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Personalized Chimeric Antigen Receptor T- Cell Immunotherapy for Patients with Recurrent Malignant Gliomas

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Abstract

The aim of our study is to determine the safety and efficacy of chimeric antigen receptor T (CAR-T) cell personalized immunotherapy for patients with recurrent malignant gliomas. Autologous T cell is transduced with a lentiviral vector expressing chimeric antigen receptor to make the CAR-T. In total, 50 patients of recurrent malignant gliomas treated with CAR-T will be recruited to this study. Our research is also based on the expression of tumor specific/associated antigens (EGFRVIII, IL13Rα2, Her-2, EphA2, CD133, GD2). Furthermore, the objective response rate (ORR): the proportion of patients who achieve radiographic partial or complete response (PR or CR), is used to calculate the validity of CAR-T therapy to recurrent malignant gliomas.

Keywords: Immune therapy; CAR-T; Recurrent malignant gliomas

Introduction

Glioblastoma is one of the most common and devastating primary malignant intracranial tumors occurring in human [1]. The current therapy for newly diagnosed glioblastoma is surgical resection followed by radiotherapy plus chemotherapy. Despite advances in treatment, the median patient survival is only 14.6 months [2]. Recurrence, despite therapy, is a hallmark of high-grade glioma, eventually occurring in all patients [3]. Treatment of recurrent glioma must be individualized, depending on a patient's clinical condition, performance status, age, stage of treatment, and disease status. The current individual therapeutic strategy to recurrent malignant glioma is based on the mutation sites, such as IDH1, 1p19q, MGMT, hTERT, ATRX, BRAF and etc. [4]. However, due to the heterogeneity of recurrent malignant glioma. It is hard to find a certain mutation site to target to, which limits the effect of targeting therapy and make the drug selection complex. So it is rather important to find alternative way to make the personalized therapy possible.

Immune therapy is designed to stimulate the patient's immune system against her/his own cancer so as to promote immune-mediated anti-tumor responses [5]. Several approaches have been developed over the years and they include (but are not limited to) ADCC, cancer immunization, oncolytic viruses, chimeric antigen receptor T cell therapy (CAR-T), cytokine treatment, DC therapy, and checkpoint blockade [5]. In CAR-T, the patient's own T cells are isolated, genetically engineered to express a chimeric antigen receptor that recognize a tumor antigen of interest, expanded *ex-vivo*, and re-infused back into the patient [6]. CAR-T cell therapy and are now undergoing clinical trials, it is a type of adoptive T cell therapy (ACT) in which genetically engineered, HLA-independent, antigen-specific receptors are inserted into T cells. Brain tumors are known to have various responses to chemotherapy due to the blood brain barrier (BBB), export bump and etc, which block the large molecules from entering brain tissue. But the origination of CAR-T can make it easy to cross BBB, so there should be no variability in their response. Besides, the cervical lymph nodes can be used to activate T cells using brain tumor antigens [7]. Based on the above advantages of CAR-T, we designed immunotherapy for patients with recurrent malignant gliomas in order to improve the therapeutic effect.

Protocol

Objective

The study is a feasibility study that is designed to demonstrate the safety and efficacy of CAR-T treatment to patient of recurrent malignant glioma. Besides, the number of cell infusions of CAR-T cells in patients with recurrent malignant gliomas and the prevention and treatment of adverse reactions are also obtained.

Endpoints

The primary endpoint of our study is determination of the optimal doses. The second endpoints are objective response rate (ORR), disease control rate, PFS, and OS.

Eligibility Criteria

Inclusion criteria

The inclusion criteria are:

Voluntary informed consent for entry of trial;

Age greater than 18 years, and less than 70 years;

Pathologically confirmed recurrent malignant gliomas;

Tumor cells from resected tissue must be available for antigen testing (EGFRvIII, IL13Rα2, Her-2, CD133, EphA2, GD2) and at least one of the targets should be tested positively by immunohistochemistry study;

If the patient is on dexamethasone, the anticipated dose must be 4 mg/day or less for at least 5 days prior to apheresis;

Patients must have a Karnofsky performance status (KPS) of greater than or equal to 70;

Life expectancy greater than 3 months;

Participants with adequate organ function as measured by: White blood count greater than or equal to 2500/mm^3; platelets greater than or equal to 100,000/mm^3, hemoglobin greater than or equal to 10.0 g/dL; without transfusion or growth factor support;

Aspartate transaminase (AST), Alanine transaminase (ALT), gamma glutamyl transpeptidase (GGT), lactic acid dehydrogenase (LDH), alkaline phosphatase within 2.5*upper normal limit, and total bilirubin less than or equal to 2.0 mg/dL;

Serum creatinine less than or equal to 1.5*upper limit of normal;

Coagulation tests prothrombin time (PT) and partial thromboplastin time (PTT) has to be within normal limits, unless the patient has been therapeutically anti-coagulated for previous venous thrombosis.

Exclusion criteria

The exclusion criteria are:

Female subjects of reproductive potential who are pregnant or lactating;

Previous treatment with any gene therapy products or other form immunotherapy;

Uncontrolled active infection;

Active or latent chronic hepatitis B (detectable hepatitis B surface antigen (HBsAg)) or active hepatitis C (positive serology (hepatitis C virus Ab)) infection;

HIV infection;

History of allergy or hypersensitivity to study product excipients (human serum albumin, Dimethyl sulfoxide, and Dextran 40);

Currently enrolled in other clinical trials.

Registration

The research information is sent to the registration center and Ethics Committee of Xuanwu Hospital, Capital Medical University.

Treatment Plan and Evaluation

Patients are required to have a survival expectation of greater than 3 months, whose KPS is more than 70. 12 CAR T-cell doses administered intracranially over a 5-week period comprised of weekly treatment cycles. T cells are infused in week 1, 2, 4 and 5, week 3 is a rest cycle. T-cell doses of 10^7, 5×10^7, and 10^8 cells per infusion are infused on days 1, 3, and 5, respectively, following by 9 additional CAR T-cell infusions of 10^8 cells over 4 weeks [8]. Contrast enhanced MRI is performed during the week 3 rest cycle and after week 5.

For the evaluation, adverse events attributed to the administration of the chimeric antigen receptor T cells (Time Frame: 1 year) are observed. We determine the toxicity profile of the chimeric antigen receptor T cells with Common Toxicity Criteria for Adverse Effects (CTCAE) version 4.0. The objective response rate (ORR) is defined as the proportion of patients who achieve radiographic partial or complete response (PR or CR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guideline.

Study Design

This pilot safety and feasibility in human study is conducted at the department of neurosurgery, Wuanwu Hospital, Capital Medical University. The research protocol was approved by the ethics committee of Ethics Committee of Xuanwu Hospital, Capital Medical University (NCT03423992). All participating patients provide written informed consent.

Confidentiality

Clinical data is used for research purposes only. Results are kept anonymous and safe.

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