A Prospective Single Arm Phase II Exploratory Study on the Combination of Whole Brain Radiotherapy, Thiotepa Intrathecal Injection and Systemic Treatment of Primary Diseases in the Treatment of Solid Tumor Leptomeningeal Metastasis

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Informed Consent Form

Dear patient

We invite you to participate in A Prospective Single Arm Phase II Exploratory Study on the Combination of Whole Brain Radiotherapy and Thiotepa Intrathecal Injection for Systemic Treatment of Primary Diseases in the Treatment of Solid Tumor Leptomeningeal Metastasis. Before deciding whether to participate in this study, please carefully read the following content, which can help you understand the study, why it is necessary to conduct this study, the program and duration of the study, The benefits, risks, and inconveniences that may arise from participating in research.

The following is an introduction to this study:

1. Research background

Tumor meningeal metastasis (LM) refers to the metastasis that occurs when tumor cells spread to the subarachnoid space and spread to the meninges with the flow of cerebrospinal fluid (CSF). The occurrence of LM is less common than brain parenchymal metastasis, but more deadly. LM can occur in non small cell lung cancer (NSCLC), breast cancer (BC), melanoma and other malignant solid tumors. Compared to the 20% to 65% incidence of brain metastasis in NSCLC patients, the proportion of LM occurring in NSCLC patients is only 3% to 5%. However, the prognosis of LM patients is worse, and for untreated patients, the median overall survival (mOS) is only 6-8 weeks. With tumor treatment, survival can be extended to several months The mOS of LM BC is approximately 3.5 to 4.4 months, LM NSCLC is 3 to 6 months, and LM melanoma is 1.7 to 2.5 months. The diagnosis and treatment of LM are extremely important and challenging.

According to the EANO-ESMO guidelines, imaging is one of the diagnostic criteria, but the positivity rate is low and the patient's condition becomes severe when imaging features are present. The treatment of LM includes comprehensive treatment methods such as intrathecal drug therapy, systemic drug therapy, and local radiotherapy. Due to the presence of the blood-brain barrier (BBB), systemic drugs cannot exert their effects at the meninges. Therefore, intrathecal injection of drugs has become the best choice for LM due to its advantage of directly acting on the lesion site. There is limited research on drugs used for intrathecal injection of LM, so the main intrathecal chemotherapy drugs in clinical practice are methotrexate, liposome cytarabine, and thiotepa. Shandong Cancer Hospital shared a case of HER2 (+) LM BC patients who achieved a 16 month survival benefit through a regimen of pyrrolitinib+vinorelbine rhythm chemotherapy+intrathecal injection of methotrexate. For LM patients whose condition worsens after treatment with methotrexate, Thiotepa can be used as a salvage treatment. A retrospective study included 30 LM patients who failed methotrexate treatment and received 10mg of intrathecal injection twice a week. Among them, 14 cases (47%) had cytological reactions to intrathecal injection of cetepete. The EANO-ESMO guidelines recommend intrathecal drug therapy if tumor cells are found in CSF, regardless of MRI findings. Radiation therapy is also one of the treatment methods, but the bone marrow suppression caused by whole brain and spinal cord radiation therapy is significant, with limited dosage, which leads to interruption of systemic treatment and poor prognosis. The combination regimen in this study can quickly control symptoms by intrathecal injection of chemotherapy drugs, while opening the blood-brain barrier through whole brain radiotherapy, combined with systemic treatment for the primary disease, to achieve better therapeutic effects.

Therefore, studying the effectiveness and safety of comprehensive treatment mainly consisting of whole brain radiotherapy combined with intrathecal injection of chemotherapy drugs for LM of different tumors can help guide clinical treatment decisions. This is a scientific problem that urgently needs to be solved in the field of cancer. Here, we conduct a single arm prospective exploratory study to provide treatment opportunities for more patients.

2. Research objectives

2.1 Research Purpose:

The aim of this prospective study is to evaluate the effectiveness and safety of whole brain radiation therapy, intrathecal injection of Thiotepa, combined with systemic treatment for primary diseases in patients with different solid tumor meningeal metastases in our hospital.

2.2 Main study endpoints:

Objective response rate (ORR) (using RANO-LM criteria).

2.3 Secondary study endpoints:

(1) Safety: The safety analysis will be conducted based on subjects who experience toxicity (as defined by CTCAE standards). CTCAE version 5.0 will be used to evaluate safety through reported adverse events. The relationship between adverse events and drugs, onset time, duration of events, their resolution, and any concomitant medication will be recorded. Adverse events (AEs) will be analyzed, including but not limited to all AEs, SAEs, lethal AEs, and laboratory changes.

(2) The disease control rate (DCR): The proportion of patients who achieve complete remission (CR), partial remission (PR), or disease stability (SD) during or after treatment.

(3) Overall survival (OS): OS was defined as the time from the initiation of treatment to death from any cause. OS was estimated using the Kaplan-Meier method, with corresponding 95% confidence intervals. Comparisons between subgroups were performed using the log-rank test, and hazard ratios (HRs) were estimated using Cox proportional hazards models.

(4) 3-month OS rate, 6-month OS rate, 9-month OS rate, and 12-month OS rate.

(5) QoL

3 Specific procedures and processes

This study is a prospective, one arm clinical exploratory study evaluating the combination of whole brain radiation therapy and intrathecal injection of Thiotepa for systemic treatment of primary diseases in patients with meningeal metastases of different solid tumors in our hospital. The study was designed with a two-stage structure, consisting of: Stage 1 (safety run-in cohort): 20 patients; Stage 2 (efficacy expansion cohort): expansion to a total of 58 patients. In the first stage, patients were enrolled to evaluate the safety and tolerability of the multimodal treatment regimen at a fixed dose. After confirmation of acceptable safety, the study proceeded to the expansion phase to evaluate antitumor activity.

The study is divided into stages: screening period,combination therapy period, and follow-up period. The screening period is 28 days before the first administration. Intrathecal injection: Subjects who meet the inclusion criteria but do not meet the exclusion criteria will undergo intrathecal injection after signing the informed consent form. The subjects received hippocampal avoiding whole brain radiotherapy (HA-WBRT). At the same time, the comprehensive treatment plan mainly

includes intrathecal injection of Thiotepa, which is administered by qualified personnel (those holding training certificates in the radiotherapy department of our hospital). All eligible patients received intrathecal injection of Thiotepa twice a week as induction treatment for 3 weeks, followed by once every week as consolidation therapy for 6 week and then once bi-weekly as maintenance therapy, until progressive disease was observed or intolerance or adverse events (AEs) developed. Before each injection, cerebrospinal fluid pressure should be measured and an equal amount of cerebrospinal fluid containing the injection drug should be taken to detect cerebrospinal fluid routine, cerebrospinal fluid biochemistry, tumor markers, IgG and albumin content, exfoliated cells, and micro single-cell sequencing. After mixing with cerebrospinal fluid, inject slowly for 5- 10 minutes. According to the Neurotumor Response Evaluation (RANO) - LM criteria for efficacy evaluation, if there is disease progression or serious adverse events, the study will be immediately withdrawn. Evaluate the efficacy and safety every 6 cycles according to RANO-LM criteria. Follow up period: After stopping the study treatment, the subjects enter the follow-up period. During the follow-up period, MRI enhanced scans will be performed every 3 months to observe PFS. For subjects who have not withdrawn their informed consent form, survival information (i.e. date and cause of death, subsequent tumor treatment, etc.) will be collected.

4 What do you need to do if you participate in the research

You will conduct screening and evaluation according to the inclusion criteria of this plan. If you agree to participate, you will sign an informed consent form (ICF). After completing all screening activities, if eligible for enrollment, intrathecal injection will be performed. The subjects received a comprehensive treatment plan consisting mainly of systemic treatment, HA-WBRT combined with intrathecal injection of Thiotepa. The efficacy and safety were evaluated every 6 cycles.

You can voluntarily withdraw from the study at any time, or the participant or sponsor may withdraw due to safety or behavior reasons

Request for withdrawal due to reasons such as failure to comply with the research visit time or steps required by the protocol

5 Possible benefits of participating in this study

1. Personal benefits: There is currently no standard protocol for patients with solid tumor meningeal metastasis. The main purpose of this study is to improve the objective response rate and survival benefits of participants, and further enhance their quality of life; At the same time, the entire

The treatment process can receive close follow-up and attention from researchers. But it is also possible that they will not benefit.

2. Social benefits: such as acquiring new knowledge: further revealing new biomarkers related to meningeal metastasis and prognosis, promoting further scientific research development, facilitating the development of more effective drugs, changing treatment standards, and promoting people's health.

6 Possible adverse reactions, risks, and risk prevention measures for participating in this study

Gastrointestinal tract: vomiting, diarrhea, mucositis, gastrointestinal bleeding, etc;

Hematological system: bone marrow suppression, bone marrow necrosis;

Liver: elevated aminotransferase, elevated bilirubin, hepatic venous occlusion disease;

Central nervous system: encephalopathy, intracranial hemorrhage, epileptic seizures, subarachnoid hemorrhage, headache, emotional apathy, consciousness disorders, etc. Adverse reactions of the nervous system are more likely to occur when high-dose medication is administered;

Skin: Some patients may experience drug allergy, and in severe cases, Stevens Johnson syndrome, toxic epidermal necrolysis, etc. may occur;

Infection: pneumonia, cytomegalovirus infection, etc;

In order to prevent the occurrence of risks, researchers will closely observe and follow up throughout the entire treatment period for timely treatment. If serious adverse events related to the study occur, we will promptly contact your agent, and the hospital will respond accordingly

The relevant laws and regulations will strive for compensation for you.

7 Explanation of cost situation

The intrathecal injection drugs used in this study are free of charge and do not incur additional examination fees.

8 Compensation for participation in research, including compensation for damages

There is no special compensation. If the research causes damage, we will provide active treatment and all related costs will be waived.

9 Alternative solutions

If the subjects do not participate in this study or withdraw from the study, they can continue to receive treatment according to the standard diagnosis and treatment plan, or participate in other studies, etc.

10 Confidentiality of your personal information

Your medical records (including research medical records and physical and chemical examination reports, etc.) will be kept in the hospital according to regulations. Except for researchers, ethics committees, monitoring, auditing, pharmaceutical management departments, and other relevant personnel who will be allowed to access your medical records, other personnel unrelated to the study have no right to access your medical records without permission. The public report of the results of this study will not disclose your personal identity. We will be within the allowed range

Internally, make every effort to protect the privacy of your personal medical information.

11 Termination of research participation

Whether to participate in this study depends entirely on your voluntary choice. You may refuse to participate in this study, or withdraw from the study without reason at any time during the study process, which will not affect your relationship with the doctor, nor will it affect the loss of your medical or other benefits. In addition, your participation may be terminated due to the following reasons

Related to this study:

1. You did not follow the instructions of the research doctor.
2. You have encountered a serious situation that may require treatment.
3. The research doctor believes that terminating the study is most beneficial for your health and well-being.

12 Ethics Committee

This study has been reported to the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. After comprehensive review by the committee and risk assessment of the subjects, it has been approved. During the research process, there were

For matters related to ethics and rights, please contact the Ethics Committee for Human Research at the Second Affiliated Hospital of Zhejiang University School of Medicine,

Phone: daytime 0571-87783759; Evening (total shift): 13757118366; Email address: HREC2013@126.com

I confirm that I have read and understood the informed consent form for this study, and voluntarily accept the treatment methods in this study, and I agree to use my medical data for the publication of this study.

Subject's signature:

Contact information:

Date:

Agent's signature:

Contact information regarding the relationship with the subject

Date(If needed)

Witness (if required):

Contact information:

Date:

I confirm that I have explained the detailed information of this study to the patient, including their rights, potential benefits, and risks, and provided them with a signed copy of the informed consent form.

Researcher's signature:

Contact information:

mobile phone：

Date: