensitizer, light and oxygen. Experimental and clinical studies indicate selective accumulation of photosensitizing drugs in brain tumors [9,20,21,28]. In clinical practice the most common photosensitizer administered for brain tumor is hematoporphyrin derivative (HPD) and Photofrin® porfimer sodium. Both of these photosensitizers are an inhomogeneous mixture of molecules that have two significant absorption peaks at 390 and 630 nm. Light penetration into brain and tumor tissue increases with longer wavelength light. Thus, because of the infiltrative nature of many brain tumors and in particular malignant gliomas, 630 nm laser light is frequently used as a light energy source. Light delivery to the tumor tissue can be accomplished via fiber optics that are directly inserted into the tumor or with an inflatable balloon adapter that is placed into the resection cavity [11,15,16,23]. Until recently both these methods depended on costly laser technology. However, based

on preliminary animal studies newer broad-spectrum high energy light-emitting diode (LED) technology might be useful in the treatment of brain tumors [24].

Clinical studies in patients with newly diagnosed and recurrent brain tumors demonstrate that PDT has acceptable toxicity and can result in significant tumor responses [11,15,16]. The most significant systemic side effect is temporary skin toxicity which can be avoided with light exposure precautions.

Neurotoxicity, including brain stem hemorrhage, necrosis, and edema of brain tissue leading to focal clinical neurologic deficits has been demonstrated in animal studies and clinical studies [17,18,29]. Because of these potential toxicities patients with a tumor in close proximity to eloquent brain are frequently excluded from clinical studies.

The goal of this study was to evaluate the toxicity of PDT and LEDs on brain tissue in patients with recurrent brain tumors near eloquent regions.

Patients and methods

Patient population

Twenty patients with recurrent brain tumors were treated with PDT according to the protocol approved by the Institutional Review Board. Patients were excluded from participation in the study on the basis of the following:

(1) life expectancy less than 2 months,
(2) pregnancy,
(3) inability to consent,
(4) previous brachytherapy,
(5) previous chemotherapy within 6 weeks of proposed PDT,
(6) other concurrent tumor therapy.

Patient's ages ranged from 1 to 51 years with a median age of 18.5 years. Sixteen tumors were supratentorial in location and four tumors were infratentorial. Tweleve patients had PDT in close proximity to eloquent brain tissue. Patient 1 had three PDT procedures (Table 1).

Photosensitizer

Photofrin® (QuadraLogic Technologies, Vancouver, B.C., Canada) is a more purified photosensitizer derived from hematoporphyrin derivative. The patients entering the study received intravenous Photofrin® at increasing doses (0.75, 1.2, 1.6, 2.0 mg kg^{-1}) 18–24 h prior to PDT.

Benzoporphyrin derivative (BPD) was provided by Novartis Pharmaceuticals and used at 0.25 mg kg^{-1} 3–6 h prior to light exposure. Doses are still escalating.

^{111}In-labeled Photofrin® uptake studies

About 2.5 mg of Photofrin® was dissolved in 1 ml of sterile water and added to 1 mCi (37 MBq) of ^{111}In-oxine (pH = 7.5). The mixture was heated at 115°C for 30 min [28]. After cooling to room temperature the final product underwent thin layer chromatography. Eighteen patients received ^{111}In-labeled Photofrin® intravenously several weeks prior to surgery. Brain scans using a gamma camera interfaced to a computer were obtained at 24 h after injection, to document preferential tumor uptake (Figure 3).

Laser light delivery and dosimetry

Photoillumination was carried out with laser or LED light. Laser light was delivered either with a fiber-optic catheter or with a laser fiber balloon adapter. The laser-balloon adapter was used for intracavitary PDT as described by Muller and Wilson [17]. The laser was tuned to emit 630 nm light to deliver a total light dose of 1 800 J. LED light was delivered with a balloon adapter that contains 144 LED chips. The LED balloon adapter and dosimetry was described by Schmidt et al. [24]. LEDs emit light with 20–25 nm bandwidth and can be manufactured to produce equivalent light doses when compared to laser light. The LED balloon adapter delivered 1 800 J of light to the exposed tissue.

PDT procedure

After patients received their assigned Photofrin® or BPD dose, light exposure photosensitivity precautions were instituted. Patients were kept out of direct light and skin surfaces were covered. Then the patient underwent the scheduled procedure. The 20 patients had a total of 22 PDT treatments with one patient receiving a total of three PDT treatments. Twenty patients underwent craniotomy or craniectomies with tumor resections. One patient had an intraventricular tumor, which was biopsied and then treated with PDT via an endoscope. Of the 23 PDT treatments, 15 treatments were performed with laser (13 by balloon and two by fiberoptic with 1.5 cm cylinder diffusion tip) and seven treatments by LED using balloon adapter.

Table 1. Patient characteristic and tumor location in relation to PDT exposed eloquent brain regions

Patient	Age	Location of tumor	Histology	Eloquency	Neurotoxicity	Relapse free survival time
1	14	Right parietal	Anaplastic ependymoma	Visual cortex	None	11 months (trial one) 3 months (trial two) 9 months (trial three)
2	21	Right temporal	Anaplastic oligoastrocytoma	Cerebral peduncle	None	7 years 7 months (to date)
3	36	Left frontal	Anaplastic oligoastrocytoma	None	None	1 year 5 months
4	17	Right frontal	Medulloblastoma	Thalamus	None	10 months
5	14	Right frontal lobe	Central neuroblastoma	Speech	None	8 weeks
6	1	Left parietal	Rhabdoid tumor	Speech	None	10 weeks
7	19	Cerebellar vermis	Anaplastic astrocytoma	Floor of the 4th ventricle	Yes	3 years 10 months
8	48	Right occipital	Glioblastoma multiforme	Visual cortex	None	9 months
9	1	4th ventricle	Ependymoma	Floor of the 4th ventricle	None	4 months
10	51	Left frontal	Anaplastic oligoastrocytoma	None	None	3 months
11	45	Right temporal	Glioblastoma multiforme	Cerebral peduncle	Yes	6 months
12	11	Brain stem & Left cerebellum	Pilocytic Astrocytoma	Infratentorial	None	6 months
13	12	Right frontal	Central neuroblastoma	None	None	4 years 5 months (to date)
14	39	Right frontal	Astrocytoma	None	None	4 years (to date)
15	20	Left frontal	Glioblastoma multiforme	None	None	4 months
16	18	Brain stem	Astrocytoma	Infratentorial, medulla oblongata	None	2 months
17	15	Right temporal	Glioblastoma multiforme	Cerebral peduncle	None	2.5 months
18	51	Left posterior frontal	Glioblastoma multiforme	Motor cortex	None	2 months
19	59	Right temporal	Adenocarcinoma	None	None	5 months
20	53	Left frontotemporal	Malignant meningioma	Speech	None	1 year (to date)

Results

^{111}In-labeled Photofrin® uptake studies

Several weeks before PDT, brain scans of all patients were performed at 24 h following the intravenous injection of ^{111}In-labeled Photofrin®. Images demonstrated increased uptake of the radioactivity in the region of brain tumor when compared to the normal brain. The exact mechanism of localization and exact structure of the radiolabeled compound are not known. The initial accumulation of the radiolabeled molecule can be attributed to the passive diffusion through the disrupted blood–brain-barrier (BBB) in the region of the brain tumor. However, brain tumor concentration of ^{111}In-labeled Photofrin® was well above that resulting from BBB breakdown as demonstrated previously in pre-clinical studies by our group [28] (Figure 3).

Toxicity

Patient 7 had an anaplastic atrocytoma including the cerebellar vermis. After resection the patient had a small residual tumor involving the cerebellar peduncle near the brain stem. A cylindrical diffuser measuring 1.5 cm in length and 1.6 mm in diameter was placed on the surface of the tumor and the patient received PDT. Immediately postoperatively the patient developed severe truncal ataxia, bilateral facial weakness as well as dysphagia.

Patient 11 had a right temporal lobe glioblastoma multiforme that had recurred after initial resection, radiation therapy and chemotherapy. He underwent an extensive reoperation exposing the dura over the geniculate ganglion followed by intracavitary laser light PDT. Post operatively the patient had a right facial nerve palsy, which improved in 3 months, but did not completely resolve.

Four patients had tumors in the posterior fossa with tumor extending either into the brain stem or immediately adjacent to it. PDT light exposure with the balloon applicator did not result in any neurotoxicity. In addition, PDT exposure of sensory cortex, motor cortex or visual cortex did not result in additional deficits.

Patient 18 had a symptomatic recurrent GBM in the motor sensory cortex. The tumor was subtotally resected and then treated with PDT. After PDT her motor strength was stable and improved over the next few weeks.

Patient 16 had a recurrent brain stem astrocytoma in the right medulla, which was biopsied and then treated with PDT (Figures 1 and 2). He experienced no new neurologic deficit after surgery. In fact, his clinical neurologic examination improved prior to discharge, in comparison to his admission examination.

Two patients had PDT exposure of the cerebral peduncle after partial resection of temporal gliomas. There were no motor, or otherwise, deficits after surgery.

Tumor response

All tumors responded after treatment, as demonstrated by either a stable appearance or decreased size of tumor or MR image studies. We analyzed the time to tumor progression (TTP) from their last treatments and from time of PDT. The mean and median TTP from the patient's last treatment prior to PDT was 30 weeks and 22 weeks (range 3–104 weeks). The mean and median time to progression after PDT was 68 weeks and 26 weeks (response range 8–394 weeks). It should be noted that the TTP calculation might be confounded by the effects of surgery and steroid tapers. Although this is a phase I toxicity study, some dramatic responses to PDT are noteworthy. Patient 1 had an anaplastic ependymoma that was diagnosed at age 11 and treated with surgical resection, focal radiation therapy and chemotherapy. At first recurrence the tumor was treated with surgery and PDT. Twelve months later a smaller local recurrence was again treated with PDT. The patient remained free of local disease progression for 3½ years. The patient had further tumor progression at another site, which was also treated with PDT. She expired from progression at this site after 1 year and 10 months.

It is also of note that patient 16 had a brain stem tumor treated with LED-PDT which resulted in clinical and MRI documented resolution of brain stem signs, and near-complete MRI documented disappearance of

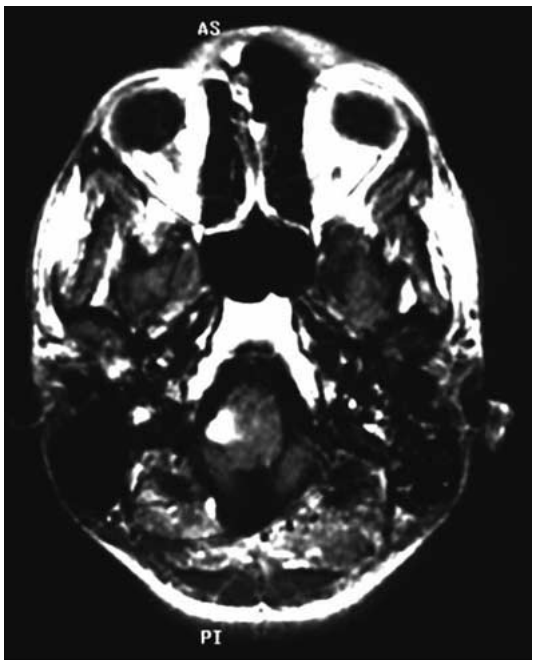

Figure 1. Gadolinium enhanced MRI scan prior to PDT.

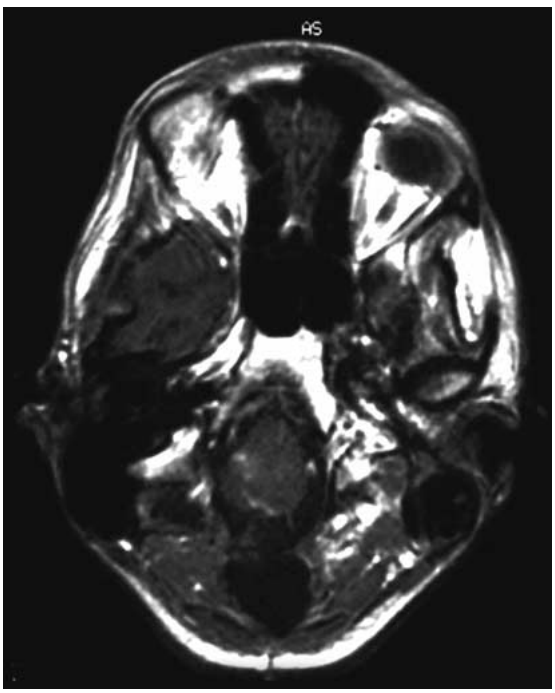

Figure 2. Gadolinium enhanced MRI scan after PDT.

gadolinium enhancement without resection of tumor (Figures 1 and 2).

There are four long-term survivors. Patient 1 survived 7 years, patient 2 has survived 7 years and is still tumor-free. Patients 13 and 14 are still tumor-free 4 years post-PDT.

Light source evaluation

We compared the results of the toxicity of patients receiving laser light and LED light. Two patients received 0.25 mg kg^{-1} of BPD. Ten patients received the maximum (2.0 mg kg^{-1}) of Photofrin®. Eight patients received lower doses of Photofrin® during dose escalation (Table 1). Eight patients received LED light. The LED probe has a continuous temperature-monitoring probe. The maximum temperature did not exceed 38°C. Laser and LED light was delivered at 100 J cm^{-2}. There was no difference in tissue toxicity between laser or LED light at equivalent light doses of 1 800 J. Treatment was prolonged due to laser malfunction in three patients.

Discussion

The use of PDT in the treatment of brain tumors has only slowly increased over the past decade. Experimental and clinical studies demonstrate that PDT can complement the existing traditional tumor therapies consisting of surgical resection, radiation therapy and chemotherapy [15,16,19,22,23]. The great potential of PDT is its unique mechanism of action, low systemic toxicity and the potential for treatment of infiltrative tumor cells into normal brain tissue.

Studies indicate that photosensitizers are accumulating in brain tissue infiltrated by tumor cells and in normal brain tissue [4,9]. Stummer et al. demonstrated the spread of Photofrin® in edematous tissue [8,26]. Brain biopsies of patients with gliomas demonstrated significant sensitizer uptake in brain adjacent to tumor (BAT) [9]. The presence of photosensitizer in these areas indicates not only potential for therapeutic effect but also the potential for normal tissue damage. In functional brain tissue this can result in neurological deficits from direct phototoxic damage, cerebral edema with resulting increased intracranial pressure. Because of this most studies have been restricted to patients with a supratentorial neoplasm away from functional cortex and the brain stem. Only Laws and collaborators treated four patients with posterior fossa neoplasm (two medulloblastomas, two ependymomas) with PDT with good results [13]. Previously, we conducted an experimental canine glioma study in which the brain stem and the floor of the fourth ventricle were exposed to PDT [29]. With high Photofrin® doses, brain stem toxicity occurred. However, lower Photofrin® doses were tolerated at equivalent light doses. During PDT in our canine model, the temperature of brain tissue did not rise more than 1°C. Because of our laboratory investigations in this canine model we felt that photodynamic toxicity of functional brain tissue could be tolerated. Thus, we initiated a clinical Phase I study with patients with recurrent brain tumors addressing this issue.

The results of this study confirm that PDT can be tolerated near functional tissue. Only one of four patients who received posterior fossa PDT developed a significant neurologic deficit. This patient received PDT with a fiber optic with small cylindrical light dispersion tip. Given the high power density of a small spherical fiber optic we believe that the deficit is related to hyperthermia at the tip. Similar effects of hyperthermia from interstitial laser irradiation on normal brain have been documented in detail in a rat brain model [7]. Careful monitoring and avoidance of hyperthermia due to high power densities possibly can avoid this side effect. Laws et al. suggested that if hyperthermia is avoided, cerebral edema does not develop [12]. Another study that tested the effects of temperature in rat brain demonstrated that mild hyperthermia combined with PDT does not worsen damage to normal brain [6]. Our patients that received light energy via an inflatable balloon adapter experienced no neurologic deficits. Power densities are not as high with the balloon adapters and hyperthermia is not as significant. In particular, the patients with a recurrent intrinsic brain stem glioma (Figures 1 and 2) experienced no side effects, using the LED balloon adapter that contained a temperature monitor.

Another aspect of this study is the use of the LED balloon adapter. LEDs emit a broad spectrum light that can be used as an energy source for photosynthesis in plants [2,3]. LEDs were originally developed to promote plant growth during space flights by NASA. This space technology was used to develop a novel balloon adapter for PDT with Photofrin® and subsequently with BPD [24,25]. Because of the broad emission spectrum of the LED (630–940 nm light) there is the potential for activation of photosensitizer deeper in brain tissue with both potential therapeutic and toxicity

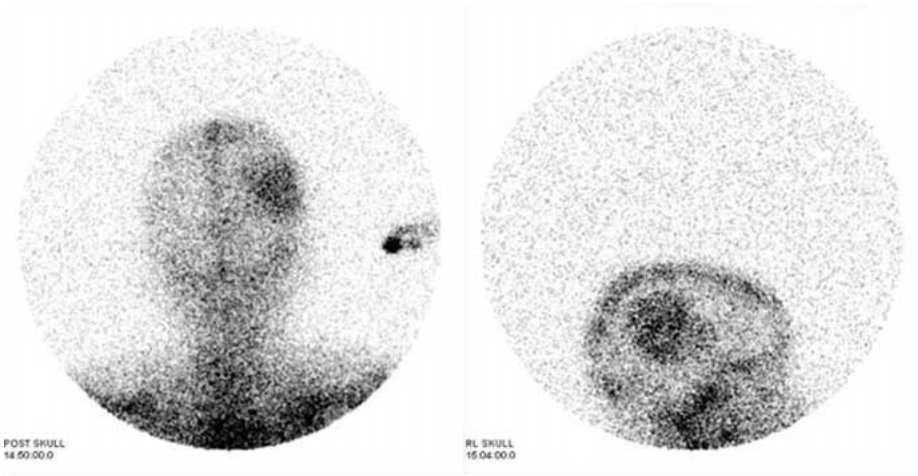

Figure 3. 24 h image of ^{111}In-labeled Photofrin®. The pictures demonstrate intense uptake of ^{111}In-labeled Photofrin® in the AP and lateral views of patients with an anaplastic ependymoma.

implications. The current study confirms the results of our prior animal studies in that LED light does not result in increased toxicity compared to laser light.

Although we demonstrated in a prior publication [24] that equivalent light doses can be delivered for Photofrin® PDT using laser or LED light, the use of Photofrin is not ideal because of the difference in the major emission (677 nm) and absorption peaks (630 nm). Thus, in three patients we used BPD as a photosensitizer. BPD has a major absorption peak of 680 nm, which is much closer to the major emission peak of the LED light source. This results in more efficient energy transfer and decreased treatment time [25]. The three patients treated with BPD and LED light experienced no systemic or neurologic side effects. In addition, BPD is eliminated from the systemic circulation within 24 h. Thus, photosensitivity precautions can be discontinued after one day compared to 6–8 weeks with Photofrin®.

Certainly this study has a number of limitations. It includes only a small number of patients with brain tumors of diverse histology and without randomization. But together with the encouraging results from other investigators and the advances in light delivery and long wavelength sensitizer biochemistry PDT deserves further clinical evaluations. The potential combination of PDT with fluorescence guided resection and PDT with agents that can be used as cytotoxic chemotherapeutic agents certainly deserves further investigations [1,5,27,30]. In addition, the application of fluorescence guided resection and PDT to less deeply infiltrating neoplasms such as pituitary tumor, metastatic tumors and ependymomas similarly warrants further exploration [10,14].

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