Clinical Research on SonodynamicTherapy Combined with Chemoradiotherapy for Brainstem Gliomas

Date：May 1st, 2025

NCT:NCT ID not yet assigned

1. Abstract: Brainstem

Diffuse midline glioma (DIPG) is difficult to completely resect surgically and cannot reach the radical radiotherapy dose. Currently, there is no effective treatment method, and the prognosis is extremely poor. Sonodynamic therapy (SDT) is a novel treatment technology developed from photodynamic therapy (PDT). The results of our Phase I clinical trial have preliminarily confirmed the safety and efficacy of SDT in the treatment of brainstem glioma. Therefore, we plan to conduct a randomized, open-label, Phase II clinical trial of SDT in the treatment of brainstem DIPG. We plan to recruit 216 patients with brainstem DIPG and divide them into an experimental group and a control group. Patients in the experimental group will receive not only SDT treatment but also treatment regimens selected by the researchers, such as radiotherapy, temozolomide, and bevacizumab. Patients in the control group will only receive the treatment regimens selected by the researchers. The follow-up period is 24 months, and brain MRI will be reviewed monthly. The treatment effect will be evaluated according to the RANO criteria. The primary endpoint is progression-free survival. The planned research period of this project is from

October 1,2024, to May 1, 2028.

2. Research Background:

Brainstem gliomas are a type of glioma that occurs in the midbrain, pons, medulla oblongata, and even the entire brainstem, and are more common in

children. Its incidence accounts for 1.3% - 2.2% of intracranial malignant tumors and 10% - 15% of pediatric central nervous system tumors[1]. Due to the special location of brainstem gliomas, surgical resection is difficult, and the radical radiotherapy dose cannot be achieved. The prognosis is very poor, with a one-year overall survival rate of only 37%. Especially for diffuse midline gliomas (diffuse intrinsic pontine glioma, DIPG), the median survival time is 10 - 11 months. 90% of children die within 18 months, and the 5-year survival rate is less than 1%. In the past few decades, many clinical trials have attempted various treatment methods for newly diagnosed brainstem gliomas, including targeted drugs, differentiation inhibitors, and radiation sensitizers, but none of them have been able to improve the overall survival rate of these patients[5]. For the treatment of recurrent brainstem gliomas, the second-line treatment options are usually very limited, lacking effective treatment methods, and the treatment is often more difficult. Currently, there is no unified and effective treatment plan for brainstem gliomas, and the prognosis is poor, causing great pain to patients and their families. Therefore, both the National Comprehensive Cancer Network (NCCN) in the United States and the Chinese Society of Clinical Oncology (CSCO) guidelines advocate giving priority to participating in clinical trials of brainstem gliomas, hoping to find safe and effective treatment methods through clinical trials, so as to maximize the extension of patients' survival time and improve their quality of life. Sonodynamic therapy (SDT) is a new technology developed from

photodynamic therapy (PDT). PDT can selectively eliminate local tumors without damaging normal tissues. It is safe, has few side effects, and can be reused. It stands out among many malignant tumor treatment options and has been included in the clinical treatment guidelines for various tumors such as skin cancer, esophageal cancer, biliary tract cancer, and bladder cancer. A large number of literatures show that the intraoperative application of PDT in the treatment of gliomas can significantly improve the prognosis of gliomas. However, due to the invasive surgical operation required by PDT and the poor tissue penetration of lasers, with a soft tissue penetration depth of only 1cm, PDT is difficult to apply to deep tumors, and its treatment scope is greatly limited. Therefore, SDT came into being. SDT uses low-intensity, low-frequency focused ultrasound (LILFU), which has strong penetration ability into biological tissues (up to 10cm deep). It can non-invasively focus acoustic energy on deeper tissues and activate sonosensitizers, thereby generating an anti-tumor effect.

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the treatment of gliomas can significantly improve the prognosis of gliomas. However, due to PDT's reliance on invasive surgical procedures and the poor tissue penetration of lasers, with a soft tissue penetration depth of only 1 cm, PDT is difficult to apply to deep - seated tumors, and its treatment scope is greatly limited[7]. Therefore, SDT came into being.SDT utilizes low - intensity, low - frequency focused ultrasound (LILFU), which has strong penetrating power in biological tissues (up to 10 cm deep). It can non - invasively focus acoustic energy in deeper tissues and activate sonosensitizers, thereby producing an anti - tumor effect[8][10]. SDT not only has the tumor-treating effect of PDT but also has deep-penetrating ability, enabling precise treatment of deep-seated lesions. It can selectively eliminate malignant tumors without damaging normal tissues, has a definite curative effect, and has few toxic and side effects. It is a promising treatment method that has developed rapidly in recent years and has attracted the attention of many researchers and clinicians at home and abroad. Currently, numerous pre- clinical studies have shown that SDT exhibits good effects in the treatment of gliomas[11][15]. Some studies have indicated that SDT can induce glioma cell necrosis and enhance the therapeutic effect of temozolomide[16]. Some literature has shown that SDT can significantly inhibit the tumor growth rate of C6 glioma - bearing mice[17]. More importantly, in our Phase I clinical trial, SDT was safe and effective in the treatment of brainstem gliomas, and the tumors of some patients with brainstem gliomas were significantly reduced. However, the patients included

in the Phase I clinical trial had large heterogeneity, a small sample size, and low test efficiency. Therefore, a Phase II clinical trial with a larger sample size is urgently needed to further verify the safety and efficacy of SDT in the treatment of brainstem gliomas.

In conclusion, due to the special growth location of brainstem gliomas and their diffuse endogenous growth pattern, surgical resection is extremely difficult, and it is impossible to deliver a curative radiotherapy dose. Currently, there are no effective treatment methods available, resulting in a dismal prognosis. This brings great distress to patients and their families. Therefore, finding a safe, highly effective, and accessible treatment approach to maximize patients' survival time and improve their quality of life has become an urgent clinical challenge.

Sonodynamic therapy (SDT), a novel, effective, safe, and non-invasive treatment technology developed from photodynamic therapy (PDT), has attracted the attention of many scholars and clinicians. SDT has demonstrated promising therapeutic effects in treating gliomas in numerous preclinical models. Moreover, the results of our Phase I clinical trial have preliminarily confirmed the safety and efficacy of SDT in the treatment of brainstem gliomas. However, the Phase I clinical trial has limitations, such as a high degree of patient heterogeneity, a small sample size, and low statistical power. Therefore, we plan to conduct a single-center, randomized, open-label, Phase II clinical trial of sonodynamic therapy for diffuse intrinsic pontine gliomas

(DIPG) in the brainstem. This study will further verify the efficacy and safety of SDT in the treatment of brainstem gliomas. The promotion and application of SDT technology will have significant social implications, not only alleviating patients' suffering but also improving their quality of life and extending their overall survival.

3. Research Objectives

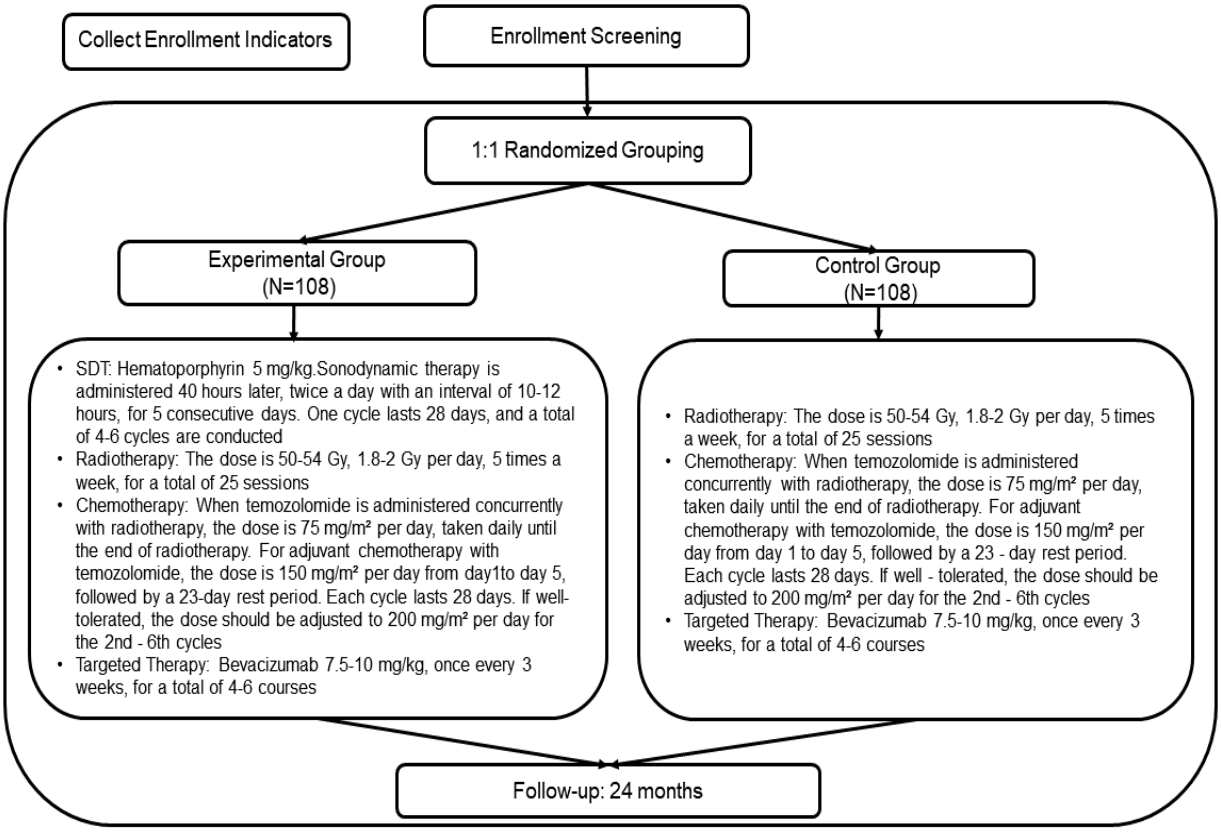
To further confirm the effectiveness, safety, and existing clinical problems of SDT in the treatment of brainstem gliomas.

4. Research Design

This study is a single-center, randomized, open-label, Phase II clinical trial of SDT in the treatment of brainstem DIPG, aiming to confirm the efficacy and safety of SDT in the treatment of brainstem gliomas.

This trial plans to recruit 216 newly diagnosed patients with brainstem DIPG. Stratification factors such as the basic clinicopathological characteristics of the subjects will be used, and they will be randomly divided into an experimental group and a control group at a 1:1 ratio.

Subjects in the experimental group will receive not only SDT but also treatment regimens selected by the researchers, such as radiotherapy, temozolomide, and bevacizumab. Subjects in the control group will only receive the treatment regimens selected by the researchers.



5. Research PopulationInclusion Criteria

5.1 Inclusion criteria：

1) All subjects or their legal representatives must voluntarily and in writing sign the informed consent form approved by the ethics committee before starting the screening process.

2) Age < 75 years old, gender is not limited.

3) Newly diagnosed patients with brainstem DIPG. It is confirmed as brainstem DIPG by histology or cytology (referring to the WHO Classification of Tumors of the Central Nervous System 2016), and there are radiologically evaluable lesions.

4) ECOG score is 0 - 2.

5) The expected survival period is ≥ 3 months.

6) The subjects have sufficient organ and bone marrow functions, without severe hematopoietic dysfunction and abnormal heart, lung, liver, kidney functions or immunodeficiency. The hematological indicators before enrollment are basically normal: white blood cell count ≥ 4×10^9/L, absolute neutrophil count ≥ 1.5×10^9/L, platelet ≥ 100×10^9/L, hemoglobin ≥ 90 g/L. The renal function is basically normal: serum creatinine ≤ 1.2 mg/dL or creatinine clearance rate ≥ 60 ml/min. The liver function is basically normal: serum total bilirubin ≤ 1.5 × ULN (if there is liver metastasis, then serum total bilirubin should ≤ 3.0 × ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.0 × ULN (if there is liver metastasis ≤ 5.0 × ULN). The coagulation function is basically normal: the international normalized ratio of prothrombin time (INR) ≤ 2.0, and PT, APTT, and TT are all within the normal range.

7) The toxic reactions of anti-tumor treatment before the administration of the test drug have decreased to Grade 1 or below, or the subjects have fully recovered from previous surgeries (judged by the researcher).

8) Women of childbearing age and all male subjects must agree to use highly effective contraceptive methods during the trial period and within 12 months after the last use of hematoporphyrin injection (such as condoms, contraceptive sponges, contraceptive gels, contraceptive membranes, intrauterine devices, oral or injectable contraceptives, subcutaneous implants, etc.), and the pregnancy test results of women of childbearing age must be

negative within ≤ 7 days before the administration of the test drug.

5.2 Exclusion Criteria：

1) Subjects known to be allergic to hematoporphyrin or other photosensitive drugs.

2) Subjects who participated in any other drug clinical trials or other interventional clinical trials within 4 weeks before the administration of the test drug, except for those who participated in observational (non-interventional) clinical studies or those who are in the follow-up period of interventional studies.

3) Subjects who have previously received SDT treatment.

4) Subjects who used other photosensitive drugs (tetracycline antibiotics, sulfonamides, phenothiazines, sulfonylurea hypoglycemic drugs, thiazide diuretics, and griseofulvin, etc.) within 4 weeks before the administration of the test drug.

5) Subjects with brainstem gliomas in a cachectic state or who are expected to be unable to tolerate SDT treatment.

6) Subjects with uncontrolled infections or clinically significant active infectious diseases.

7) Subjects with positive test results for any one or more of hepatitis C virus (HCV) antibody, syphilis antibody, or human immunodeficiency virus (HIV) antibody, or subjects with active hepatitis B (defined as HBV DNA ≥ 2000 IU/mL or HBV DNA ≥ 10^4 copies).

8) Difficult-to-control epilepsy and/or increased intracranial pressure and/or hypertension and/or hyperglycemia.

9) Subjects with severe or uncontrolled cardiovascular and cerebrovascular diseases and lung diseases (including myocardial infarction, Class III - IV heart failure, cardiac insufficiency, Grade 2 or above heart block, severe arrhythmia, cerebral infarction, cerebral hemorrhage, asthma attack, or severe respiratory failure).

10) Subjects who have had other malignant tumors in the past 5 years and have not been effectively controlled.

11) Subjects with uncontrolled mental illnesses/social situations that are expected to limit their compliance with the research requirements or impair the subject's ability to sign the informed consent form in writing.

12) Pregnant or lactating women.

13) Subjects with other reasons judged by the researcher to be unsuitable for participating in this trial, such as those with large brain tumor lesions.

5.3 Withdrawal Criteria:

For effectiveness and/or safety evaluation.

5.4 Withdrawal/Termination Criteria：

1) The subject withdraws the informed consent and requests to withdraw.

2) Other situations where the researcher deems it necessary to withdraw from the study.

6.Trial Procedure:

Photosensitizer: Hematoporphyrin Injection (Xipofen).

Machine: Transcranial Ultrasound Therapy Apparatus.

Treatment method:

1) After the patient is admitted to the hospital, complete various pre-treatment laboratory tests. For those who have not undergone a head MRI examination within one month before admission, a reexamination of MRI is required.

2) After completing various examinations and relevant procedures for clinical treatment, using stratification factors such as the basic clinicopathological characteristics of the subjects, randomly divide them into an experimental group and a control group at a 1:1 ratio.

3) Subjects in the experimental group will receive not only SDT but also treatment regimens selected by the researchers, such as radiotherapy, temozolomide, and bevacizumab. Subjects in the control group will only receive the treatment regimens selected by the researchers.

4) Treatment regimens selected by the researchers: Radiotherapy combined with chemotherapy:

a) The total radiotherapy dose is 50 - 54 Gy, 1.8 - 2 Gy per day, 5 times a week, for a total of 25 times.

b) When temozolomide is given concurrently with radiotherapy, the dose is 75 mg/m^2/day, and it is taken daily until the end of radiotherapy. For adjuvant chemotherapy with temozolomide, the dose is 150 mg/m^2/day,

taken continuously for 5 days, with a 23 - day rest period, and each cycle is 28 days. If tolerated, the dose in the 2nd - 6th cycles should be adjusted to 200 mg/m^2/day.

c) For targeted therapy, bevacizumab is used at a dose of 7.5 - 10 mg/kg, once every 3 weeks, for a total of 4 - 6 courses.

5)SDT

a) Administer "Xipofen" at a dose of 5 mg/kg body weight. For children, it is given intravenously systemically; for adults, it is locally administered by percutaneous arterial catheterization drug perfusion. After administration, place the patient in a ward with controlled light intensity.

b) Start sonodynamic therapy 40 hours after administration. Before SDT treatment, position the ultrasonic head on the scalp according to the MRI image to determine the tumor treatment range. Shave the area where the ultrasonic head is placed.

c) Set the SDT treatment parameters. Acoustic intensity: 1 - 1.25 W/cm^2; frequency: 800 KHz - 1 MHz; time: 15 min.

d) After treatment, keep the patient away from light for one month.

e) Treatment frequency: Treat twice a day at 24h, 48h, and 72h after administration. For the handling of relevant adverse reactions and treatment adjustments: Systemic symptoms such as phototoxic reactions, fatigue, weakness, fever, and pain; skin and mucosal symptoms such as rashes, ulcers, and bleeding; digestive tract symptoms such as diarrhea, nausea, vomiting,

anorexia, and melena; respiratory system symptoms such as cough, asthma, hemoptysis, and dyspnea; as well as symptoms of the nervous and cardiovascular systems. If photosensitizer allergic reactions, shock, etc. occur, immediately stop the drug infusion and carry out anti - allergic and anti - shock treatment.

7.Research Endpoints

7.1 Efficacy Evaluation Endpoints： Primary research endpoint: Progression - free survival (PFS). Secondary research endpoints: 1) Overall survival time. 2) Tumor control rate. 3) Incidence of treatment - related adverse events.

7.2 Safety Evaluation Endpoints: The incidence, severity, and duration of any adverse events and drug - related adverse events.

8.Data Collection

8.1 Data Source: This study plans to collect data from 216 newly diagnosed patients with diffuse midline glioma.

8.2 Data Collection Content:

Basic information: Gender, age, height, weight, ethnicity, smoking history, drinking history, allergy history, disease history, surgical history.

Clinical diagnosis and staging: Blood routine, liver and kidney function before and after treatment, tumor location, tumor size, TNM staging, clinical staging, ECOG score or KPS score, EGFR expression, and the Common Toxicity Criteria for Anticancer Drugs of the WHO .

Information related to previous treatments:

1) Surgical treatment: Name of the surgery, surgical information.

2) Radiotherapy: Radiotherapy technique, total radiotherapy dose, irradiation site, fractionated dose, and number of times.

3) Chemotherapy: Chemotherapy drugs, usage and dosage, treatment cycle.

4) Other information related to anti - tumor treatments.

Information related to concurrent treatments:

Name of the concurrent treatment, drugs, usage and dosage, start and end times, and the reasons for concurrent medications and treatments.

Imaging data:

Use MRI. Complete the imaging examinations related to tumor efficacy evaluation within 2 weeks before treatment. After the end of treatment, perform MRI reexamination once every 4 weeks for evaluation until the disease progresses, the subject cannot tolerate it, or withdraws. The examination time window is ±7 days.

Clinical follow - up information:

1) Conduct a descriptive statistics on all treatment - related adverse events that occur, list the events, duration, severity, and the relationship with SDT treatment. Calculate the incidence of adverse events and serious adverse events.

2) Short - term efficacy: Collect the imaging data of the included patients. After one cycle of SDT treatment, evaluate the efficacy of the patients to obtain complete remission (CR), partial remission (PR), stable disease (SD), and

progressive disease (PD). Calculate the objective remission rate (ORR) and disease control rate (DCR) of the tumor based on the best efficacy evaluation results within 12 months after the end of treatment.

3) Long - term efficacy: Collect the survival data of the included patients. Record the date of death and the cause of death. Evaluate the survival status of the patients 1 year, 2 years, and 3 years after treatment, calculate the 1 - year OS rate, 1 - year PFS rate, and safety, and record the median PFS and median OS.

9.Statistical Analysis

1) Safety analysis: Conduct a descriptive analysis of the occurrence of all adverse events (AE) and serious adverse events (SAE) collected.

2) Efficacy analysis: Use the Kaplan - Meier method to draw survival curves, and use the Log - rank test to evaluate survival differences. Use the Cox proportional hazards model for multivariate analysis to evaluate the role of prognostic factors. Unless otherwise specified, all statistical tests will use a two - sided test with $\alpha = 0.05$, and calculate the two - sided 95% confidence interval.

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