

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

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Study Protocol and Statistical Analysis Plan

Background:

Vitamin C (VitC) infusion are widely used by integrative and complementary cancer practitioners for many years. In the last 10 years, many studies have shown that pharmacological concentrations of VitC can selectively kill tumor cells. A series of in vitro experiments [1], animal experiments [2-4] and Phase I-II clinical trials [5-7] have successively confirmed that VitC at pharmacological concentrations has the effect of inhibiting the growth of various tumors, including lung cancer.

Our Phase I clinical study, "The safety and pharmacokinetics of high dose intravenous ascorbic acid synergy with modulated electrohyperthermia in Chinese patients with stage III -IV non-small cell lung cancer", confirmed the safety of high-dose vitamin C in combination with deep hyperthermia in advanced non-small cell lung cancer, the concentration is as high as 1.5g/kg.d, 3 times a week. There were no significant adverse reactions. And it can significantly improve the quality of life (QoL). Our Phase II clinical trial in 2018 confirmed that IVC + mEHT treatment can significantly improve QoL, prolonge progression free survival (PFS) and overall survival (OS), and moderate cancer-related inflammation in advanced NSCLC patients. The article is already in the submission stage.

Recently we noticed that patients with epidermal growth factor receptor (EGFR) mutation who were taking tyrosine kinase inhibitor (TKI) with intravenous VitC every week had a relatively longer drug resistance time in our oncology center. We believe that it is necessary to observe whether intravenous VitC simultaneously with TKI can prolong the time of drug resistance in patients with EGFR mutations.

Objectives:

The purpose of this study was to investigate the effect of intravenous VitC in combination with TKI on the tumor size, QoL, PFS and OS in lung adenocarcinoma patients with EGFR mutation

Inclusion Criteria:

- 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.

Study design:

Experimental period: 12.05.2018~31.12.2019

Method:

In experimental group: 75 patients received a weekly intravenous Vitamin C injection (dose: 30 g / time, once a week, treatment termination when the disease progress is confirmed) in combination with daily TKI; In the control group: 75 patients received only TKI daily. (dose: Osimertinib 80 mg/d, or Tarceva 150 mg/d, or Iressa 0.25 g/d.)

Outcome:

Primary outcome was PFS. Secondary outcome include: OS, QoL, tumor size.

Observations and assessments:

To evaluate the effects of the above treatments on patient safety, tumor size, tumor markers, inflammatory factor levels, quality of life, progression-free survival and overall survival time. General information was collected before and after treatment, and the QoL was assessed on the quality of life questionnaire (QLQ-C30) scale. Chest CT enhancement, brain MRI, liver color Doppler ultrasound, adrenal gland ultrasound, blood test for liver and kidney function, blood and urine routine, tumor markers, tumor necrosis factor, interleukin-6 level were checked every month.

Statistical methods:

The effect of treatment on PFS, OS was analyzed by using Kaplan-Meier probability estimates. Comparison of tumor markers and immune factors was performed using t-test.

Key issues to be addressed:

To explore whether intravenous VitC can prolong resistance time of TKI on lung adenocarcinoma patients with EGFR mutations. To observe whether the combination treatment can benefit NSCLC patients.

Expected results:

Intravenous VitC in combination with TKI can significantly prolong the time of drug resistance, improve the quality of life, and have a positive effect on the prognosis of lung adenocarcinoma patients with EGFR mutations.

Safety measures and emergency plan:

Diarrhea, rash, liver dysfunction and other adverse reactions may occur during the treatment, but the above reactions will be eliminated under the doctor's treatment. If patients experience any discomfort during the study, or if there is a new change in the condition, or any unforeseen circumstances, whether or not related to treatment, patients should promptly notify their doctor, who will make a judgment and medical treatment. If the condition of the disease changes to a certain standard (if the condition progresses), the trial may be terminated earlier after discussion by the research group.

Reference

1. Hoffer LJ, Levine M, Assouline S. et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol*, 2008, 19: 1969—1974.
2. Chen Q, Espey MG, Krishna MC, et al. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proc Natl Acad Sci USA*, 2005, 102:13604—13609.
3. Du J, Martin SM, Levine M, et al. Mechanisms of ascorbate induced cytotoxicity in pancreatic cancer. *Clin Cancer Res*. 2010, 16:509-520
4. Chen, Q., Espey, M. G., Sun, A. Y., et al. Pharmacologic doses of ascorbate act as a prooxidant and decrease growth of aggressive tumor xenografts in mice. *Proc. Natl. Acad. Sci. USA*, 2008, 105:11105—11109.
5. Chen Q, Espey MG, Sun AY, et al. Ascorbate in pharmacologic concentrations selectively generates ascorbate radical and hydrogen peroxide in extracellular fluid in vivo. *PNAS*, 2007, 21: 8749-8754.
6. Hoffer LJ, Levine M, Assouline S, et al. Phase I clinical trial of i.v. ascorbic acid in advanced malignancy. *Ann Oncol*. 2008, 19:1969-1974.
7. Abou-Jawde RM, Reed J, Kelly M, et al. Efficacy and safety results with the combination therapy of arsenic trioxide, dexamethasone, and ascorbic acid in multiple myeloma patients: a phase 2 trial. *Med Oncol*. 2006, 23:263-272.
8. Luo, J., Shen, L., Zheng, D., 2014. Association between vitamin C intake and lung cancer: a dose-response meta-analysis, *Scientific Reports*. 4:6161, doi: 10.1038/srep06161.
9. Welsh JL, Wagner BA, van't Erve TJ, et al. Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial. *Cancer Chemother Pharmacol*. 2013, 71:765-775.