Phase II Study of Combined Chemotherapy With Arsenic Trioxide in Stage 4/M Neuroblastoma

(NCT03503864)

Informed Consent Form

Version:2.0

March 17 2020

Dear Sir/Madam,

After examination, your child has been diagnosed with neuroblastoma (Stage 4/M). You are invited to voluntarily participate in a prospective, single-arm, open, multi-center clinical study to evaluate the effectiveness and safety of arsenic trioxide in combination with chemotherapy for the treatment of Stage 4/M neuroblastoma (NB). The objective is to evaluate the effectiveness and safety of arsenic trioxide (ATO) combined with chemotherapy in treating Stage 4/M NB and to provide a new effective treatment to improve the survival rate of children with Stage 4/M NB.

1. Background

Neuroblastoma (NB) is the most common extracranial solid tumor in children, accounting for about 8%-10% of pediatric malignancies and 15% of cancer-related deaths in children. NB is highly malignant and often metastasizes early; approximately 50% of children with NB have distant metastases at diagnosis, referred to as Stage 4/M NB (high risk). Despite the recent international adoption of comprehensive measures such as chemotherapy, radiotherapy, and hematopoietic stem cell transplantation, the cure rate for Stage 4/M NB remains low, with a high risk of relapse and drug resistance, and a five-year event-free survival rate of less than 50%.

Due to the significant side effects of radiotherapy and the current difficulty in implementing autologous hematopoietic stem cell transplantation in China due to the lack of pretreatment drugs like Marilan, targeted immunotherapy drugs are expensive and not yet approved for the domestic market, making chemotherapy the main method for treating high-risk NB in China. Currently, the available drugs for treating drug-resistant NB in children are very limited. It is crucial to explore and try the combination of effective drugs, especially those already approved by the Chinese drug regulatory authority, to develop new treatment regimens and strategies for high-risk NB.

Arsenic trioxide (ATO) has a long history of use in chemotherapy for inducing tumor cell differentiation and apoptosis. In the 1970s, Chinese scholars discovered that ATO

could induce differentiation and apoptosis in tumor cells of acute promyelocytic leukemia (APL) and achieved remarkable therapeutic effects in the clinical treatment of new and relapsed APL. Existing in vitro studies have shown that regular doses of ATO can effectively kill various tumor cells, such as multiple myeloma, ovarian cancer, breast cancer, liver tumors, osteosarcoma, chronic granulocytic leukemia, lymphoma, lung cancer, and colorectal cancer, suggesting that ATO has a broad anti-tumor spectrum and potential clinical value.

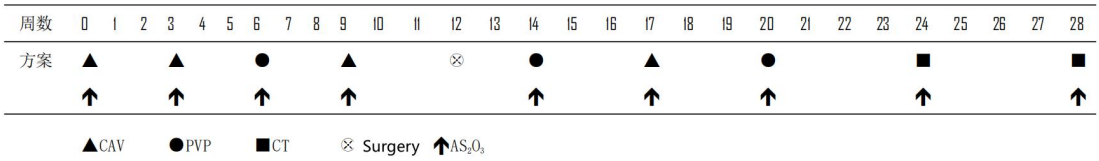
Currently, numerous basic and clinical studies domestically and internationally suggest that ATO can act on NB cells through various mechanisms in vitro, promoting apoptosis and reducing chemotherapy resistance in NB cells. The combination of ATO with traditional chemotherapy drugs can enhance the chemotherapeutic effect. Our research group's preliminary studies have found that ATO can kill different NB cells, and as the concentration and duration of ATO treatment increase, the expression of chemotherapy-resistant proteins (P-gp) in NB cells does not increase. Moreover, with the increase in the concentration of ATO, the expression of the TrKA receptor, which promotes NB differentiation and apoptosis, significantly increases. Further research has found that the combination of ATO with chemotherapy drugs (including vincristine, doxorubicin, etoposide, and cisplatin) enhances their lethal effects on NB cells, with the half-maximal inhibitory concentration (IC50) approaching the effective plasma concentration of ATO used clinically for treating APL. This suggests that a similar ATO combined chemotherapy regimen could be safely used for NB treatment. Several Phase I and II clinical trials have already been conducted to study the efficacy and safety of ATO combined with chemotherapy in treating high-risk NB children. The Memorial Sloan-Kettering Cancer Center in the United States has completed a Phase II clinical trial of ATO in treating children with refractory/recurrent solid tumors (including NB), showing that ATO has a certain capability to treat refractory/recurrent NB. Our previous clinical studies also indicate that intravenous ATO combined with chemotherapy can effectively treat relapsed/refractory NB with minimal toxic side effects. Out of 7 cases treated in our department for relapsed/refractory NB, where the disease progressed during chemotherapy or initial

poor prognostic indicators were present, the combination of intravenous ATO in chemotherapy resulted in an effective rate of 66.67% after several treatment cycles. This clinical study mainly explores the clinical efficacy and safety of ATO combined with chemotherapy in treating Stage 4/M NB, offering a new treatment option for relapsed or refractory NB.

2. Introduction

The induction treatment regimen for Stage 4/M NB includes chemotherapy, surgery, and radiotherapy. The traditional induction regimen consists of 9 chemotherapy cycles: cycles 1, 2, 4, and 6 follow the CAV regimen (cyclophosphamide + pirarubicin + vincristine); cycles 3, 5, and 7 follow the PVP regimen (cisplatinum + etoposide); cycles 8 and 9 follow the CT regimen (cyclophosphamide + topotecan). The chemotherapy intervals for the CAV and PVP regimens are 2-3 weeks, and the CT regimen interval is 3-4 weeks. Surgery is generally scheduled between the 4th and 5th cycles (as shown in Table 1). Radiotherapy is generally performed within a month after surgery for children aged ≥1 year, and the remaining chemotherapy is completed according to the respective intervals. This study plans to administer ATO chemotherapy alone for two days at the start of each chemotherapy cycle, beginning on the third day in combination with our hospital's pediatric oncology specialty's standard induction chemotherapy regimen for Stage 4/M NB (CAV, PVP, CT regimens, totaling 9 cycles), with ATO used for a total of 10 days per cycle (9 cycles in total). Finally, by follow-up observation and statistical analysis of the induction remission rate of the experimental group combined with chemotherapy, compared with the reported remission rate of Stage 4/M NB treatment in the literature, and by observing and recording chemotherapy-related adverse reactions, we will explore the efficacy and safety of intravenous ATO combined with chemotherapy for Stage 4/M NB.

Table 1. Composition of the Induction Treatment Regimen



3. Clinical Research Process:

(1)Signing the informed consent form.

(2)Clinical research screening.

(3)If the child meets the inclusion criteria, they will be enrolled in the trial group and receive treatment with ATO combined with the traditional induction chemotherapy regimen. The standard treatment includes the following:

- Starting chemotherapy blood criteria: neutrophils $>0.5\times10^9$/L, platelets $>50\times10^9$/L.
- Admission criteria for using ATO treatment: a. Serum potassium: 3.5-5.3 mmol/l, serum magnesium: 0.74-1.03 mmol/l, serum calcium: 2.02-2.60 mmol/l; b. Total bilirubin ≤1.5mg/dl, serum creatinine ≤1.5mg/dl; c.12-lead ECG: QT interval <0.5s.
- Each chemotherapy cycle starts with ATO chemotherapy alone for two days, followed by combination with the regular induction chemotherapy regimen (CAV, PVP, CT regimen) from day three, with ATO used for a total of 10 days (d1-10).
- ATO dosage and administration: 0.16mg/kg.d, mixed in 5% glucose solution or 0.9% normal saline 250-500ml, iv drip, PI >4h; vitamin C is administered concurrently to reduce adverse reactions and increase its in vivo efficacy: vitamin C 0.5-1.0g, mixed in 5% glucose solution 100-250ml, administered concurrently with ATO by iv drip.
- In the CAV regimen, cyclophosphamide requires pre-hydration and alkalization half a day in advance, along with Mesna (started synchronously with cyclophosphamide, daily dose of 1200mg/m2, divided into 3 doses, used for 2 days, synchronous total dose is 100% of cyclophosphamide), alkalization,

hydration, diuresis, antiemetic, etc., starting from the first day of cyclophosphamide, continuous hydration, and alkalization for at least 5 days; pirarubicin (THP) dissolved in 5% glucose solution 250ml-500ml iv drip, PI>3h, given antiemetic; vincristine dissolved in normal saline 100ml iv drip, PI=2h, maximum daily dose ≤0.67mg, total injection dose over 3 days ≤2mg.

- In the PVP regimen, starting from the day of DDP administration, continuous hydration, and alkalization for at least 7 days, fluid replacement 3000ml/m2.d, 20% mannitol diuresis, urine output monitoring, urine routine monitoring; before administering DDP, give mannitol (20% mannitol 1.25-5.0ml/kg + normal saline 100-250ml, iv drip fast), hydration treatment starts 2 hours later, urine output reaches 250ml/h, then start administering DDP (in normal saline, concentration not exceeding 1mg/ml, iv drip=6h, infusion bottle protected from light); if cardiovascular function is abnormal (output <45%), hydration amount and single dose of DDP may be appropriately reduced; antiemetic; pay attention to DDP-induced renal tubular toxicity and severe persistent electrolyte disorders, monitor renal function biochemistry during the treatment process, and address any significant hyponatremia, hypomagnesemia, hypocalcemia, or hypokalemia promptly, these abnormalities can occur several days after DDP treatment; for DDP-induced allergic reactions, treatment with adrenaline, antihistamines, and glucocorticoids is effective; etoposide dissolved in normal saline 250ml-500ml (note drug configuration concentration limit, not exceeding 0.25mg/ml) iv drip, PI>4h, used for 3 days, avoid using glucose solution for configuration, require slow drip.
- In the CT regimen, cyclophosphamide requires pre-hydration and alkalization half a day in advance, along with Mesna (started synchronously with cyclophosphamide, daily dose of 1200mg/m2, divided into 3 doses, used for 2 days, synchronous total dose is 100% of cyclophosphamide), alkalization, hydration, diuresis, antiemetic, etc., starting from the first day of cyclophosphamide, continuous hydration, and alkalization for at least 5 days; topotecan dissolved in normal saline 250ml-500ml iv drip, PI=24h (24-hour

continuous iv drip, preferably protected from light), used for 3 days, given antiemetic.

- Every two cycles using a regimen containing cisplatin (Cisplatinum, DDP) requires an audiometric test (ENT examination items: a. pure tone audiometry b. acoustic impedance + stapes muscle reflex attenuation c. ear acoustic reflex).
- Routine physical examination, laboratory examination, and imaging examination to assess the overall condition before treatment, collect a urine sample at any time before arsenic treatment to test for urinary arsenic and urinary creatinine. A complete blood count, routine biochemistry, and ECG/echocardiogram are required before each chemotherapy cycle. During chemotherapy, observe and record in detail bone marrow suppression, gastrointestinal reactions, liver and kidney damage, cardiopulmonary toxicity, neurological toxicity, allergic reactions, local toxicity, and other chemotherapy toxic side effects. Perform 24-hour urinary VMA, blood NSE tests after each chemotherapy cycle, and perform imaging examinations of the lesion (abdominal CT and/or chest CT), bone marrow or peripheral blood minimal residual disease, etc., every 2-3 cycles to assess the tumor condition.
- Post-treatment follow-up: ①Four weeks after the completion of all ATO combined chemotherapy regimens, comprehensive re-examinations including complete blood count, routine biochemistry, ECG, echocardiogram, chest and abdominal CT or whole-body PET-CT, human arsenic content testing (hair, nails, 24-hour urine), etc.; ②During the first year after all treatments, re-examine abdominal B-ultrasound, chest radiograph, ECG, and perform growth and development physical examinations (measuring height and weight) every three months; re-examine abdominal CT and echocardiogram, complete blood count, and routine biochemistry (liver and kidney function and electrolytes), and perform growth and development physical examinations every six months; ③During the second year after all treatments, re-examine abdominal B-ultrasound or CT, chest radiograph, echocardiogram, complete

blood count, and routine biochemistry (liver and kidney function and electrolytes), and perform growth and development physical examinations (measuring height and weight) every six months; ④After the third year of all treatments, perform regular re-examinations of abdominal B-ultrasound or CT, chest radiograph, ECG, echocardiogram, complete blood count, and routine biochemistry (liver and kidney function and electrolytes), and perform growth and development physical examinations (measuring height and weight) annually.

(4) During the study period, you also have some corresponding responsibilities, such as visiting the hospital on time and undergoing examinations. At the same time, you have the responsibility to report any changes in your physical and mental condition during the study process to the doctor, whether or not these changes are related to the study. Please be sure to inform your doctor about any other medications you are currently using and those used during the study period. During the study period, please do not use any other drugs to treat neuroblastoma; if other treatments are needed, please contact your doctor in advance to obtain formal medical guidance.

4. Possible Benefits

1. Increased induction chemotherapy remission rate.
2. Reduced occurrence of tumor drug resistance.
3. Lowered probability of disease recurrence.
4. Improved long-term survival rate, achieving longer disease-free survival time.

5. Costs Related to This Study

Compared to the traditional treatment regimen, the additional costs of this study are mainly for intravenous ATO and auxiliary medications, which vary depending on the child's age, weight, response to chemotherapy drugs, and market price fluctuations of the drugs. According to our hospital's drug catalog, the current price of ATO injection powder (specification 10mg/vial) is about 155 yuan per vial, and the roughly

calculated additional cost for the child using this study's regimen compared to the traditional regimen is about 2000-3000 yuan per treatment cycle. This cost is borne by the subject.

6. Possible Risks

It must be recognized that the current drug instructions for ATO do not include pediatric neuroblastoma as an approved indication. Although ATO can be used for the treatment of certain pediatric malignancies, doctors will strictly follow the recommended dosage range, treatment duration, and "contraindications," "precautions," etc., for using the aforementioned drugs. Like any drug, ATO may cause discomfort and unpredictable risks to the patient. According to literature reports and combined with our department's previous experience using ATO to treat other pediatric malignancies such as acute promyelocytic leukemia, intravenous ATO chemotherapy may cause but is not limited to the following adverse reactions:

(1) Leukocytosis syndrome: A small number of patients experience an increase in white blood cells, occurring 2-3 weeks after starting the drug, not requiring treatment cessation, white blood cells can decrease on their own or can be reduced with oral hydroxyurea after 1 week.

(2) Digestive system: Nausea, vomiting, anorexia, abdominal pain, and diarrhea are common adverse reactions, symptomatic treatment is provided, and these reactions disappear after stopping the drug. Some patients may experience liver damage, including elevated transaminases, jaundice, hepatoprotective drugs may be added, liver function can return to normal after stopping the drug.

(3) Fluid retention: Patients may experience weight gain, pleural effusion, pericardial effusion, and facial edema during treatment.

(4) Urinary system: Acute renal failure is rare, renal function changes may occur, generally reversible after stopping the drug.

(5) Neurological damage: Polyneuritis and polyradiculitis may occur about 10-20 days after starting the drug. Patients experience limb pain, numbness, and sensation

changes from hypersensitivity or abnormal development to delayed or absent pain, temperature, and touch sensation, even sensory ataxia. Concurrently, there is limb weakness, distal muscle atrophy, and significant autonomic nervous disturbances. Arsenic-induced peripheral neuropathy is indistinguishable from general ataxia. Approximately 34% of patients experience varying degrees of transient cerebral vasospasm-induced headaches early in the treatment.

(6) Cardiovascular system: Palpitations, chest tightness, ECG changes may occur, including sinus tachycardia, ST segment depression, T wave inversion or flattening, PR interval prolongation or complete atrioventricular block, but most are reversible; prolonged QT interval and ventricular arrhythmias based on this may occur.

(7) Skin dryness, erythema, or hyperpigmentation.

(8) Induced differentiation syndrome: Commonly seen in the early stages of arsenic-induced treatment, manifested by increased white blood cells, fever, weight gain, musculoskeletal pain, respiratory distress, pulmonary interstitial infiltration, pleural effusion, pericardial effusion, skin edema, hypotension, acute renal failure, and even death; severe leukocytosis can also lead to pulmonary, cerebral, and other organ embolism.

(9) Other unpredictable adverse reactions.

Additionally, although numerous in vitro studies have supported the effective killing action of ATO on NB cells, its efficacy in vivo remains uncertain, and disease progression or relapse may still occur during the combined chemotherapy process, or it may not effectively prevent the deterioration of the condition or even death.

During the treatment process, we will take active preventive and therapeutic measures to minimize the occurrence of ATO-related toxic side effects. If it is determined that the patient cannot tolerate it, adjustments or discontinuation of ATO use will be made; for patients who experience disease progression or relapse during the treatment process, the treatment regimen will be promptly adjusted to potentially save the child's life.

If any personal injury related to the trial occurs during the study period, the doctor will provide active treatment, and the sponsor will bear the related medical expenses

and other costs as stipulated by law.

7. Confidentiality Measures

The results of this clinical study are used only for scientific research purposes, therefore, your participation in the study and your personal information during the study are confidential and will be protected according to legal regulations, without disclosing your name and identity. Your name will not appear in any research reports or public publications. The hospital ethics committee, researchers, etc., may access all your research data, including clinical observation forms and experimental data, as required for work.

8. Rights

This clinical study has been reviewed and approved by the Medical Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University, and the study design meets ethical requirements, ensuring that your rights are not violated in this study.

Your participation in this clinical study is entirely voluntary. You can refuse to participate or withdraw at any time without facing discrimination or retaliation, and your medical treatment and rights will not be affected. If you withdraw from the clinical study, for safety reasons, you should complete some corresponding medical examinations at the time of withdrawal. If the doctor believes that you are not suitable to continue participating during the study period, to protect your interests, the doctor has the right to decide to discontinue your participation in this clinical study. Additionally, during the study period, you can obtain information about the study drug at any time. If we learn of any new information about this study, we will promptly notify you to decide whether to continue participating in the study.

During the clinical study, if you experience any discomfort or worsening of your condition, please notify your research doctor immediately, and we will take appropriate medical measures promptly; if you experience any adverse events related to the study drug according to the trial protocol, the researchers will provide active

treatment.

9. Contact Information

If you have any concerns or questions about participating in this study, or if you experience any unusual reactions while participating in this study, or in the event of an emergency, you should contact:

Doctor: Phone number:

If you have any complaints or concerns about the way the research doctor conducts the study or questions about your rights as a research subject, you can contact the following ethics committee personnel:

Name: Lin Shuangxiu Phone number: 81332587

Informed Consent Form – Consent Signature Page

Participant (Guardian) Statement

I have carefully read this informed consent form. The researchers have provided me with detailed explanations and answered my related questions. I am fully aware of the following:

(1) As a participant (guardian), I will comply with the requirements for participants, voluntarily participate in this study, and cooperate fully with the researchers, providing truthful and objective information about my health condition and related circumstances before participating in this study.

(2) The results of this clinical study are used only for scientific research purposes. Except for the ethics committee and researchers, my participation in the study and personal information during the study are confidential and will be protected according to legal regulations.

(3) I voluntarily participate in this study. If I experience any adverse reactions related to the study during the clinical study, I will receive appropriate and active treatment.

(4) My participation in this clinical study is entirely voluntary. I can refuse to participate or withdraw at any time without facing discrimination or retaliation, and my medical treatment and rights will also not be affected.

I also declare:

(1) I am willing to comply with the methods of using the study drug.

(2) During the study period, I am willing to cooperate with the doctor to visit the hospital at the specified times and undergo the corresponding examinations.

(3) I have received this informed consent form.

Participant (Guardian) Signature: Contact:

Date:

Participant's Legal Representative Signature (if necessary): Contact:

Date:

Witness Signature (if necessary): Contact:

Date:

Researcher Statement

I have fully explained and clarified the purpose, research methods, procedures, potential risks, and potential benefits of this clinical study to the participant, and have satisfactorily answered all related questions from the participant.

Researcher (Informer) Signature: Contact:

Date: