

Clinical outcomes of intravenous vitamin C synergy with Tyrosine kinase inhibitor in lung adenocarcinoma patients with epidermal growth factor receptor mutations

November 14, 2018

Informed consent

Dear patients,

You have been diagnosed with non small cell lung cancer.

We invite you to our clinical trial study of intravenous vitamin C combined with Tyrosine kinase inhibitor (TKI) drug in patients with lung cancer, in order to observe the effects of these treatments on quality of life, immune function and survival.

Before you decide whether to attend this study, please read the following consent as carefully as possible, which could help you better understand the whole program, benefits, risks and discomfort after participating this study. We strongly recommend you discuss it with your family or your doctor to help you make a decision.

Background and purpose

Primary lung cancer is one of the most common malignant tumors in our country, which has top morbidity and mortality rate. And this rate is rising, which is expected to exceed 800 thousands to 2020 in China. At the same time, the number of deaths will be close to 700 thousands. Non small cell lung cancer (NSCLC) take 80% of all lung cancer, can be divided into different histology type, including adenocarcinoma(>40%) and squamous cell carcinoma(30%), and the rare large cell carcinoma(LCC,10%). At present, the treatment for different types of NSCLC include surgery, radiotherapy, chemotherapy and molecular targeted drug therapy. However, the efficacy of the treatment is unsatisfactory. Therefore it is necessary to explore other auxiliary treatment to improve patient's quality of life and prolong the survival period.

Ascorbic acid (VitC), as a non mainstream alternative to anti-tumor therapy, has been used for many years. In the last 10 years, an increasing number of studies have indicated that VitC with pharmacological concentration can selectively kill tumor cells. In 2008, the U.S. National Institutes of Health (NIH) conducted a phase I clinical trial on VitC(1.5g/kg, 90-120mins, 3 times a week is safe, not found significant adverse reactions.) Foreign scholars in the phase II clinical trials suggest that intravenous VitC and chemotherapy drugs at the same time can effectively reduce the toxic side effects of chemotherapy drugs, which main research object are patients with ovarian cancer, breast cancer and prostate cancer. A research published in the Journal Science 2015 conducted that VitC can selectively kill colon cancer cells with KRAS and BRAF mutations, suggesting that VitC has a significant effect on some types of cancer. The mechanism of action is

not only to kill cancer cells by hydrogen peroxide, but also kill cancer cells by breaking the pathway of ATP after the inhibition of GAPDH.

We have accumulated many successful cases in the treatment of lung cancer. There are many patients taking tyrosine kinase inhibitor (TKI) drugs and VitC treatment in the outpatient clinic every week, lived longer than other patients. Based on this, we think it is necessary to conduct in-depth study of these two treatments to explore the best model for our treatment, to provide the opportunity for more NSCLC patients.

The aim of this study is to observe the effect of VitC combined with TKI drugs on quality of life, immune function and survival of patients with lung cancer.

This study will be conducted in Clifford hospital, and is expected to have 150 volunteers participating.

This study has been considered by the ethics committee of our hospital, and is in accordance with the principle of the Helsinki declaration and the medical ethics.

Inclusion Criteria:

Patient primary histological diagnosed with non small cell lung cancer.

Disease must have progressed for which no available treatment provides clinical benefit.

- Primary non-small cell lung cancer (adenocarcinoma) with EGFR mutations on exons 19 and 21.
- 18 years old to 75 years old.
- During the trial, patients were prescribed TKI (received initial treatment within 2 months, or change medication within 2 months) and did not receive chemotherapy or radiotherapy at the same time.
- Eastern Cooperative Oncology Group(ECOG) performance status are 0 to 2.
- Expected survival over 3 months.
- Household registration is Guangdong Province.

Exclusion Criteria:

- Co-morbid conditions that affect survival: end stage congestive heart failure, unstable angina, myocardial infarction (within the past 6 weeks), and uncontrolled blood sugars of greater than 300 mg/dL, known chronic active hepatitis or cirrhosis.
- Glucose-6-phosphate dehydrogenase deficiency (G6PD) (a relative contraindication).

- Patients who are allergic to VitC.
- Patients with HIV and other infectious diseases.
- Patients who are taking anticoagulants and have coagulopathy;
- Combine dysfunction of important organs such as heart, lung, liver and kidney;
- Patients with impaired renal function (serum creatinine content > 1.2 mg/dL)
- Compromised liver function with evidence of Serum total bilirubin content, ALT and AST > 2 times normal reference value.
- Pregnant or lactating female.
- Smoking and alcohol abuse patients;
- Anti-infective treatment is required for systemic or localized serious infections;
- Patients with hyperuric acidosis (normal: 91-456 $\mu\text{mol} / 24\text{h}$ (8-40mg / 24h));
- Wilson's disease.
- Evidence of significant psychiatric disorder by history or examination that would prevent completion of the study or preclude informed consent.
- Any condition that impairs the patients' ability to swallow, which impairs drug absorption or drug kinetic parameters, including any kind of gastrointestinal resection or surgery;
- History of surgery of visceral organs within 6 weeks before the trial.

Prepared work before participating

1. You will receive following tests to determine if you can take part in the research. The doctor will ask and record your medical history. You need to have Chest CT enhancement, brain MRI, liver color Doppler ultrasound, adrenal gland ultrasound, blood test for liver and kidney function, blood, urine routine, G6PD, tumor markers, tumor necrosis factor, interleukin-6.

2. If you have complete above examination, the following steps will be taken:

The study begins with a random number based on computer, which determines the treatment options you will receive (including nutritional counseling, evaluation and guidance, VitC infusion therapy combined TKI treatment , or TKI treatment only). We will notice you about the specific treatment and plan before the study.

3. Other things you need to cooperate with:

You must follow the doctor and your appointment to the hospital. The follow-up program is very important, in which doctors will evaluate the benefits of the treatment.

Benefits of participating

You and the community will likely benefit from this research. This benefit may include improvement of your disease, and developing a new treatment for patients with similar conditions.

You will get good medical care during the study.

Possible adverse reactions, risks and discomfort

During the treatment, there may be adverse reactions, such as hypoglycemia, nausea, vomiting, allergic reactions. But these reactions are eliminated by the doctor. If you do not have any discomfort, or have a new changing of your disease, or any accident, whether or not to be associated with the treatment, you should notify your doctor immediately, he/she will make a judgment and medical treatment. The study group will terminate the program if the condition of the disease reaches a certain standard.

You need to go to the hospital on time for follow-up physical and chemical examination, which are likely to cause trouble or inconvenience to you.

Related expenses

The hospital will pay VitC treatment cost during the study. (the medical treatment cost from the adverse reactions caused by the treatment will be paid by the hospital.)

If you are combined with other disease, the treatment and inspection will not be free of charge.

Personal information is confidential?

Your medical record (research medical records, physical and chemical inspection report, etc) will be kept in the hospital. The doctor will record the results in your outpatient medical records. The researchers and ethics committee will be allowed to review your medical records. But any public report on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information in the scope of law.

How to get more information?

You can ask any questions about this study at any time. Your doctor will give you a phone number to answer your question. If there is any important new information of the study, your doctor will inform you in time.

What should be done now?

Make your own decision about whether to participate in this study.

Please ask your doctor about questions of this study to make you better understand the whole

program.

Thank you for reading this consent. If you decide to take part in this study, please contact Doctor

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