Adjuvant high-dose photoradiation therapy in the treatment of cerebral glioma: a Phase 1–2 study


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A Phase 1–2 study of high-dose photoradiation therapy was performed in 23 patients with cerebral tumors. Twenty-two patients had high-grade gliomas (13 glioblastomas, six recurrent glioblastomas, two anaplastic astrocytomas, and one recurrent anaplastic astrocytoma) and one had a right frontal metastasis from a carcinoma of the lung. Hematoporphyrin derivative was administered to these patients in a dose of 5 mg/kg and, 24 hours later, they all underwent a craniotomy with radical excision of the tumor. The tumor bed was then irradiated with 630 nm of laser light from either an argon dye laser or a gold metal vapor laser for between 43 and 94 minutes, receiving total doses of 70 to 120 J/sq cm (six cases) or 120 to 230 J/sq cm (17 cases). The temperature of the tumor bed was kept below 37°C by irrigation. Fifteen patients who developed new tumors underwent postoperative radiotherapy (45 Gy in 20 divided doses).

There was no evidence of increased cerebral edema and no other toxicity from the therapy. All patients were discharged from the hospital within 18 days of surgery. Four of seven patients with gliomas have suffered a further recurrence at 12 to 16 weeks, and two of 15 patients with primarily treated gliomas experienced recurrence at 3 and 13 months following therapy. Fifteen patients have had no recurrence of their tumor and are alive and well at a median follow-up period of 7 months (range 1 to 16 months). It is concluded that photoradiation therapy using 5 mg/kg of hematoporphyrin derivative and 630 nm light at doses of up to 230 J/sq cm can be used as an adjuvant to surgery and radiotherapy with no additional complications.

KEY WORDS · brain neoplasm · hematoporphyrin derivative · glioma · photoradiation therapy

At the present time there is no satisfactory treatment for malignant cerebral glioma. The best available treatment, which consists of surgery, radiation therapy, and systemic chemotherapy, results in a median survival time of less than 1 year.25,26,28 Most treatment failures occur because of local recurrence of the glioma, indicating that a more aggressive local therapy to the tumor could be beneficial. Recently, it has been suggested that photoradiation therapy could be useful for the therapy of gliomas.7,15,18-21,27

Photoradiation therapy is a form of local treatment that has been used successfully for several different tumor types including tumors of the esophagus, bladder, skin, and lung, and it has been demonstrated to be useful for the control of local disease.1,8-11,16 This method depends on the selective retention of a photosensitizer such as hematoporphyrin derivative (HPD) by malignant tissue, and uses laser light of appropriate wavelength to activate the sensitizer.

In vivo studies have demonstrated that malignant cells retain HPD selectively,2,9,10,14,27 and selective uptake of HPD by cerebral tumors has been demonstrated both in experimental14,17,25 and in clinical studies.27 The initial clinical studies of photoradiation therapy were disappointing.18-21 However, these studies15,18-21 often reported treatment of recurrent gliomas and the doses of light irradiation given were 10- to 100-fold lower than those used in systemic tumor.8 This was done because of the fear of side effects of photoradiation therapy at high doses6,23 (especially when combined with x-ray therapy24) and for lack of availability of powerful light-producing sources.

Studies in animal glioma models have demonstrated both tumor selectivity of HPD9,15,14,27 and a selective destruction of the tumors.3,13 We have therefore undertaken a dose-escalation study of HPD photoradiation therapy to determine whether high doses could be tolerated in a Phase 1–2 study of 23 patients with malig-
Photon ablation of gliomas: An alternative to surgery and radiotherapy

TABLE 1
Characteristics of 22 patients with recurrent and primarily treated gliomas

<table>
<thead>
<tr>
<th>Factor</th>
<th>Recurrent Gliomas</th>
<th>Primarily Treated Gliomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>median age (yrs)</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>no. of males</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>anaplastic astrocytoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>glioblastoma multiforme</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>duration of symptoms (mos)</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Karnofsky performance scale score</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>type of laser</td>
<td>gold metal vapor</td>
<td>gold metal vapor</td>
</tr>
<tr>
<td>dose of laser light (J/sq cm)</td>
<td>120</td>
<td>12</td>
</tr>
<tr>
<td>laser power</td>
<td>&lt; 1.5 W</td>
<td>&gt; 1.5 W</td>
</tr>
<tr>
<td>cases with recurrence</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

The patients were pre-sensitized with HPD prior to surgery and treated with 630 nm of light emitted by either an argon pumped dye laser (continuous light) or a gold metal vapor laser (pulsed light). The pulsed laser allowed higher doses of light to be used than in other studies.

Clinical Material and Methods

Patient Population

Twenty-three patients (11 men and 12 women) were treated with photoradiation therapy. The group included all patients with high-grade gliomas in whom a tumor debulking procedure was feasible and logistically possible and who were referred to one neurosurgeon (A.H.K.). Small deep basal ganglia tumors where a biopsy only was indicated and brain-stem tumors were not considered suitable subjects for this study. A summary of the patient data is shown in Table 1. Twenty-four hours following administration of HPD a craniotomy was performed and the tumor was radically excised with the aid of the Cavitron ultrasonic surgical aspirator. All operations were performed by one surgeon (A.H.K.). In four patients, it was thought that a complete macroscopic excision was achieved. In the remaining 19 patients, it was considered at surgery that there was residual tumor despite extensive macroscopic tumor resection.

Operative Procedure and Photoradiation Therapy

The details of the photoradiation therapy are shown in Table 1. Twenty-four hours following administration of HPD a craniotomy was performed and the tumor was radically excised with the aid of the Cavitron ultrasonic surgical aspirator. All operations were performed by one surgeon (A.H.K.). In four patients, it was thought that a complete macroscopic excision was achieved. In the remaining 19 patients, it was considered at surgery that there was residual tumor despite extensive macroscopic tumor resection.

Laser light at 630 nm was generated using an argon pumped rhodamine dye laser for treatment of nine patients and using a gold metal vapor laser for treatment of 14 patients. The light was delivered through a flat cut-quartz fiber (600 μ in diameter in 17 patients, 1 mm in diameter in six patients) which was placed in a photoelectric cell for calculation of the dose. The laser power was between 0.7 and 2.2 W at the fiber tip. The surface area to be irradiated was calculated, the fiber was attached to a Yasargil brain retractor arm, and the tumor bed was irradiated for between 43 and 94 minutes (median time 60 minutes). To ensure even distribution of the hot spot from the fiber tip, the fiber was moved at regular intervals to completely and evenly cover the surface of the tumor bed. If the tumor resection had resulted in a cavity to be irradiated, 0.5% gliomas underwent postoperative radiotherapy (45 Gy in 20 divided doses) commencing 4 to 6 weeks following surgery; the 15th patient died 15 days postoperatively. One patient, a 36-year-old woman, who presented with a metastatic tumor from carcinoma of the lung, underwent radiotherapy 4 weeks postoperatively (30 Gy in 10 increments to the whole head and 40 Gy to the lung cancer). All patients were followed with regular clinical and computerized tomography (CT) review.

Preparation and Administration of HPD

The photosensitizer HPD was prepared by the acetylation of hematoporphyrin using the technique described by Forbes et al. and was sterilized by passing it through millipore filters. The preparation (5 mg/kg of HPD in 200 ml of normal saline) was administered by intravenous injection over a period of 30 minutes, 24 hours before surgery.
Intralipid (an intravenous fat emulsion) was used as a diffusing agent, except in two patients where there was communication with the lateral ventricle. The temperature on the surface of the brain was monitored using a thermal diffusion cerebral blood flow monitor,* and the brain deep to the irradiated surface was monitored using a trigeminal neuralgia electrode lesion generator† inserted to a depth of 2 mm. The temperature was kept below 37°C by irrigation with either normal saline (seven patients) or 0.5% Intralipid (16 patients).

Following the photoradiation therapy the dura was closed, the bone flap replaced, and the craniotomy wound closed. The total time for the surgery including the photoradiation therapy varied from 31/2 to 5 hours.

Results

Outcome

The characteristics of the patients are summarized in Table 1. All patients underwent CT scanning prior to surgery. The argon pumped rhodamine dye laser was used in the early part of the series. Because the power that could be obtained from this instrument was less than 1.5 W at the fiber tip, the maximum dose of light to the tumor bed was 145 J/sq cm. In the later part of the series, the gold metal vapor laser was used. This laser produced a power of up to 2.2 W at the fiber tip and so higher doses of light could be delivered in a practical time period (less than 85 minutes). The patients were followed for between 1 and 16 months.

Two of the 15 patients with primarily treated gliomas had a recurrence observed clinically and on CT scans at 2 and 13 months following therapy. One additional patient died of an acute myocardial infarction 15 days postoperatively, and an autopsy was refused by the relatives. The other 13 patients were followed clinically for 1 to 16 months (median follow-up time 5 months) with no clinical evidence of tumor recurrence. The CT scan showed no evidence of disease in eight of these cases, a stable minor abnormality in two cases (a very small area of contrast enhancement on CT), and a stable abnormality in three cases. Four of the seven patients with recurrent gliomas have suffered further recurrence and have died. In all of these cases the clinical recurrence became apparent between 12 and 16 weeks after the photoradiation therapy. The other three patients are clinically disease-free at 2, 6, and 13 months. The CT scans in these three patients showed no evidence of disease in two cases (2 and 13 months after treatment) and a stable minor abnormality in one case. The patient with the metastatic adenocarcinoma that had been completely excised at operation died 9 months from the time of surgery. At autopsy there was no evidence of central nervous system tumor.

Toxicity of Therapy

There were no direct complications from photoradiation and no significant increase in neurological deficit following surgery. One patient, a 73-year-old man, died 15 days after surgery from an acute myocardial infarction. The other patients were discharged from the hospital within 18 days of surgery, at which time all were ambulatory. Blood chemistry investigations performed at regular intervals for 3 weeks following the administration of HPD indicated no evidence of hematological, hepatic, or renal toxicity from the therapy. There was no evidence of increased cerebral edema. The total mean dose of dexamethasone required to control postoperative cerebral edema was 32 mg (range 28 to 34 mg) on the 1st postoperative day, and steadily declined to 16 mg/day on Day 5, 8 mg/day on Day 10, and 4 mg/day on Day 18.

There was no increase in the toxicity of postoperative radiotherapy in the 15 patients who received this treatment after the photoradiation therapy. Two patients had increased skin pigmentation in the radiation field. There was no excessive cerebral edema during the radiotherapy, and all patients received dexamethasone between 4 and 16 mg/day to control symptoms during the course of therapy. No patient required hospitalization during radiotherapy and the course of treatment did not have to be stopped in any patient. All patients were advised to remain out of direct sunlight for 4 weeks.

Survival curves were prepared using standard Kaplan-Meier calculations and were compared by the log-rank test. Survival graphs for primarily treated glioma patients and recurrent glioma patients are shown in Fig. 1. It is clear that the treatment had little impact on recurrent tumors, as four of seven patients relapsed between 3 and 4 months afterward. However, the survival time of the patients with nonrecurrent (primarily treated) tumors was longer than that for patients with recurrent gliomas, and a median survival time has not yet been reached. Eleven of the 13 patients who received higher doses of light (> 120 J/sq cm) from the gold metal vapor laser had an improved survival time, although statistical significance has not been reached. The number of cases is too small and the follow-up period too short to determine any significant difference in time to recurrence or survival comparing the type of laser (Fig. 1C), the preoperative Karnofsky status (Fig. 1B), the patient's age, or the extent of tumor resection.

Discussion

The main findings of this Phase 1-2 study were that photoradiation therapy using HPD, 5 mg/kg, and 630 nm light up to 230 J/sq cm is a safe adjuvant treatment and that it can be followed by conventional radiotherapy without additional side effects. The number of patients at present is too small and the follow-up duration too short to make conclusions concerning the efficacy of the therapy.
Photoradiation therapy for cerebral glioma

Since 1978, 41 cases of cerebral tumors treated with photoradiation have been reported. The light has been administered by either a xenon arc light, or a helium neon laser, or a gold metal vapor laser. The laser light sources have the advantage that the light output can be accurately measured, the light can be administered selectively to parts of the tumor cavity, deep cavities can be irradiated effectively, and higher doses of light can be used as required. There is also the possibility of using this technique in conjunction with stereotaxic surgery.

Our study has used higher laser doses for photoradiation than in previous series (Table 2). The laser power in previous studies has varied from 2.5 mW to 460 mW and we used from 0.7 W to 2.2 W. There are difficulties in determining the exact dose of laser light administered as a function of surface area irradiated, and not all series mention the dose of light used in joules/sq cm. We carefully measured the surface area to be irradiated, estimated the percentage of light lost from the field, and endeavored to ensure an even distribution of light to the whole surface. This required moving the fiber at regular intervals to achieve an even distribution of the “hot spot.” If the tumor resection resulted in a cavity to be irradiated, 0.5% Intralipid was used as a diffusing agent provided that the cavity did not communicate with the lateral ventricles (suggested to the authors by Dr. E. Laws of the Mayo Clinic, Rochester, Minnesota). The dose of laser light used in this series was higher than in other reports where tumor resections have been performed. The doses in those series have varied from 0.9 to 9 J/sq cm, 8 to 68 J/sq cm, and 100 mW/sq cm. The outcome in previous

![Graph](image-url)
series has usually been poor, although a few long-term survivors have been reported.\textsuperscript{15,18} The apparent reasons for using low irradiating doses included fear of additional toxicity (mainly cerebral edema) and instrumentation that allowed only low powers to be administered. With the development of the gold metal vapor laser, higher powers are possible and the light is pulsed so that high peaks of power are produced. Only one previous case has been reported in which the gold metal vapor laser was used to treat a glioma; in that case a total dose of 1620 J was given.\textsuperscript{18} Our study shows that treatment with the gold metal vapor laser is safe, but the number of patients in our series is too small and the follow-up period too short to determine if the higher doses of light (> 120 J/sq cm) and the pulsed light it delivers are more effective than the lower doses of continuous light previously used; however, the outcome data did show a favorable trend. Although hyperthermia may enhance the effect of photoradiation therapy,\textsuperscript{7} we maintained the temperature at 37°C with irrigation solution. The 5-mg/kg dose of HPD used was based on previous studies \textit{in vivo} and corresponded to the dose used in some other series.\textsuperscript{15,18,21,27}

There was no significant complication as a result of photoradiation. Increased cerebral edema following photoradiation therapy has been reported previously\textsuperscript{18} but was not evident in our patients. The patient who died had a history of cardiovascular disease and had made an uneventful recovery from the surgery until he suffered a sudden fatal myocardial infarction. Patients remained out of direct sunlight for 4 weeks and suffered no significant skin toxicity.

Photoradiation therapy is still in the early stages of development. The present study has extended previous reports by showing that, when used as an adjuvant to tumor resection, doses of up to 230 J/sq cm delivered by the gold metal vapor laser are safe and can be followed by conventional radiotherapy. A further follow-up period is required to determine if photoradiation therapy is a beneficial adjuvant to surgery and x-irradiation therapy. A problem with testing photoradiation as an adjuvant is that tumor responses are difficult to measure. However, since depths of tumor kill of only 0.5 to 1.0 cm can be expected with photoradiation,\textsuperscript{13} as the sole therapy it has little to offer patients with large tumors. It is not clear whether recurrence of tumors is due to failure of the treatment in the whole cavity or in a region of undertreatment because of difficulties in delivering a uniform dose to all parts of the cavity. A major improvement is required in the light delivery and distribution techniques. There is also a need to develop more selective and powerful sensitizers and better sensitizer-activating systems, and to devise procedures to adapt the treatment for deep inoperable tumors.

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**References**

17. Little FM, Gomer CJ, Hyman S, et al: Observations in studies of quantitative kinetics of tritium labelled hematoporphyrin derivatives (HPDI and HPDII) in the nor-
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