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Clinical Trial Protocol Editorial

First-in-Human Trial of Photodynamic Therapy for Spinal Cord Malignant Astrocytoma: Study Protocol

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Our extensive basic research on photodynamic therapy (PDT) application in models of intracranial malignant astrocytoma led to its clinical application for intracranial malignant astrocytoma in Japan. Having considered the safety and effectiveness of this pathology, we initiate a first-in-human clinical study of PDT for spinal cord malignant astrocytoma. This study has an open-label, single-arm design. The initial follow-up period is 12 months, at the end of which we will quantify survival after PDT for spinal cord malignant astrocytoma as primary objective. The secondary objective is to quantify the overall progression-free survival of treated patients and the percentage of patients surviving 6 months after PDT without recurrence. Twenty patients suffering from spinal cord malignant astrocytoma will be recruited. In particular, 10 of those should be newly diagnosed World Health Organization grade 4. After obtaining consent, each patient will receive a single intravenous injection of talaporfin sodium (40 mg/m^2) 1 day before tumor resection. One day after completing tumor removal, the residual lesion and/or resection cavity will be irradiated using a 664-nm semiconductor laser with a radiation power density of 150 mW/cm^2 and a radiation energy density of 27 J/cm^2. The procedure will be performed 22–26 hours after talaporfin sodium administration. This study protocol has been reviewed and approved by the Certified Committee in the Japanese Ministry of Health, Labor, and Welfare University Hospital Medical Information Network Clinical Trials Registry (Japan Registry of Clinical Trials number, jRCT2021220040).

Keywords: Photodynamic therapy, Spinal cord malignant astrocytoma, Protocol

INTRODUCTION

Intramedullary spinal cord tumors are rare, accounting for 2%–4% of all central nervous system tumors,[1] of those astrocytoma of all grades comprise 10%–15% of intramedullary tumors.[2,3]

In addition, 20% of astrocytic tumors correspond to malignant astrocytoma.[3,4] The standard treatment is surgical removal followed by radiation and chemotherapy. However, this disease has an extremely poor prognosis with a 1-year survival rate of approximately 50% and a median survival time ≤ 1 year.[5,6] One of the reasons for the poor prognosis is that the tumor diffusely invades the spinal cord parenchyma, preventing adequate tumor removal.

Similarly, primary malignant brain tumors have a poor prognosis. However, using photodynamic therapy (PDT) as adjuncts to standard treatments for primary malignant brain tumors improved the prognosis.[7] In fact, median survival improved up to 24.8 months with PDT, compared to 14.8 months without. PDT causes selective necrosis of tumor cells due to the accumulation of a photosensitive substance in tumor cells combined with laser light irradiation to induce a photochemical reaction with

strong oxidative effects.[8] Since the photochemical reaction occurs only at the site where the photosensitive substance is present and under laser irradiation, PDT is a selective local therapy targeting tumor cells.

Given the therapeutic effect of PDT in intracranial malignant astrocytoma, we hypothesized that PDT could have the same effect in malignant spinal cord astrocytoma. Thus, this clinical trial aimed to investigate the efficacy and safety of PDT for this devastating disease. Importantly, the protocol for this study was meticulously developed in accordance with specific recommendations from the Certified Committee in the Japanese Ministry of Health, Labor, and Welfare. Their directive required strict adherence to the PDT protocol previously established for brain tumor treatments, thereby ensuring regulatory approval and a robust safety framework tailored to clinical implementation.

METHODS

1. Study Design and Objectives

We have designed this study as a multicenter, nonrandomized, single-arm phase II trial to evaluate the safety and efficacy of PDT in patients with malignant spinal cord astrocytoma. The study protocol has been reviewed and approved by the Certified Committee in the Japanese Ministry of Health, Labor, and Welfare and registered with the Japanese Clinical Trials Registry (jRCT2021220040). It has also been approved in institutional review board in Tohoku Medical and Pharmaceutical University Hospital (TMP-42).

The primary objective is to examine whether PDT can improve the survival of patients suffering from spinal cord malignant astrocytoma at the 12-month follow-up, since several published papers exist that allow for an evaluation of the efficacy of PDT when compared to existing treatments.[5,6] This will be accomplished through comprehensive evaluation of postprocedural mortality and morbidity, assessment of adverse events (AEs), and detailed analysis of treatment effects on motor and sensory function as well as quality of life. Secondary objectives include evaluation of overall survival (OS) from the date of PDT initiation, progression-free survival (PFS), and treatment response rate according to standardized criteria. The safety profile will be thoroughly analyzed through careful documentation of AEs, their correlation with treatment parameters, and their time course of development and resolution.

We have established a planned enrollment period of 20 months, during which time we aim to recruit the target number of patients. The target number of cases is 20 including 10 initial cases of grade 4 primary malignant spinal cord tumors. The main inclusion and exclusion criteria are listed in Table 1. Each participant will be followed for a minimum of 12 months after treatment, resulting in a total study duration of 36 months. To maintain consistent quality across all participating centers, we have implemented a central review board system that will regularly evaluate protocol compliance, standardization of PDT procedures, AE reporting, and data collection processes.

Table 1. Eligibility criteria for study enrollment

Criteria category	Requirements
Inclusion criteria	
Disease characteristics	• Patients scheduled for surgical resection of a primary malignant spinal tumor • WHO grade 3 or 4 based on CNS tumors, 4th edition (WHO 2016) • MRI: intramedullary tumor with indistinct boundary • No dissemination
Patient characteristics	• Age ≥ 15 years • KPS score ≥ 70 • KPS score of 50 or 60 due solely to the neurological symptoms caused by the tumor • Written informed consent
Laboratory requirements	White Blood cell ≥ 2,000/mm^3 Hemoglobin ≥ 8.0 g/dL Platelets ≥ 8×10^4/mm^3 AST/ALT ≤ 100 IU/L Creatinine < 1.5 mg/dL
Exclusion criteria	
Medical conditions	• Photosensitivity/porphyria • Severe organ dysfunction • Severe hemorrhage or in a state of shock • Severe infections
Other factors	• Gadolinium MRI contraindication • Pregnancy/lactation • Other malignancies • Concurrent trial participation • Investigator-determined unsuitability

CNS, central nervous system; WHO, World Health Organization; KPS, Karnofsky Performance Status; AST, aspartate transaminase; ALT, alanine transaminase; MRI, magnetic resonance imaging.

2. Treatment Protocol

The investigational intervention consists of a carefully planned sequence combining PDT with standard surgical procedures (Fig. 1). The investigational drug, talaporfin sodium, was administered as a single intravenous injection at 40 mg/m^2, approximately 20 hours before entering the operating room. The administration time can be adjusted depending on each subject's tumor location, disease condition, and scheduled surgery time

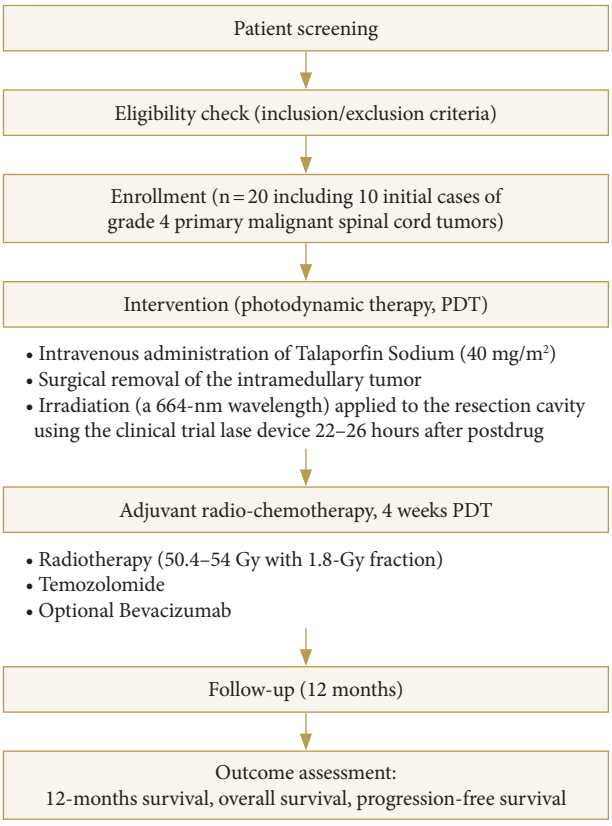

Fig. 1. A flow diagram illustrating the clinical trial design. The diagram outlines the key steps, including patient enrollment, interventions (PDT treatment, tumor resection and adjuvant therapies), follow-up periods, and outcome assessments. PDT, photodynamic therapy.

to ensure that laser irradiation can be performed 22–26 hours after drug administration. The interval is set according to dosage and usage guidelines for PDT in primary malignant brain tumors, as this is an approved treatment protocol. To prevent burns due to photosensitivity, prolonged, continuous use of monitoring devices operating on light-based principles (such as pulse oximeters) should be avoided after administration.

The clinical trial device (PDT Semiconductor Laser) is set to provide laser irradiation under the following conditions:

- Wavelength: 664 ± 2 nm
- Maximum laser output: 500 mW
- Energy density: 27 J/cm²
- Power density: 150 mW/cm²

On the day after investigational drug administration, the primary malignant spinal tumor will be surgically removed. Note, surgical resection of primary malignant spinal tumors will be conducted according to the standard protocols and procedures of each participating medical institution. Precaution is ensured to limit surgical lighting (e.g., shadowless lamps) to the minimum necessary. Maintain room lighting at ≤ 500 lux until completing draping after the patient enters the operating room. After 22–26 hours from drug administration, a 664-nm wavelength laser light will be applied to the resection cavity including the remaining lesion using the trial device. The irradiation range and frequency will be determined appropriately by the principal investigators based on the size of the resection cavity or residual lesion. Care should be taken to minimize exposure to normal tissues and blood vessels.

After PDT, standard radiotherapy and chemotherapy will be administered. The beginning of radiotherapy and chemotherapy is set at 4 weeks after PDT. Standard radiotherapy involves local irradiation of the spinal cord area, including the tumor resection cavity, at 50.4–54 Gy (1.8 Gy per fraction). Standard chemotherapy involves the use of temozolomide according to standard protocols for malignant astrocytoma.[9] The principal investigators should adjust the dosage, continue, pause, or discontinue these treatments according to the latest protocol and patient condition. Additionally, bevacizumab, approved for use in malignant gliomas, may be administered at the discretion of the principal investigators. Note that temozolomide and bevacizumab are used as standard therapies and not considered investigational drugs in this trial. During the clinical trial, postoperative adjuvant therapy should follow the guidelines below until disease progression or recurrence is observed. No treatment following disease progression or recurrence is specified in this protocol.

To assess the efficacy and safety of PDT for patients with primary malignant spinal tumors, spinal cord magnetic resonance imaging (MRI) and whole brain and spine MRI will be used. The enhanced lesion will be calculated using the former. After comparison with the imaging baseline, disease progression is defined using 3 key criteria: the appearance of new enhancing lesions exceeding the 80% isodose line of radiation therapy, evidence of tumor dissemination or new mass-like lesions, and a cumulative increase in the primary tumor diameter of 25% with an absolute increase greater than 5 mm. Initial assessment of MRI imaging will be conducted by the principal investigator or subinvestigator at each participating institution, followed by a central review by the Imaging Evaluation Committee for standardization of response assessment. The central committee's evaluation will be considered final for the study analysis. This dual-review system ensures consistency in radiological assessment across all study sites while maintaining high quality standards in imaging evaluation.

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Table 2. Adverse events categories and monitoring

Category	CTCAE*	Adverse events	Monitoring
Neurological events	Grades 1–2	Sensory disorders Mild spinal edema Bladder/rectal dysfunction (mild)	Modified NANO scale Regular neurological examination MRI monitoring
	Grades 3–4	Spinal cord injury Spinal bleeding Spinal infarction Severe spinal edema Partial quadriplegia Partial paraplegia	
PDT-specific events	Grades 1–2	Mild skin photosensitivity Skin erythema Mild rash	Daily skin assessment Light exposure precautions Patient education
	Grade 3	Severe photosensitivity reactions Blisters Severe edema	
Laboratory abnormalities		Hematologic -Decreased lymphocyte count -Decreased hemoglobin -Increased WBC -Increased neutrophil percentage	Blood tests including liver function monitoring and complete blood count
		Biochemical -Liver enzymes elevation -LDH increase -Decreased albumin -CRP increase	
General events	Grades 1–2	Fever Nausea/vomiting Constipation Mild fatigue Injection site reactions	Vital signs Symptom assessment Patient reporting
	Grades 3–4	Severe infection Severe gastrointestinal symptoms	
Serious adverse event criteria	Grades 3–5	Death Life-threatening condition Required/prolonged hospitalization Persistent disability Congenital abnormality	*Reporting timeline -Within 24 hours for SAE -Within 7 days for unexpected fatal events -Within 15 days for other unexpected events

NANO, Neurologic Assessment in Neuro-Oncology; MRI, magnetic resonance imaging; PDT, photodynamic therapy; SAE, serious adverse event; WBC, white blood cell; LDH, lactate dehydrogenase; CRP, C-reactive protein.
*CTCAE (Common Terminology Criteria for Adverse Events): a standardized classification of adverse event severity graded from 1 to 5, where grade 1 represents mild symptoms; grade 2, moderate; grade 3, severe; grade 4, life-threatening; grade 5, death.

For the comprehensive evaluation of clinical symptoms, including neurological improvement, the principal investigator at each participating medical institution will conduct the assessment using a modified version of the Neurologic Assessment in Neuro-Oncology (NANO) scale.[10] This scale will be used to assess clinical deterioration due to primary spinal lesions and disseminated lesions. The modified NANO scale consists of 9 items (gait, muscle strength, sensory function, vision, eye movement, facial movement, hearing, swallowing function, and consciousness), each rated on a scale from 0 to 3, with 0 indicating normal and 3 the highest severity.

Disease progression is defined by either a deterioration ≥2 levels in any item or worsening to the highest severity level in any item.

3. AEs Reporting and Monitoring

All AEs, as listed in Table 2 will be recorded throughout the study period. When an AE is observed, the date, content, and

severity level of nonserious and serious AE s will be recorded. Events will be graded using the CTCAE (Common Terminology Criteria for Adverse Events) from grade 1 (mild) to grade 5 (death). Neurological disorders will be monitored through regular neurological examinations and MRI, using the modified NANO scale. Laboratory abnormalities will be tracked through regular blood tests and biochemistry panels. PDT-specific effects, particularly skin photosensitivity, will require specific light exposure precautions and regular skin assessments.

Serious AEs require expedited reporting within 24 hours. For unexpected life-threatening events or deaths, reporting to the Pharmaceuticals and Medical Devices Agency in Japan within 7 days, if it was unexpected and resulted in death or was a life-threatening event. If the events were expected, the time limit will be 15 days.

AEs will be assessed for their causality with the investigational drug/PDT treatment based on the following terms: related, probably related, possibly related, not related, or unknown. An independent Data Safety Monitoring Board will review safety data at predetermined intervals.

If any health damage occurs to participants as a result of this clinical trial, the implementing medical institutions will provide necessary treatment and take all appropriate measures. In cases where liability for damages arises due to health damage caused by this clinical trial, the parties responsible for the incident (e.g., the principal investigator, implementing medical institutions) will share the compensation costs proportionately according to their respective levels of responsibility. The principal investigator and subinvestigators at each implementing institution are required to enroll in medical professional liability insurance. Furthermore, the implementing medical institutions will also subscribe to hospital liability insurance or equivalent coverage, as needed.

4. Statistical Analysis

To assess efficacy, we defined the following 2 analysis populations:

(1) Full analysis set (FAS): All patients who receive the investigational drug/PDT treatment will be included in this population.

(2) Per protocol set (PPS): The PPS will consist of cases from the FAS that do not have any major protocol deviations. The primary efficacy analysis population will focus on patients with grade 4 primary malignant spinal glioma within the PPS group.

For efficacy analysis, a stratified analysis will be performed based on histopathological subtypes, with the primary efficacy analysis focusing on the PPS population diagnosed with grade 4 primary malignant spinal glioma. The 12-month post-PDT survival rate and the 6-month PFS rate post-PDT will be calculated. For the primary endpoint, the 12-month survival rate post-PDT will be set and an exact test conducted. In addition, the median OS and PFS periods, along with their 95% confidence intervals, will be estimated. For analyses related to the primary endpoint, the 1-sided significance level will be set at $\alpha = 0.05$ for tests, and confidence intervals with a 1-sided confidence level $(1-\alpha) = 0.95$ will be used for estimations. For secondary endpoints, a 2-sided significance level of 5% will be used for tests, and 2-sided confidence intervals with a 95% confidence coefficient will be applied for estimations.

For safety analysis, all patients who receive the investigational drug/PDT treatment will be included. The safety evaluation included the following:

(1) Incidence of AEs and side effects

(2) Trends in Karnofsky Performance Status, vital signs (body temperature, blood pressure, pulse), and clinical laboratory values

(3) Results of skin photosensitivity tests

(4) Occurrence of malfunctions in the trial device

The frequency of AEs and side effects will be calculated. Additionally, the aggregated data will be classified based on the timing of occurrence, severity (grade), and seriousness.

DISCUSSION

1. Significance of PDT in the Treatment of Primary Malignant Spinal Cord Tumors

The treatment of primary malignant spinal cord tumors presents unique challenges, especially in selectively damaging tumor cells while preserving the surrounding normal spinal cord tissue. This is particularly critical in regions where invasive tumor cells and normal tissue closely coexist. Achieving selective tumor cytotoxicity is a crucial step toward overcoming the dual goals of eradicating tumor cells and maintaining neurological function. In this regard, PDT offers a targeted approach that could extend the time to tumor recurrence postsurgery while preserving neurological function. The primary objective of PDT in the context of spinal cord tumors is to target the residual invasive tumor cells that may remain after maximal surgical resection. By integrating PDT—a treatment that utilizes a light-activated photosensitizer to induce selective cytotoxicity—as an adjunct to surgery, we anticipate an additive effect to conven-

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tional multimodal therapies, which could translate into higher survival rates and quality of life.

2. Mechanism of Action and Advantages of PDT Using Talaporfin Sodium

Talaporfin sodium served as photosensitizer in this trial, activated by a semiconductor laser (PD Laser BT). Compared to first-generation photosensitizers like Photofrin, talaporfin sodium has a shorter half-life, thus reducing the duration of photosensitivity and the associated lifestyle limitations. This second-generation photosensitizer requires only 2 weeks of low-light precautions postadministration, compared to the 1 month with Photofrin.[8]

Further, the compact and portable design of the semiconductor laser offers significant logistical advantages over older devices such as the excimer dye laser. This new laser system is user-friendly, energy-efficient, and requires minimal maintenance, making it practical for routine clinical use. Previous preclinical studies and clinical trials on malignant brain tumors demonstrated that PDT with talaporfin sodium induces selective tumor necrosis through photochemically generated reactive oxygen species, which corroborates the potential of PDT as a targeted therapy in malignancies requiring preservation of surrounding tissues.[7]

3. Anticipated Efficacy in Primary Malignant Spinal Cord Tumors Based on Brain Tumor Data

PDT's efficacy in brain tumors, particularly in malignant gliomas, has been previously demonstrated, with PDT significantly improving the median survival and 1-year survival rates.[7] Given that primary brain tumors and spinal cord tumors share similar pathological features, there is a strong expectation for comparable outcomes in spinal cord tumors treated with PDT. The primary goal of this trial thus is to determine whether adding PDT to surgical resection can replicate or surpass the success observed in brain tumor cases, especially in terms of PFS and OS.

4. Enrollment Criteria and Rationale for Sample Size

Due to the rarity of primary malignant spinal cord tumors, enrolling eligible patients is challenging. A retrospective study conducted from 2009 to 2020 identified an average of 6 cases per year of grade 3 and grade 4 malignant spinal gliomas, further highlighting the need for a realistic enrollment strategy.[3,4] Given these constraints, the study allows enrollment of grade 3 cases after the target of 10 grade 4 initial cases is reached. This strategy ensures that the trial can attain a comprehensive dataset for safety and efficacy evaluations while accommodating the limited patient population. The enrollment target was set at 20 cases, with an anticipated distribution of approximately 10 cases each for grades 3 and 4. Based on Beyer et al.'s historical data on malignant glioma survival rates,[6] we adopted a conservative 1-year survival for efficacy evaluation, with an expected 90% survival rate based on PDT's observed outcomes in brain tumors.

5. Safety Profile and Anticipated AEs

Talaporfin sodium and PDT have shown a favorable safety profile in brain tumor studies; however, while no deaths were attributable to AEs, transient liver enzyme elevation, mild photosensitivity, and neurological effects were reported.[7,8] This trial will carefully monitor patients for similar AEs, especially neurological symptoms, laboratory abnormalities, general symptoms, and skin photosensitivity reactions. AE data will be crucial for refining the safety protocols and validating the PDT's risk-benefit ratio in spinal cord tumor applications.

6. Limitations and Future Directions

This study faces certain limitations, such as its uncontrolled design and the small sample size due to the rarity of the target disease. The lack of a control group limits direct comparisons, although historical controls will be used as benchmarks for survival analysis.[5,6] Future studies could aim at performing randomized controlled trials comparing PDT with other adjunct therapies, further exploring the role of PDT in spinal tumors and potentially broadening its application to other tumor types within the CNS. Further research into dose optimization, timing of light exposure, and combination treatments may increase PDT's efficacy and safety profile. Expanding upon the current findings could lead to the broader adoption of PDT as a standard adjunct treatment for both brain and spinal malignancies, improving long-term outcomes for patients facing these challenging diagnoses.

CURRENT TRIAL STATUS/CONCLUSION

At the time of writing (September, 2024), we have started to recruit patients in the following facilities: Tohoku Medical and Pharmaceutical University Hospital (Sendai, Japan), Tokyo Medical University Hospital (Tokyo, Japan), Hokkaido University (Sendai, Japan), National Cancer Center (Tokyo, Japan), Nagoya University (Nagoya, Japan), and Osaka Medical and Pharmaceutical University (Osaka, Japan).

NOTES

Conflict of Interest: The authors have nothing to disclose.

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