

Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors

Clinical article

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Object. The objective of the present study was to perform a prospective evaluation of the potential efficacy and safety of intraoperative photodynamic therapy (PDT) using talaporfin sodium and irradiation using a 664-nm semiconductor laser in patients with primary malignant parenchymal brain tumors.

Methods. In 27 patients with suspected newly diagnosed or recurrent primary malignant parenchymal brain tumors, a single intravenous injection of talaporfin sodium (40 mg/m²) was administered 1 day before resection of the neoplasm. The next day after completion of the tumor removal, the residual lesion and/or resection cavity were irradiated using a 664-nm semiconductor laser with a radiation power density of 150 mW/cm² and a radiation energy density of 27 J/cm². The procedure was performed 22–27 hours after drug administration. The study cohort included 22 patients with a histopathologically confirmed diagnosis of primary malignant parenchymal brain tumor. Thirteen of these neoplasms (59.1%) were newly diagnosed glioblastomas multiforme (GBM).

Results. Among all 22 patients included in the study cohort, the 12-month overall survival (OS), 6-month progression-free survival (PFS), and 6-month local PFS rates after surgery and PDT were 95.5%, 91%, and 91%, respectively. Among patients with newly diagnosed GBMs, all these parameters were 100%. Side effects on the skin, which could be attributable to the administration of talaporfin sodium, were noted in 7.4% of patients and included rash (2 cases), blister (1 case), and erythema (1 case). Skin photosensitivity test results were relatively mild and fully disappeared within 15 days after administration of photosensitizer in all patients.

Conclusions. Intraoperative PDT using talaporfin sodium and a semiconductor laser may be considered as a potentially effective and sufficiently safe option for adjuvant management of primary malignant parenchymal brain tumors. The inclusion of intraoperative PDT in a combined treatment strategy may have a positive impact on OS and local tumor control, particularly in patients with newly diagnosed GBMs. Clinical trial registration no.: JMA-IIA00026 (<https://dbcentre3.jmacct.med.or.jp/jmacctr/App/JMACTRS06/JMACTRS06.aspx?seqno=862>). (<http://thejns.org/doi/abs/10.3171/2013.7.JNS13415>)

KEY WORDS • malignant brain tumor • malignant glioma • oncology • photodynamic therapy • talaporfin sodium • outcome

Abbreviations used in this paper: GBM = glioblastoma multiforme; OS = overall survival; PDT = photodynamic therapy; PFS = progression-free survival; PS = performance status; 5-ALA = 5-aminolevulinic acid.

MALIGNANT brain tumors are characterized by invasive growth into adjacent normal neuronal tissue. Therefore, it is crucial that their man-

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

agement is directed not only to maximal possible resection (while ensuring preservation of the functionally important anatomical structures), but on suppressing the growth of the residual infiltrative tumor cells. Despite aggressive surgical removal followed by postoperative radiotherapy and chemotherapy, between 50% and 85% of WHO Grade IV gliomas recur locally.^{9,16} This emphasizes the need for additional options to improve their growth control.

Photodynamic therapy (PDT) is a treatment method that involves administration of a photosensitizer that accumulates in tumor tissue and newly formed neoplastic vessels. During subsequent irradiation with a laser beam of a specific wavelength, the photosensitizer undergoes a photochemical reaction that produces singlet oxygen possessing strong oxidation properties that cause alteration of the cells. Because singlet oxygen has a short lifetime (0.04–4 μ sec), the PDT-induced cell death is realized only locally in the areas irradiated by the laser beam.^{2,7,8,15}

Talaporfin sodium (mono-L-aspartyl chlorine e6, or NPe6) is a relatively novel photosensitizer for PDT. Its administration in combination with a semiconductor laser has been approved in Japan for clinical use in cases of early stage lung cancer. Nonclinical pharmacological studies directed to its possible application for management of malignant brain tumors were initiated starting in 2001.^{12–14} Experiments with glioblastoma cell lines demonstrated that such therapy induces mitochondrial apoptotic cell loss accompanied by tumor necrosis.^{13,14} Our recent single-center pilot clinical study on the use of talaporfin sodium and a semiconductor laser in patients with malignant gliomas demonstrated promising results with regard to tumor response rates and treatment safety.¹ Therefore, the present open-label, prospective, multicenter clinical trial was initiated for evaluation of the potential efficacy and safety of such therapy. This study was the first investigator-initiated clinical trial in Japan that planned to assess the use of talaporfin sodium and a semiconductor laser for intraoperative PDT as part of a combined management of primary malignant parenchymal brain tumors.

Methods

Patients with suspected primary malignant parenchymal brain tumors, either newly diagnosed or recurrent, which according to preoperative neuroimaging corresponded to a WHO histopathological grade of III or IV,¹¹ were enrolled in this study. The recruitment of patients and analysis of treatment efficacy were mainly focused on newly diagnosed glioblastoma multiforme (GBM). The main inclusion criteria included agreement of the patient to provide written informed consent to participate in the study; age between 20 and 69 years at the time of informed consent; performance status (PS) score of 0, 1, 2, or 3 according to Eastern Cooperative Oncology Group PS scale (a PS score of 3 was accepted only when the score was attributable to neurological symptoms caused by the tumor); supratentorial location of the tumor not including neoplasms originating from the optic pathways and pituitary gland; absence of subarachnoid dissemination; and eligibility for aggressive resection of

the lesion. The main exclusion criterion was a history of photosensitivity or porphyria.

Study Design

This prospective clinical trial was developed and carried out in 2 neurosurgical centers with well-established neurooncology programs, namely Tokyo Women's Medical University and Tokyo Medical University. An open-label, investigator-initiated clinical study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Pharmaceuticals and Medical Devices Agency of Japan as well as by the ethics committees and institutional review boards of both participating universities. A special review board was formed for central radiology assessment, evaluation of data related to treatment efficacy and safety, and handling of the enrolled cases and overall data management. Additionally, a pathology board was created for central review of the permanent formalin-fixed tissue specimens to determine the histopathological tumor type and grade. The 3-year study period was scheduled from March 21, 2009, to February 28, 2012. The clinical trial information for this study can be found at <https://dbcentre3.jmacct.med.or.jp/jmacctr/App/JMACTRS06/JMACTRS06.aspx?seqno=862>.

Patients who were considered eligible for enrollment into study received a single intravenous injection of talaporfin sodium (Laserphyrin, Meiji Seika Pharma Co., Ltd.) in a dose of 40 mg/m² on an inpatient basis 1 day prior to undergoing the elective craniotomy. The next day, surgery was done, the neoplasm was resected, and irradiation of the resection cavity with a 664-nm semiconductor laser beam (Panasonic Healthcare Co., Ltd.), with a diameter of 1.5 cm, radiation power density of 150 mW/cm², and radiation energy density of 27 J/cm², was performed. Particular emphasis was put on irradiation of the areas at risk for recurrence, such as the genu of the corpus callosum.⁹ If tumor resection was incomplete and the residual lesion was macroscopically identified, additional irradiation by the laser was applied at 1 to 3 sites with avoidance of overlap of the irradiation areas. In all cases laser irradiation was done 22–27 hours after administration of talaporfin sodium.

Postoperative Treatment and Follow-Up

Postoperatively all patients with newly diagnosed gliomas underwent fractionated radiotherapy (total dose 60 Gy) with concomitant and adjuvant chemotherapy using ACNU (in cases of WHO Grade III tumors) or temozolomide¹⁸ (in cases of GBM). Patients with recurrent neoplasms were treated according to the preference of their doctors, taking into consideration the details of the primary management.

Adverse effects of treatment were graded according to the Common Terminology Criteria for Adverse Events version 3.0.³ Follow-up examinations were performed every 2–3 months and included physical and neurological assessments with evaluation of PS score, blood and urine tests, and contrast-enhanced MRI. Tumor progression was defined as a 25% or greater increase in the volume of the contrast-enhanced lesion or the appearance of

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new brain lesions. At the time of recurrence the salvage treatment was applied according to the preference of the individual doctors and usually included a combination of re-resection, second-line chemotherapy, and/or vaccine therapy.

End Point Evaluation

The primary end point of the study was overall survival (OS) rate at 12 months after PDT. Secondary end points were progression-free survival (PFS) and local PFS rates at 6 months after PDT. The OS, PFS, and local PFS were all estimated from the date of surgery. Additionally, in cases with a maximal diameter of the residual neoplasm of 16 mm or more, the overall tumor response to treatment was evaluated. All brain MRI data before surgery and during follow-up were assessed by review board members. Safety end points included rates of adverse events, side effects, and results of skin photosensitivity testing.

Data Analysis

Analysis of the treatment efficacy was done in all patients who underwent PDT based on administration of talaporfin sodium and intraoperative laser irradiation of the residual neoplasm and/or resection cavity if the diagnosis of primary malignant parenchymal brain tumor was confirmed by the pathology review board after investigation of the permanent formalin-fixed tissue sections (study cohort). Separate analysis of the treatment efficacy was also done in the subgroup of patients with newly diagnosed GBMs. Survival was assessed using the Kaplan-Meier method. Analysis of the treatment safety was done in all patients initially enrolled into the study who received talaporfin sodium.

Results

Patient Characteristics

Detailed characteristics of patients enrolled in the study are presented in Table 1. In all, 27 patients initially received talaporfin sodium. However, 3 patients were deemed ineligible for study participation during surgery and did not receive irradiation with the laser based on the results of the intraoperative histopathological investigation of the resected tissue on the frozen sections, which revealed lymphoma, low-grade glioma, and cavernoma (1 case each). Additionally, 2 patients were excluded from the study later on because the pathology review board did not confirm the diagnosis of a primary malignant parenchymal brain tumor based on the postoperative examination of the permanent formalin-fixed tissue sections. Therefore, the study cohort included 22 patients with a male/female ratio of 1:1 and a median age of 50.5 years (range 24–69 years). The frontal lobe was affected most frequently (59.1% of cases). In 72.7% of patients the tumor was located within or close to eloquent brain areas. Total, subtotal (> 90% of the lesion volume), and partial resections of the neoplasm were performed in 36.4%, 50%, and 13.6% of cases, respectively. No significant differences in

clinical characteristics were observed between the entire group of initially enrolled patients ($n = 27$) and the study cohort ($n = 22$). Thirteen (59.1%) of 22 patients included in the study cohort had newly diagnosed GBMs and corresponded to recursive partitioning analysis Classes III (4 cases), IV (5 cases), and V (4 cases).⁶

Treatment Efficacy

Among all 22 patients included in the study cohort, 1 death occurred within 12 months after surgery. This patient died 3.4 months after resection and PDT of a newly diagnosed gliosarcoma due to local progression of the tumor. Therefore, the 12-month OS rate was 95.5%. Two tumors demonstrated progression despite treatment within 6 months after surgery, and both recurrences were local. Therefore, the 6-month PFS and local PFS rates were 91%. The maximum length of follow-up was 38.6 months. The median OS was 27.9 months (95% CI lower, 24.8 months; upper, not estimated), the median PFS was 20 months (95% CI lower, 10.3 months; upper, not estimated), and the median local PFS was 22.5 months (95% CI lower, 17.2 months; upper, not estimated).

Among 13 patients with newly diagnosed GBM, the 12-month OS, 6-month PFS, and 6-month local PFS rates after surgical removal of the tumor and PDT were all 100% (Fig. 1). In this subgroup the maximum length of follow-up was 32.0 months. The median OS was 24.8 months (95% CI 18.5–32.0 months), the median PFS was 12.0 months (95% CI 10.3–24.2 months), and the median local PFS was 20.0 months (95% CI 16.2–32.0 months).

In only 1 patient was it possible to evaluate the overall tumor response to treatment. In this case, a newly diagnosed GBM showed complete response 4 months after surgery and PDT.

Treatment Safety

Among all 27 patients who received talaporfin sodium the day before surgery, serious adverse events were noted postoperatively in 6 patients (22.2%). These included aphasia (2 cases) and hemiplegia, hemiparesis, unilateral blindness, visual field defect, homonymous hemianopia, postoperative pyrexia, and infection (1 case each). The overall frequency and distribution of postoperative adverse events were within the range of our usual neurosurgical practice in cases of primary malignant parenchymal brain tumors, and their causal relationships with administration of talaporfin sodium and/or intraoperative laser irradiation were very unlikely. None of these adverse events resulted in the death of a patient.

The laboratory test results in all patients were abnormal, most frequently with an increase in γ -glutamyltransferase (59.3%), alanine aminotransferase (48.1%), aspartate aminotransferase (37.0%), blood alkaline phosphatase (25.9%), and blood lactate dehydrogenase (22.2%). In 18 (66.7%) of 27 patients such abnormalities could be considered as side effects after administration of talaporfin sodium. Postoperative adverse events by system organs, particularly abnormal liver function, were relatively frequent but never exceeded Grade 3 toxicity (Table 2). Only 2 patients (7.4%) had skin disorders, which could be con-

TABLE 1: Characteristics of patients enrolled into study

Demographics & Clinical Characteristics	Initially Enrolled Patients (n = 27)	Value*	
		Total (n = 22)	Study Cohort Newly Diagnosed GBM (n = 13)
age in yrs			
mean \pm SD	47.1 \pm 13.5	48.1 \pm 13.5	46.0 \pm 14.1
median (range)	50.0 (24–69)	50.5 (24–69)	49.0 (24–69)
sex			
male	13 (48.1)	11 (50.0)	6 (46.2)
female	14 (51.9)	11 (50.0)	7 (53.8)
histopathological type of tumor†			
GBM	13 (48.1)	13 (59.1)	13 (100.0)
gliosarcoma	1 (3.7)	1 (4.5)	0 (0)
anaplastic astrocytoma	3 (11.1)	3 (13.6)	0 (0)
anaplastic oligoastrocytoma	2 (7.4)	2 (9.1)	0 (0)
anaplastic oligodendroglioma	2 (7.4)	2 (9.1)	0 (0)
pilocytic astrocytoma w/ anaplastic features	1 (3.7)	1 (4.5)	0 (0)
oligodendroglioma	2 (7.4)	0 (0)	0 (0)
central review not performed‡	3 (11.1)	0 (0)	0 (0)
WHO grade†			
IV	14 (51.9)	14 (63.6)	13 (100.0)
III	8 (29.6)	8 (36.4)	0 (0)
II	2 (7.4)	0 (0)	0 (0)
central review not performed‡	3 (11.1)	0 (0)	0 (0)
tumor status			
newly diagnosed	26 (96.3)	21 (95.5)	13 (100.0)
recurrent	1 (3.7)	1 (4.5)	0 (0)
tumor location			
frontal lobe	16 (59.3)	13 (59.1)	7 (53.8)
temporal lobe	5 (18.5)	3 (13.6)	2 (15.4)
parietal lobe	4 (14.8)	4 (18.2)	3 (23.1)
occipital lobe	2 (7.4)	2 (9.1)	1 (7.7)
tumor side			
rt	13 (48.1)	12 (54.5)	8 (61.5)
lt	14 (51.9)	10 (45.5)	5 (38.5)
tumor functional grade			
located in eloquent area	13 (48.1)	12 (54.5)	7 (53.8)
adjacent to eloquent area	6 (22.2)	4 (18.2)	2 (15.4)
located in noneloquent area	8 (29.6)	6 (27.3)	4 (30.8)
PS before treatment§			
0	14 (51.9)	10 (45.5)	3 (23.1)
1	10 (37.0)	9 (40.9)	8 (61.5)
2	0 (0)	0 (0)	0 (0)
3	3 (11.1)	3 (13.6)	2 (15.4)
extent of tumor resection			
total	9 (33.3)	8 (36.4)	5 (38.5)
subtotal (>90% of lesion vol)	13 (48.1)	11 (50.0)	8 (61.5)
partial	5 (18.5)	3 (13.6)	0 (0)

* Unless otherwise stated, values represent cases (%).

† According to central review based on WHO criteria.

‡ These patients did not receive laser irradiation during surgery due to results of the intraoperative histopathological investigation of the resected tissue on the frozen sections and exclusion of the diagnosis of primary malignant parenchymal brain tumor.

§ According to the Eastern Cooperative Oncology Group Performance Status Scale.

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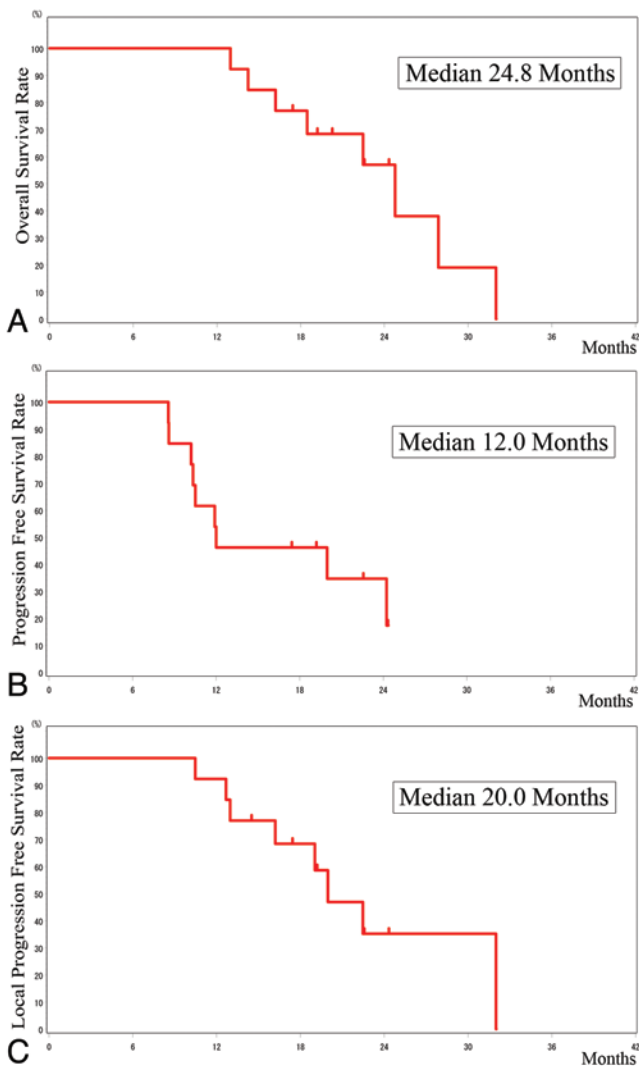


FIG. 1. Kaplan-Meier curves for OS (A), PFS (B), and local PFS (C) in the subgroup of patients with newly diagnosed GBM included in the study cohort. Censored observations are marked.

considered as side effects after administration of talaporfin sodium. It included rash (2 cases), blister (1 case), and erythema (1 case).

Photosensitivity test results were relatively mild and most patients had a score of 1 (barely perceptible erythema) or 2 (distinct erythema); no patient had a score of 3 (marked erythema or edema). These reactions completely disappeared within 4, 8, and 15 days after administration of talaporfin sodium in 55.6%, 77.8%, and 100% of patients, respectively (Table 3).

Discussion

Management of primary malignant parenchymal brain tumors represents a significant challenge. According to the latest edition of the Japan Brain Tumor Registry, 1-, 2-, and 3-year survival rates of patients with high-grade gliomas constitute 64%, 37%, and 28%, respectively.⁵ The poor survival rates are mainly due to an inability

to perform complete removal of the neoplasm due to its infiltrative growth into functionally important neuronal structures, as well as the limited effectiveness of the post-operative radiotherapy and chemotherapy. Therefore, finding additional effective and safe treatment options in such cases is required.

As a highly selective treatment with minimal injury to the adjacent normal structures, PDT has demonstrated promising potential for management of the various cancers and nonneoplastic disorders, such as age-related macular degeneration, local infection, dermatological diseases, arteriosclerosis, and rheumatoid arthritis.⁷ However, despite a large amount of basic and clinical research conducted during several decades and directed on testing of the various photosensitizers, light sources, irradiation types, and treatment regimens, PDT still was not approved to be used as a standard treatment for malignant brain tumors.^{2,10} During the last decade there was considerable interest in the use of 5-aminolevulinic acid (5-ALA) in the surgical management of gliomas. Nevertheless, while its application for photodynamic diagnosis and fluorescence-guided resection was associated with a significant impact on effectiveness of tissue sampling, tumor resection rates, and clinical outcomes,^{4,17} the attempts to use this photosensitizer for PDT were not so impressive.² These unimpressive results might be particularly caused by insufficient incorporation of the drug in the neoplastic cells, especially in necrotic regions and at the periphery of the neoplasm.²

In the present study PDT was based on administration of the relatively novel second-generation photosensitizer talaporfin sodium. This water-soluble compound is derived from plant chlorophyll. In the living body it binds to albumin and does not pass the blood-brain barrier. In neoplastic cells it is primarily distributed in the lysosomes.¹⁴ Compared with conventional photosensitizers, talaporfin sodium is activated by light with longer wavelengths; therefore, its light absorption is not affected by hemoglobin and penetrates deeper.¹³ Additionally, talaporfin sodium more selectively accumulates in glioma tissue, is rapidly eliminated from the normal tissues, and is less likely to cause adverse reactions.¹⁴ It was demonstrated that PDT based on administration of talaporfin sodium with subsequent irradiation using a 664-nm laser led to necrosis and apoptosis of cultured human glioblastoma cells¹³ and experimental tumors¹⁴ in a dose- and time-dependent fashion. The adverse effects on the peritumoral brain were limited to mild temporary edema, and no damage to neurons or the myelin sheath was observed.¹⁴ A pilot clinical study on 14 adult patients with unresectable malignant gliomas showed a median PFS of 23 months in newly diagnosed neoplasms.¹ In concordance, in our present prospective investigation, which included 21 patients with newly diagnosed high-grade gliomas treated according to strict research protocol, the median local PFS constituted 22.5 months.

The most impressive results of our study were obtained in patients with a newly diagnosed GBM. In this subgroup, the 12-month OS and 6-month PFS rates were 100%, and the median OS and median PFS were 24.8 and 12.0 months, respectively. These rates compare favorably

TABLE 2: Frequency of adverse events and side effects by grade*

System Organ Class†	No. of Patients (%)					Total (n = 27)
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
adverse events						
investigations	3 (11.1)	12 (44.4)	10 (37.0)	2 (7.4)	0 (0.0)	27 (100.0)
gastrointestinal disorders	5 (18.5)	16 (59.3)	0 (0.0)	0 (0.0)	0 (0.0)	21 (77.8)
general disorders & administration site conditions	15 (55.6)	6 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	21 (77.8)
nervous system disorders	1 (3.7)	17 (63.0)	2 (7.4)	0 (0.0)	0 (0.0)	20 (74.1)
skin & subcutaneous tissue disorders	10 (37.0)	8 (29.6)	0 (0.0)	0 (0.0)	0 (0.0)	18 (66.7)
injury, poisoning, & procedural complications	9 (33.3)	6 (22.2)	0 (0.0)	0 (0.0)	0 (0.0)	15 (55.6)
eye disorders	7 (25.9)	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	9 (33.3)
infections & infestations	1 (3.7)	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	6 (22.2)
renal & urinary disorders	3 (11.1)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (18.5)
psychiatric disorders	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.8)
respiratory, thoracic, & mediastinal disorders	4 (14.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.8)
vascular disorders	0 (0.0)	0 (0.0)	4 (14.8)	0 (0.0)	0 (0.0)	4 (14.8)
musculoskeletal & connective tissue disorders	1 (3.7)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.1)
blood & lymphatic system disorders	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)
metabolism & nutrition disorders	0 (0.0)	0 (0.0)	2 (7.4)	0 (0.0)	0 (0.0)	2 (7.4)
cardiac disorders	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
ear & labyrinth disorders	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)
side effects						
investigations	7 (25.9)	6 (22.2)	5 (18.5)	0 (0.0)	0 (0.0)	18 (66.7)
skin & subcutaneous tissue disorders	1 (3.7)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.4)

* According to the Cancer Therapy Evaluation Program.³

† According to the Medical Dictionary for Regulatory Activities version 14.1 (<http://www.meddra.org>).

with contemporary results obtained in such tumors with standard treatment. In a global Phase III randomized controlled study on radiotherapy with concomitant and adjuvant temozolomide for GBM, Stupp et al.¹⁸ demonstrated a

TABLE 3: Skin photosensitivity test results in 27 patients*

No. of Days†	No. of Patients (%)	Cumulative No. of Patients (%)
3	4 (14.8)	4 (14.8)
4	11 (40.7)	15 (55.6)
8	6 (22.2)	21 (77.8)
10	1 (3.7)	22 (81.5)
13	2 (7.4)	24 (88.9)
14	1 (3.7)	25 (92.6)
15	2 (7.4)	27 (100)

* For the skin photosensitivity test, between 11 a.m. and 2 p.m., the back of the individual's hand was exposed to direct sunlight for 5 minutes, and the occurrence of any photosensitivity reaction, such as erythema, was assessed. In cases in which photosensitivity reactions were detected, the subject was kept shielded from light until the reaction disappeared, and the skin photosensitivity test was subsequently repeated.

† From administration of talaporfin sodium to disappearance of reaction.

12-month OS rate of 61%, a 6-month PFS rate of 54%, a median OS of 14.6 months, and a median PFS of 6.9 months. In the series by Stummer et al.¹⁷ on fluorescence-guided resection of malignant gliomas with the use of 5-ALA, the 6-month PFS rate was 41% and the median PFS period was 5.1 months. Moreover, in our patients with a newly diagnosed GBM, the median local PFS was nearly two times longer than the median PFS (20.0 vs 12.0 months). It can therefore be speculated that prolonged survival was caused by improved local tumor growth control due to intraoperative PDT. It should be emphasized that in the present series all patients with newly diagnosed GBM underwent either total or subtotal resection. Aggressive removal of the tumor may be an important prerequisite for clinical effectiveness of intraoperative PDT, since the penetration depth of a laser is approximately 2.5–5 mm; therefore, the corresponding effective distance for irradiation is limited to 0.75–1.5 cm.^{1,2} The limitations of the efficacy of PDT in bulky target tissues and recurrent tumors have been demonstrated.¹ It is also possible that metabolically active infiltrating tumor cells in the periphery of the GBM may be more sensitive to PDT because of incorporation of a greater amount of photosensitizer. It was reported that the tissue concentration of a photosensitizer directly correlates with the grade of malignancy of the neoplasm.²

In the present study PDT showed a high level of safe-

ty. While laboratory investigations have frequently revealed abnormalities likely attributable to the administration of talaporfin sodium, only 2 patients (7.4%) had definite symptoms on the skin, which did not exceed Grade 2 toxicity. In no case did we encounter brain edema or cerebral infarction, which may complicate PDT.^{1,2} Therefore, the risk of clinically significant side effects caused by the administration of talaporfin sodium and intraoperative irradiation of the residual tumor and peritumoral brain with a 664-nm laser 22–27 hours thereafter may be considered low. Moreover, according to photosensitivity test results, any reactions completely disappeared in all patients within 15 days after administration of the drug.

The main limitations of the present study are related to its design. A nonrandomized noncontrolled prospective investigation was performed in just 2 neurosurgical centers with well-established neurooncology programs and enrolled a limited number of highly selected cases with rather heterogeneous histopathological diagnoses of malignant parenchymal brain tumors. It is evident that to prove clinical efficacy of the intraoperative PDT with talaporfin sodium and a semiconductor laser, further carefully designed Phase III studies should be performed in a sufficiently large number of patients with possible initial stratification according to tumor resection rate. Testing of the proposed treatment method is also planned in cases of low-grade gliomas and in incompletely resected benign extraaxial neoplasms, such as pituitary adenomas and meningiomas. Since appropriate use of equipment for PDT requires specific skills, the dedicated training program for neurosurgeons is currently under organization. Finally, advanced experimental investigations directed at further understanding the basic mechanisms of the therapeutic effectiveness of intraoperative PDT are also required, and additional studies to search for the most optimal treatment regimens should be continued as well.

Conclusions

The results of the present study demonstrate that novel PDT based on administration of talaporfin sodium and subsequent irradiation with a 664-nm semiconductor laser may provide an additional benefit to the combined management of primary malignant parenchymal brain tumors through possible improvement of their local growth control, which, in turn, may lead to prolongation of the patient's survival. The therapy seems sufficiently safe with a minimal risk of serious side effects. Therefore, application of the intraoperative PDT along with aggressive resection, radiotherapy, and chemotherapy may be of clinical significance, particularly in patients with newly diagnosed GBM.

Disclosure

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