Chapter 13

Photodynamic Therapy Using Talaporfin Sodium and Diode Laser for Newly Diagnosed Malignant Gliomas

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1. Introduction

Wilson et al. [1] investigated the progression of glioblastoma (Grade 4) at the cellular level and showed that cells from tumors of 4 cm or greater in diameter on diagnostic imaging are considered to be present in both normal and affected brain tissues, with a distribution of 92% of tumor cells in the tumor bulk, 6% in areas within a 2-cm margin around the tumor, and 1.8% within an additional 2-cm area surrounding this margin. The majority of recurrent malignant gliomas develop in this marginal area, and therefore, controlling infiltrating cells in this region while protecting normal brain cells is critical to inhibit tumor recurrence.

In photodynamic therapy (PDT), a photosensitizer taken up in tumor tissues and neovascularized tumor vessels is administered to cancer patients. Tumor tissues are then later irradiated using a laser to induce a photochemical reaction in the photosensitizer, thereby selectively causing tumor cell apoptosis and necrosis. This tumor cell apoptosis and necrosis result from the strong oxidative effect of singlet oxygen (active oxygen) produced by the photochemical reaction in the photosensitizer, induced by a laser at a specific wavelength [2].

We previously reported that PDT using talaporfin sodium (TS), a second-generation photosensitizer, induced tumor coagulation necrosis and tumor cell-selective apoptosis in rats in which C6 glioma cells had been transplanted into the brain [3]. In the present study, we evaluated the safety and efficacy of PDT in areas with tumor invasion following tumor removal in patients with malignant glioma.

2. Materials

Eligible subjects were patients with a first time diagnosis of adult intracranial malignant glioma (Grade 3 or 4) based on preoperative diagnostic imaging and with a tumor bulk adja-

cent to the eloquent areas of the brain associated with language, motor, sensation and vision, for which a wide resection of the tumor much larger than the tumor bulk was impossible. Selective treatment of the infiltrating tumor cells by PDT was considered necessary because of tumor invasion into the eloquent areas, despite the fact that the tumor bulk had been removed as extensively as possible. PDT was performed after a rapid intraoperative pathological diagnosis confirmed malignant glioma. We excluded patients who had received radiotherapy or chemotherapy within 3 weeks prior to the surgery, patients with bleeding or abnormal coagulation test results, and patients with porphyria or porphyrin hypersensitivity. This clinical study was approved by the Institutional Review Board of our institution. All subjects provided written informed consent. The subjects were consecutive 8 patients (7 men and 1 woman) treated at our hospital between May 2006 and Mar 2009 and aged 48 to 82 years (median, 58 years). The tumors were localized in the frontal lobe in 4 patients, temporal lobe in 2 patients, insular gyrus in 1 patient and parietal lobe in 1 patient. Preoperative Karnofsky Performance Scale (KPS) was 50 to 80 (median 60). The extent of tumor resection was subtotal in 7 patients and partial in 1 patient. The final pathological diagnosis was Grade 3 in 3 patients, and Grade 4 glioblastoma in 5 patients. As postoperative adjuvant therapy, 4 patients received irradiation in combination with temozolomide (TMZ) and 2 patients received irradiation and ACNU-based multidrug chemotherapy.

3. Methods

3.1. Talaporfin sodium and diode laser

Talaporfin sodium (TS: Laserphyrin®, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) is a photosensitizer utilized in PDT which was approved for use in Japan in 2003 as treatment for early-stage lung cancer, in conjunction with a diode laser (PD Laser®, Panasonic HealthCare Co., Ltd., Ehime, Japan) at a wavelength of 664 nm [4]. (Fig. 1A and B) Talaporfin sodium is a second-generation photosensitizer which is more quickly excreted from the body than the first-generation porfimer sodium (Photofrin®, Pfizer Japan Inc.,Tokyo, Japan). It is characterized by the rapid resolution of a skin photosensitive reaction, which is important with the use of photosensitizers. This has enabled the period of necessary light shielding in a room with measurement of < 500 lux to be reduced to 2 weeks for talaporfin sodium, whereas porfimer sodium requires patients to stay in a semi-dark(< 300 lux) room for 1 month after administration. The diode laser instrument is a compact system weighing 14 kg, has low power consumption, and can be easily maintained without the need for dye exchange. (Fig. 2A).

3.2. Operating microscope equipped with diode laser

The PD Laser® (Panasonic HealthCare Co., Ltd.), installed in the MM30 microscope (Mitaka Kohki Co., Ltd., Tokyo, Japan), is combined into a system which provides laser irradiation from the operating microscope from a plane nearly coaxial to the surgical view. The laser is introduced into the microscope by a quartz fiber, and providing a laser transmission path close to an observation light path using a conventional halogen light. This allows surgeons to accurately identify an irradiation target area during surgery. (Fig. 2A, B)

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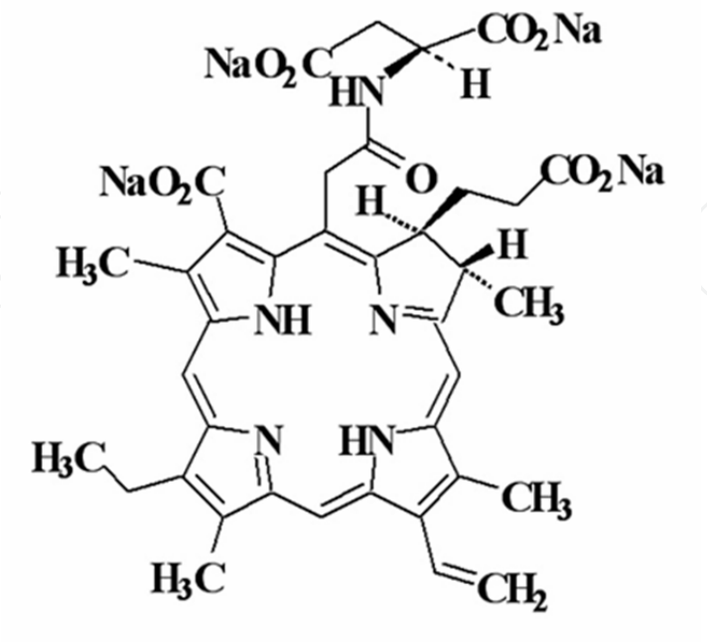

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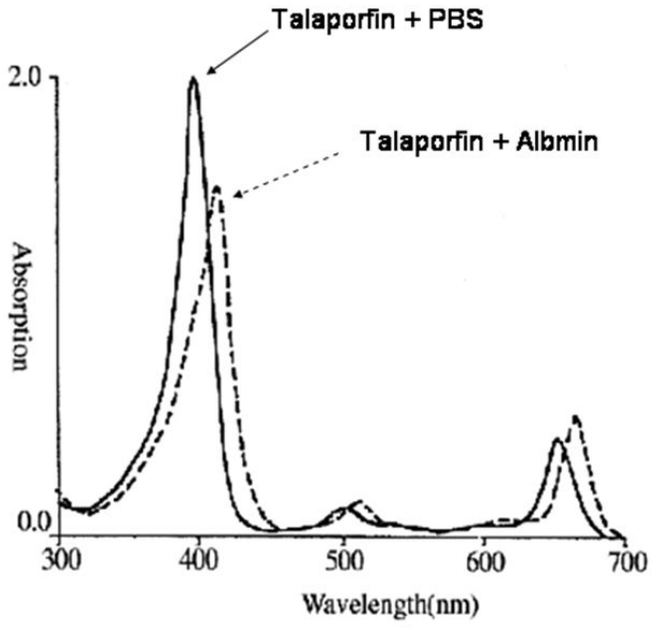
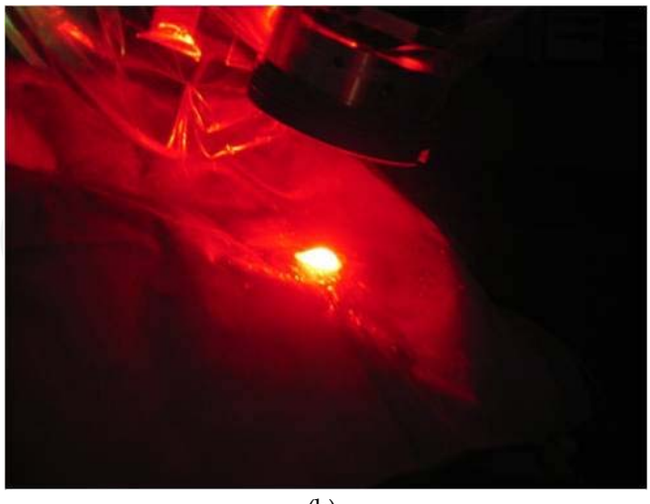


(b)

Figure 1. Second-generation photosensitizer, Talaporfin sodium. A:Chemical structures of talaporfin sodium (mono-L-aspartyl chlorine e6, NPe6) *N*-[[(2S,3S)-18-carboxy-2-(2-carboxyethyl)-13-ethyl-2,3-dibydro-3,7,12,17-tetramethyl-8-vinylporphyrin-20-yl]-L-asparatic acid. B:Absorption spectrum of talaporfin sodium and change in absorption wavelength following conjugation with albumin (solid line; talaporfin sodium and phosphate buffer solution, dotted line; talaporfin sodium conjugated with albumin) talaporfin sodium has absorption peaks in the Soret band (398nm) and Q bands (502, 530, 620 and 654nm) in pH 7.4 phosphate buffer solution (PBS). When it conjugates with albumin, its absorption band wavelength becomes approximately 10nm longer (bathochromic shift).

(a)



(b)

Figure 2. Diode laser with a neurosurgical operating microscope. A: MM80® microscope (Mitaka Kohki Co., Ltd.) equipped with a compact-size diode laser (PD Laser®, Panasonic Health Care Ltd., arrow). B: From the operating microscope, the diode laser irradiates the surgical field with an irradiation diameter of 1.5 cm^2.

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3.3. Photodynamic therapy (PDT)

TS was administered bolus intravenously at a dose of 40mg/m^2 in shielded conditions 24 hours prior to surgery. At surgery, maximal resection of the tumor was performed usually utilizing optical navigation system and electrophysiological monitoring leaving a tumor bed area to be irradiated. The surface area of tumor bed was observed under operative microscope and optimal navigation system, and identified the optimal target for PDT. PDT covering an area of 1.5 cm^2 diameter was used for any tumor growth in these area. When 2 sites were to be irradiated, we took care to avoid overlapping the irradiated areas under operative microscope. Irradiation energy density of 27 J/cm^2 (power density of 150mW/cm^2, irradiation time of 180 seconds) of 664nm diode laser for PDT was irradiated superficially to one or two targets of tumor bed.

3.4. Skin photosensitive reaction test

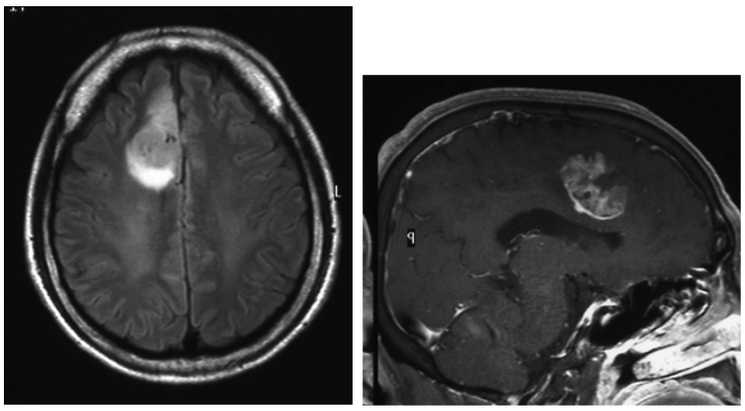
The administration of TS enhances sensitivity to light, and which may produce a photosensitive reaction. Patients should therefore avoid direct sunlight immediately after the administration of talaporfin sodium and stay in a room where the illumination intensity is adjusted to < 500 lux using a shading curtain. After surgery, patients were required to expose the back of the palm of the hand to direct sunlight for 5minutes every day between 11:00 and 14:00 to evaluate the development of erythema. However, even when the result of this skin photosensitivity test confirmed the resolution of a photosensitive reaction (defined by the absence of evident erythema) and the restriction for shading at < 500 lux could be removed, patients were advised to avoid further direct sunlight for 2 weeks after the administration of talaporfin sodium. In particular, we recommended that special shading eye goggles should be used worn 7 days after the administration of talaporfin sodium to avoid exposing the retinas to direct sunlight.

4. Results

4.1. Selected case

A 65-year-old man presented with 2 months history of headache and gradually worsened. Head MRI showed a tumor in the right frontal lobe, and edema extending as far as the premotor area at the posterior edge of the tumor bulk. On a sagittal view, part of the posterior edge of the tumor bulk extended posteriorly, and this part was determined to have invaded the supplemental motor area(SMA) (Fig. 3A and B). Using optical navigation system and motor evoked potential (MEP) monioring, we performed craniotomy in order to resect the tumor, and rapid pathological diagnosis confirmed that the tumor was a glioblastoma. From the optical navigation images, the posterior margin of the tumor bulk was confirmed to have reached the pre-motor area (SMA-proper) (Fig.3C), and a single session of PDT at 27 J/cm^2 (diameter of the irradiated area: 1.5 cm^2) was performed at this site (Fig 3.D and E). Under a pathological diagnosis of glioblastoma, the patient given postoperative irradiation

and chemotherapy with oral TMZ. On day 3 after surgery, MRI showed remaining contrast-enhanced tumor growth in the pre-motor area, but by the end of radiotherapy (on day 51 after surgery, Fig. 3F), complete response was confirmed at this site. His headache was disappeared and he enjoyed a play of weekly golf until 3 years after operation.



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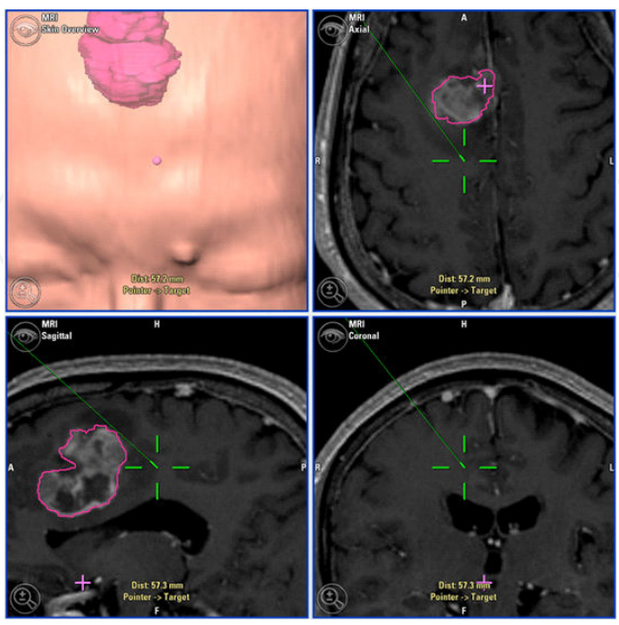

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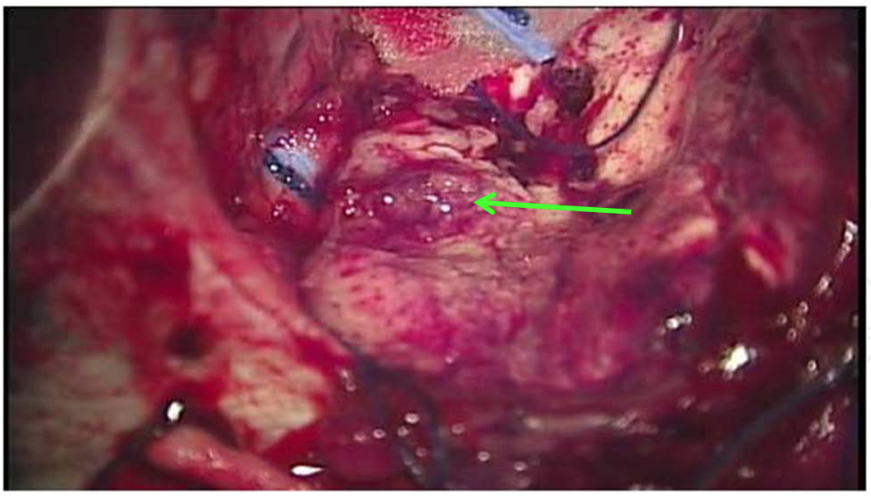

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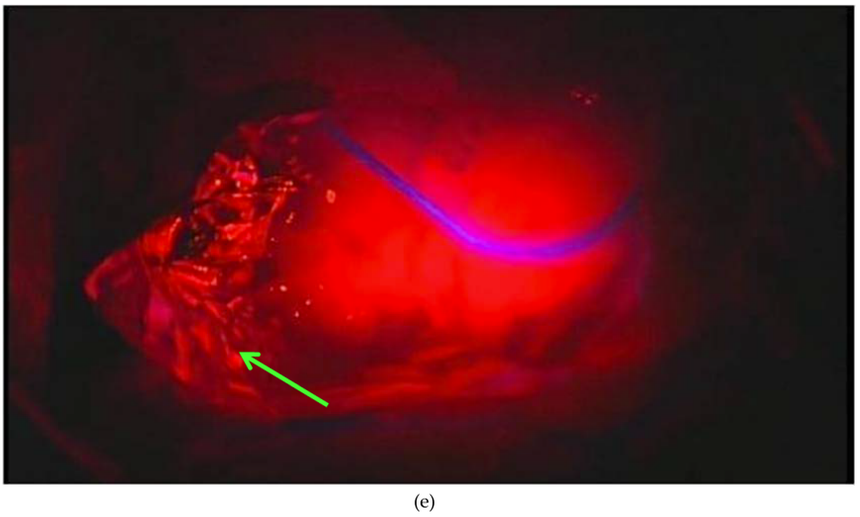

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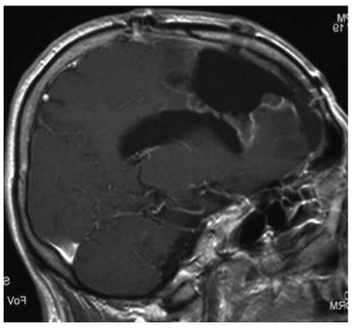

(f)

Figure 3. PDT and changes over time on postoperative magnetic resonance imaging (MRI) in Case 3. A: Preoperative axial FLAIR image showed the right frontal tumor and the peri-tumoral edema extending to the right pre-motor cortex. B: Preoperative gadolinium-enhanced T1-weighted sagittal imaging showed a heterogeneously enhanced tumor was present in the right superior frontal gyrus to supplementary motor cortex. C: Based on intra-operative optical navigation images, it was determined that the tumor had reached a portion adjacent to the ambulatory motor area (green cross). D: The tumor was remained in this area (arrow). E: PDT at 150 mW/cm^2 and 27 J/cm^2 (diameter of the irradiation area: 1.5 cm^2) was performed for tumor infiltration into this area. (aluminum foil protected the anterior cerebral arteries, arrow). F: Gadolinium-enhanced T1-weighted sagittal imaging on days 51 after surgery showed that gadolinium-enhancement at the site of PDT had disappeared.

4.2. Summary

In the evaluation of patients, of the 6 patients who were assessable after surgery, 3 achieved complete response, 2 achieved partial response, and 1 had progressive disease. The response rate was high at 83.3%. Regarding adverse events associated with PDT, brain edema involving a large part of the middle cerebral artery perforator region occurred during PDT after insular glioma resection in Case 1. While it remains uncertain whether this was associated with the surgical procedure or PDT, the effect on normal capillary vessels should be closely monitored. No other obvious adverse events were observed. In most patients, postoperative chemo-radiation therapy was initiated, but recurrence was observed at the site of PDT in 7 patients. Despite recurrence, the progression-free survival time was 1 to 34 months (median: 22 months), and in cases receiving treatment after recurrence, 5 patients had a survival time of 6 to 14 months (median: 6 months). A further 3 patients of Grade 3 were alive during a follow-up period of 42 to 74 months (median: 50 months). An evaluation of 5 patients with glioblastoma also showed a median progression-free survival time of 14 months and a median survival time of 26 months.

While it was possibly an adverse event associated with the surgical procedure, a causal relationship with the PDT could not be excluded. In terms of photosensitivity, the photosensitive reaction resolved within 3 days after surgery (within 4 days after the intravenous injection) in all patients, at which point light shading at 500 lux was discontinued.

5. Discussion

The objective of PDT is to selectively kill infiltrating tumor cells via a photochemical reaction, and this selectivity facilitates optimal local control therapy [2], making it possible to maintain brain function. PDT is designed to cause damage at the cellular level in the form of apoptosis [2]. There are numerous studies which have reported that the main mechanism of PDT is the induction of vascular occlusion from fibrin thrombus formation due to vascular endothelial cell damage [5]. In particular, it has been assumed that the main mechanism on cellular damage induced by PDT using TS in conjunction with a diode laser irradiation is indirect damage in the form of coagulation necrosis by tumor vascular occlusion [5]. In our basic experimental study, C6 glioma tissue showed coagulation necrosis in tissues located in a portion near the tumor surface that was laser irradiated, and cellular death in the distal portion [3]. However, in the actual area of tissue damage, 80% of the area was considered to be tissue damage caused by the coagulation necrosis. Yamamoto et al. [5] reported that factor XIII was activated by vascular endothelial cell damage within 20 seconds following PDT of cancer tissue. A fibrin thrombus formed as a consequence, which appeared to be the main mechanism of PDT.

Our strategy was to optimally reduce vascular damage caused by PDT, and to ensure safety to avoid ischemic damage to normal brain tissues. Madsen et al. [6] reported that the factors which influence the effects of PDT were tissue factors and irradiation laser factors. The tissue factors included the tissue concentrations of the photosensitizer, the level of tissue oxy-

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genation, and the depth from the site of laser irradiation. The irradiation laser factors included irradiation level and duration. How the cytotoxic effects can be enhanced while minimizing the vascular effects, and how ischemic damage to normal brain tissues can be minimized may well be the keys to determining whether or not PDT can be developed for the treatment of malignant glioma.

In the present study, we selected a dose of 40 mg/m^2 of TS and performed PDT approximately 24 hours after the administration of TS. The practice of the PDT was performed on the diode laser (664nm) irradiation at a power density of 150 mW/cm^2 for 180 seconds (27 J/cm^2). We previously reported that this PDT protocol was considered safe in terms of the protection of early vascular endothelial cell damage and normal brain tissues, and could induce the selective tumor cell damage by singlet oxygen [7].

Although there were only consecutive 8 patients of newly diagnosed malignant glioma in this series, PDT achieved a response rate of 83.3% and a median progression-free survival time of 14 months, a median survival time of 26 months in the glioblastoma patients who eventually died, and all 3 cases of Grade 3 patients were survived for 50 months median follow up period. In the 5 patients who achieved complete or partial response, preoperative KPS was improved. None of the patients had adverse events unequivocally attributable to PDT. The brain edema observed in Case 1 was possibly due to the surgical procedure, but the possibility of direct laser irradiation of brain blood vessels inducing vascular occlusion due to PDT could not be completely excluded. Therefore, normal blood vessels should be covered with aluminum foil whenever possible.

Response	RTx	Chemo Tx	KPS after treatment	Progression	PFS	Prognosis, Survival period
NE	60Gy	ACNU/VCR/IFN	50	(+)	22 mon.	Dead: 36 mon.
CR	60Gy	IFN	70	(+)	24 mon.	Alive: 74 mon.
CR	60Gy	TMZ	90	(+)	34 mon.	Dead: 40 mon.
PR	60Gy	TMZ	90	(+)	14 mon.	Dead: 26 mon.
PR	60Gy	(-)	50	(+)	24 mon.	Alive: 50 mon.
PD	(-)	TMZ	40	(+)	1 mon.	Dead: 7 mon.
CR	60Gy	PCZ/ACNU/VCR	80	(+)	6mon.	Dead: 12mon.
NE	60Gy	TMZ	90	(-)		Alive: 42mon.

KPS: Karnofsky Performance Scale, PDT: photodynamic therapy, RTx: radiation therapy, Chemo Tx: chemotherapy, PFS: progression-free survival, Rt: right, Lt: left, Bil: bilateral, Anapl: anaplastic, CR: complete response, PR: partial response, PD: progression disease, NE: not evaluable, TMZ: temozolomide, VCR: vincristine, IFN: interferon-beta, PCZ: procarbazine, mon. months

Table 1. Clinical summary of patients with newly diagnosed malignant glioma who received photodynamic therapy (PDT)

The present study of PDT using talaporfin sodium in conjunction with diode laser irradiation for malignant glioma supports the validity of PDT for malignant glioma in Japan. Laser irradiation used to activate TS has a longer wavelength (664 nm) than that used with other photosensitizers, such as Porfimer sodium [8-11], 5-ALA [12-14] and m-THPC [15, 16], and theoretically, it can penetrate brain tissue to a greater depth. We believe that our strategy will demonstrate a therapeutic effect not to be inferior to those of previous reports [17] using other photosensitizers. In future, it is necessary to perform the larger-scale prospective clinical study to confirm the clinical feasibility of this novel therapeutic option to malignant gliomas.

6. Conclusions

We performed PDT using TS in conjunction with diode laser irradiation in areas of tumor invasion, following resection of adult malignant glioma which had infiltrated the eloquent areas. We selected a 24 hours interval after the administration of TS before commencing PDT and reduced irradiation energy intensity of the diode laser to 27 J/cm^2 to preserve normal brain function. The therapy achieved with no adversed event directly attributable to PDT and a response rate of 83.3% in patients with a newly diagnosed malignant gliomas.

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The authors report no conflict of interest concerning the materials or methods used in this study and findings specified in this paper.

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