.0Version Number: 2 Version Date: 2024.07.01

Evaluation of clinical clinical diseases and Mechanism of acupuncture-

Evaluation of the clinical efficacy of acupuncture for improving the immune response in cervical cancer patients

informed consent

Dear lady:

Your doctor has clearly identified your diagnosis.

We will invite you to participate in the clinical efficacy evaluation of acupuncture to improve the immunotherapy response rate in cervical cancer patients. Before you decide whether to participate in the study, read the following as carefully as possible. It will help you understand the study and why the study was conducted, the procedures and duration of the study, the benefits, risks and discomfort you may have after participating in the study. If you wish, you can ask your doctor in charge to explain, or discuss with your relatives and friends to help you make a decision.

1. research background:

Cervical cancer is one of the most common gynecological malignancies. In China, the incidence rate and mortality rate of cervical cancer is relatively high. For patients with recurrent / metastatic cervical cancer, After first-line treatment failure (before 2020) National Comprehensive Cancer Network (National Comprehensive Cancer Network, NCCN) clinical practice guidelines in oncology have recommended bevacizumab, bizumab, topotecan, docetaxel, albumin paclitaxel, Its progression-free survival (Progression-Free-Survival, PFS) not exceeding May months, Overall survival (Overall Survival, OS) is only about 10 months old.in recent years, With the rise of immunotherapy, For patients with second-line and above recurrent / metastatic cervical cancer, As suggested in the study of carlizumab and apatinib in patients with advanced cervical cancer, Immunosuppressants combined with small-molecule tyrosine kinase inhibitors

(tyrosine kinase inhibitor, TKI), That is, the clinical study of carlilizumab and apatinib mesylate for second-line treatment of recurrent, metastatic cervical cancer, Its overall objective response rate (Overall Response Rate, The ORR) was 55.6%, The overall median PFS was 8.8 months.

Although immunotherapy partly improves survival in patients with recurrent / metastatic advanced cervical cancer, there is still a low response to immunotherapy in cervical cancer. For the data of patients with metastatic / recurrent cervical cancer, the objective response rate of PD-L1 expression-positive was 14.3% to 17.0% for pabizzumab therapy. Several phase I / clinical studies showed that the objective response rate of Nuumab was 4.0% to 26.0% in the treatment of metastatic / recurrent cervical cancer. A randomized controlled clinical study showed that electroacupuncture stimulation can increase the number of NK cells in patients and reduce the tumor volume.

This study aims to improve the immune status of cervical cancer patients through acupuncture to improve the response rate of immunotherapy and reduce the adverse reactions of immunotherapy; fill the gap of acupuncture combined immunotherapy for cervical cancer patients, explore the mechanism of synergistic effect of immunotherapy for cervical cancer patients, and provide evidence-based medical evidence for its treatment.

2. purpose of research:

1. Clarify the synergistic effect and safety of acupuncture therapy on immunotherapy for cervical cancer patients, and provide evidence-based medical evidence for the clinical efficacy of acupuncture therapy in immunotherapy for cervical cancer;

2. Take patient blood, stool and tongue coating samples for cytokine testing and 16S rDNA / metagenomic testing, and explore the mechanism of acupuncture therapy to improve patients' immune response through microflora.

III. Basic information of researchers and qualification of research institutions:

The principal investigator of this subject is Zhang Ying, chief physician

of Oncology Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, who has been engaged in clinical and research of integrated Chinese and Western medicine for more than 20 years.

The research institution is Guang'anmen Hospital of China Academy of Chinese Medical Sciences, and a third-class a traditional Chinese medicine hospital directly under the State Administration of Traditional Chinese Medicine, integrating medical treatment, teaching, scientific research and preventive health care.

Cooperation unit for the Chinese academy of medical sciences Peking union medical college hospital, Beijing maternity hospital affiliated to the capital university of medical sciences, Beijing university tumor hospital (Beijing institute of tumor prevention and control), Chinese academy of medical sciences tumor hospital, Sichuan tumor hospital, tumor hospital of Hunan province, Shanghai university of traditional Chinese medicine affiliated Yueyang combine traditional Chinese and western medicine hospital.

四、 Source and ethical review of the project:

This project comes from the clinical research and achievement transformation ability improvement project of the Central High-level TCM Hospital-TCM Clinical evidence-based research project-clinical efficacy evaluation and action mechanism of acupuncture and moxibustion. The project number is: HLCMPP2023089. This study has been reviewed by the Ethics Committee of Guang'anmen Hospital, Chinese Academy of Chinese Medical Sciences.

5. Study Overview:

(1) Number of subjects: This study intends to conduct a preliminary exploratory study, using small samples for clinical observation. 90 patients will be included to be assigned to the test group and the control group according to 1:1,45 cases in each group, a total of 90 subjects.

(2) Group: You will be randomly assigned to the control group and the trial group (1:1).

(3) Treatment:

① Trial group used acupuncture treatment + immunotherapy + targeted therapy / acupuncture treatment + immunotherapy + chemotherapy

② The control group was treated with immunotherapy + targeted therapy / + immunotherapy + chemotherapy

Electroacupuncture therapy started simultaneously with immunization and targeted therapy, with 1-2 electroacupuncture per week; 2 immunotherapy, at least 4 acupuncture, and at least 4 cycles of treatment.

Carrelizumab (for injection, manufactured by Suzhou Shengdiya Biomedical Co., Ltd., approval number: S20190027), 200mg / dose, intravenously, once every 2 weeks).

The targeted therapy is apatinib (apatinib tablets mesylate, manufacturer: Jiangsu Hengrui Pharmaceutical Co., Ltd., approval number: H20140103), 250mg / time, oral administration, once a day.

When you develop a treatment-related adverse event, reduce the dosage of apatinib as follows:

Dose grade	dosage
initial dose	250mg, qd (250mg / 1 day)
Grade 1 dose reduction	250mg, oral 2 days off 1 day (500mg / 3 days)
Grade 2 dose reduction	250mg, 1 day off 1 day (250mg / 2 day)

Note: carilizumab is not allowed; apatinib is not allowed to increase the dose after reduction.

Chemistry therapy: The specific chemotherapy regimen, drug usage and dosage, and frequency of chemotherapy should be determined by oncology clinicians according to the NCCN guidelines (2023) and the patient's condition.

Both groups may be treated with symptomatic supportive care according on their disease. The investigator should record in detail the treatment of both groups, including the following aspects: ① pain management; ② nutritional

support; ③ psychopsychological intervention; ④ tumor treatment prevention and side effects.

Specific process:

6. Inclusion criteria

(1) Patients with metastatic, recurrent or persistent squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or cervical cancer unsuitable for surgery and / or radiation therapy;

(2) Age: 18-70 years old;

(3) Having at least one measurable lesion according to RECIST 1.1;

Note: Measurable lesions are defined as lesions that can be accurately measured in at least one dimension (the longest diameter recorded by computed tomography (CT) scan, magnetic resonance imaging (MRI) is 10mm; lymph nodes must be 15mm on the short axis. Tumors within the previously irradiated area will be designated as "nontarget" lesions unless progression is recorded at least 90 days after completion of radiotherapy or a biopsy is performed to confirm persistence.

(4) The ECOG score is 0 or 1 point;

(5) The life expectancy exceeds 3 months;

(6) The patient has normal vital organ function, specifically as follows:

① Absolute neutrophil count (ANC) 1.510 ^ 9 / L;

② Platelet count: 8010 ^ 9 / L;

③ Hemoglobin: 90g / L;

④ Total bilirubin 1.5 upper limit of normal (ULN);

⑤ Asparpartate aminotransferase (AST) and alanine aminotransferase (ALT) 2.5 ULN;

Note: If the patient has liver metastasis, the AST and ALT levels are 5 ULN;

⑥ Creatinine 1.5 ULN or creatinine clearance 60 ml/min (Cockcroft-Gault formula);

⑦ Baseline albumin: 28g / L;

(7) Thyroid-stimulating hormone (TSH) level of 1 ULN;

Note: Patients with a free triiodothyronine [FT3] or a free thyroxine [FT4] level of 1 ULN may be included.

(8) Patients may sign a written informed consent form.

7. Who should not participate in this study

(1) Histopathological diagnosis of tumors other than squamous cell carcinoma, adenosquamous cell carcinoma, or adenocarcinoma;

(2) Participated in other clinical trials, or completed other clinical trials within 4 weeks;

(3) Previous use of immune checkpoint inhibitors, including but not limited to other anti-PD-1 and anti-PD-L1 antibodies;

(4) known history of allergy to any component of carlizumab or other monoclonal antibodies;

(5) The current need to use immunosuppressive drugs;

Note:> 10 mg/d prednisone or equivalent dose were prohibited for 2 weeks prior to study drug administration.

(6) patients with any history of active autoimmune disease or autoimmune diseases, including but not limited to the following diseases: hepatitis, pneumonia, uveitis, colitis (inflammatory bowel disease), hypophysitis, vasculitis, nephritis, hyperthyroidism and hypothyroidism, need intermittent use of bronchodilators or other medical intervention of asthma patients;

Note: except for vitiligo, resolved pediatric asthma / atopic subjects.

(7) Clinically significant cardiovascular disease, including but not limited to congestive heart failure (New York Heart Association (NYHA) grade> 2), unstable or severe angina, severe acute myocardial infarction within 1 year prior to enrollment, supraventricular or ventricular arrhythmias requiring medical intervention, or QT interval 470 milliseconds (female);

(8) arterial thrombosis or venous thrombosis occurs within 6 months;

(9) Hypertension drugs are not well controlled by hypertension (systolic blood pressure 140 mmHg and / or diastolic blood pressure 90 mmHg);

(10) Proteinuria (+ +) or total urine protein in 24 hours> 1.0 g;

(11) Coagulation abnormalities (INR> 2.0, PT> 16s), have a bleeding tendency or are receiving thrombolysis or anticoagulant therapy;

(12) No recovery from previously administered adverse events (except alopecia) (i. e., grade 1 or baseline);

(13) Known as having active central nervous system metastases;

(14) Patients with a previous invasive malignancy and with any evidence of disease within the past 5 years;

Note: Skin basal cell carcinoma, skin squamous cell carcinoma or cervical cancer in situ with potentially curative treatment.

(15) Active infection that requires systemic treatment;

(16) History of immunodeficiency, including seropositivity for human immunodeficiency virus (HIV) or other acquired or congenital immunodeficiency diseases;

(17) Hepatitis B virus (HBV)> 2000 IU / ml or DNA 110 ^ 4 / ml; or hepatitis C virus (HCV) RNA 110 ^ 3 / ml);

(18) Live vaccine was received within 4 weeks before the first trial treatment;

Note: Administration of an inactivated virus vaccine against seasonal influenza is allowed.

(19) Patients with suspected intestinal obstruction or risk of vaginorectal fistula or vaginal vesical fistula;

(20) Any other medical, mental or social condition whose rights, safety, welfare, or ability to sign informed consent, collaboration and study participation or may interfere with the interpretation of the results.

VIII. Reasons for the possible study termination

(1) The subject volunteered to withdraw;

(2) The subject has poor compliance and the investigator cannot continue the clinical investigator;

(3) The subject experienced pregnancy, death, or was lost to follow-up;

(4) The Sponsor terminates the study;

(5) The competent administrative department cancels the test;

(6) Other circumstances deemed necessary to withdraw from the study.

The investigators should do their best effort to enable each subject to continue the appropriate treatment unless stopping participation in the study is most beneficial. If the subject's study treatment stops, then the investigator should do his best to evaluate the subject's study results.

Subjects should also enter the follow-up period after treatment termination or withdrawal from the study. Participants will be followed up periodically (every 12 weeks ± 1 week, telephone or outpatient follow-up) to understand survival status, followed up to endpoint events (i. e. patient death or follow-up for 2 years). At the same time, the subject may receive other anti-tumor therapy after termination or withdrawal from the study, and the investigator shall record the anti-tumor treatment regimen.

9. Standards for entering the follow-up phase after the end of treatment

Treatment is stopped prior to follow-up in one of the following conditions:

(1) The treatment period is up to 2 years;

(2) The patient has disease progression;

(3) Patients have unacceptable toxic effects;

(4) Using taboo therapy, patients have received antitumor treatment other than the therapeutic drugs specified in the study protocol or oral and injection of traditional Chinese medicine decoction and proprietary Chinese patent medicine with anti-cancer effect;

(5) The investigator decides to stop the protocol or the patient withdraws his consent;

(6) Treatment can be discontinued if patients with a confirmed complete response have received at least 8 cycles of immunotherapy, including at least 2 cycles beyond the complete response.

X. Reasons for early study termination / site closure

Reasons for early termination or site closure may be but not limited to the following reasons: finding of new drug toxicity, results of any interim analysis,

subject enrollment and follow-up completion, non-protocol adherence, changes to the study schedule, slow enrollment, or poor quality of clinical data. When the study is terminated, your relevant disease information will be properly stored and destroyed to avoid the disclosure of your information. At the same time, the investigator will give a suitable treatment plan for you.

十一、 Other alternative treatments

If you decide not to participate in this study, you will receive other standardized treatments, such as surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, TCM therapy, etc., and your investigator will give a suitable treatment plan for you. Your investigator will also be happy to explain the possible benefits and risks of other methods used to treat your disease.

12. What do you need to do if you participate in the research program

1. Before you are selected for the study, you will undergo the following tests to determine whether you can participate in the study: ECOG score, physical examination, whole blood cell analysis, complete biochemistry, seven coagulation, four thyroid function, and urine routine. Your doctor will ask and record your medical history and confirm whether you have distant metastases and serious complications in other organs.

2. If your E COG score, physical examination, whole blood cell analysis, biochemistry, coagulation, thyroid function and urine routine examination pass, it will be conducted in the following steps:

(1) Completed before enrollment: cooperate with doctors to carefully fill in relevant questionnaires and medical history records, including demographic data, diagnostic data, physical examination, body status score, clinical symptoms, tongue pulse, TCM syndrome, quality of life questionnaire; and complete blood routine, biochemical, tumor markers, T and NK cell level, urine routine, stool routine, thyroid coagulation, blood coagulation 6ml + 2ml, stool sample 5g, tongue coating sample for preservation, and explore the mechanism of acupuncture therapy to improve the immune response of patients.

(2) Every 8 weeks / 12 weeks ± 2 weeks: cooperate with doctors to carefully fill in relevant questionnaires and medical history records, including physical examination, physical status score, clinical symptoms, tongue pulse, TCM syndrome, and quality of life questionnaires; and complete blood routine, biochemical, tumor markers, T and NK cell level, urine routine, stool routine, electrocardiogram, thyroid function and coagulation. Imaging examination should be completed, and 6ml + 2ml blood sample, 5g stool sample and tongue coating sample should be retained for preservation, so as to explore the mechanism of electroacupuncture therapy to improve the immune response of patients.

(3) In the whole treatment process, it is necessary to cooperate with doctors to complete the anti-tumor treatment combined with or without the combined acupuncture treatment, and record the treatment situation and adverse reactions in detail.

(4) During the whole treatment process, the patient should cooperate with the doctor to record the combined medication situation.

(5) After the end of treatment, you will enter the follow-up phase. You will be followed up in the clinic or telephone once every 12 weeks ± 1 week. You need to cooperate with medical staff in the clinic or telephone follow-up.

Xiii. Potential benefits, risks and inconveniences of participating in the study

1. Expected benefits:

Research may cure the disease or stop / slow the disease, but we cannot guarantee that. Your participation may benefit future patients suffering the same way. All subjects can obtain professional medical staff and professional knowledge related to cervical cancer treatment and disease guidance during the target free treatment, and can be added by Director Zhang Ying of oncology Department of Guang'anmen Hospital (registration fee).

2. Expected risk and inconvenience:

(1) This study is a randomized controlled clinical study, and there is a risk of information disclosure during the study. This study will take confidential measures to avoid information disclosure. During the study,

necessary imaging and blood tests should be conducted to evaluate the efficacy and safety, and patients are required to cooperate with the relevant questionnaire survey. This study will assist you to complete the questionnaire filling;

(2) Possible side effects and adverse reactions of acupuncture: halo acupuncture, stagnation needle, muscle spasm, pain, infection, etc., may occur in the process of electrical acupuncture. If you have any discomfort, or new changes in your condition, or any accident, regardless of whether it is related to electroacupuncture, you should inform the study doctor promptly, and the study doctor will make a judgment and medical treatment.

(3) Adverse reactions of targeted therapy, immunotherapy and chemotherapy: including infection, bone marrow suppression, hypothyroidism, loss of appetite, hypoproteinemia, hypertension, diarrhea, rash, abnormal liver and kidney function, etc. If you have any discomfort, or new changes in your condition, or any unexpected situation, whether it is related to targeted and immunotherapy, you should inform the study doctor, and the study doctor will pay close attention to your relevant examination, and make a judgment and medical treatment.

(4) Expected risk of invasive examination: risk of blood drawing, including transient, mild pain, local blue, mild dizziness in a few people, or extremely rare needle infection; risk of contrast allergy, etc.

(5) Other risks: There may also be some currently unpredictable risks, discomfort, drug interactions, or adverse reactions.

14. Medical treatment and compensation for research-related injuries

If you have an adverse event during the study, the investigator will decide between the study drug and the diagnostic tests required for the study protocol. If there are adverse events and harm due to the study drug and the diagnostic tests required for the study protocol, you can receive active treatment at your study hospital. The Guang'anmen Hospital of the Chinese Academy of Traditional Chinese Medicine will make appropriate compensation.

Xv. Related expenses

The electroacupuncture treatment used in this study trial group is provided free of charge. Patients in the test group may receive more than 4 electroacupuncture treatments per cycle (28 days).

2. During the target free treatment, patients in the group of test can receive free weekly blood routine and weekly biochemical examination at Guang'anmen Hospital of China Academy of Chinese Medical Sciences, and the cost shall be borne by our research group.

3. Immunotherapy and targeted therapy for all subjects using study drug regimen, specifically carlizumab, 2 cycles for 2 cycles; apatinib until the end of treatment.

4. The test group will receive a transportation subsidy of 100 yuan per cycle.

5. The blood sample collection tubes and tongue coating collection tubes used in this study are provided free of charge. The cytokine and 16S rDNA / metagenomic test analysis of blood and stool collection are free of charge, and the long-term preservation of biological samples does not require you to pay any fees.

6. Other drugs (such as symptomatic treatment drugs) and related examination expenses shall be borne by themselves.

7. The inspection items of the subject observation are all routine review items of your condition, and the inspection expenses shall be paid by yourself. This research project will not increase your cost; if you combine the treatment and examination required for other diseases, the cost shall be paid by yourself.

16. Confidentiality of personal information

Your medical records (study medical records, examination reports, etc.) will be kept intact in the hospital, and the doctor will record the examination results on your outpatient medical records. The investigator, representatives of the research sponsor, ethics committees and superior authorities will be allowed access to your medical records. No public report on the results of this study will disclose your personal identity. We will make every effort to protect the privacy of your personal medical information as permitted by law.

17. You will be promptly informed of any information that may affect the subject's continued participation in the trial.

How to get more information

You can find more information by calling Guanganmen Hospital at 010-810-88001500.

What is it to do now?

Your participation in this study is solely on your own free will. You may refuse to participate in this study or withdraw at any time after your participation in this study without any discrimination or retaliation. Your participation in this study or your withdrawal from this study will not affect your medical treatment and interests. You can discuss it with your family or friends before making a decision. Before you make your decision to participate in the study, please ask your doctor any questions until you fully understand the study.

Thank you for reading the above materials. If you decide to participate in this study, please tell your doctor or research assistant that he / she will arrange everything for you about the study. Please keep this information.

.0Version Number: 2 Version Date: 2024.07.01

Informed consent form • signature page

Topic name: Clinical efficacy evaluation of acupuncture to improve the response rate of immunotherapy in cervical cancer patients

Contractor: Guang'anmen Hospital, China Academy of Chinese Medical Sciences

Ethical approval number:

Subject Statement:

I have read the study materials and have received satisfactory answers of all questions, fully understanding the information on the medical study and the possible risks and benefits of the study; confirming that there is sufficient time to consider; knowing that participation in the study is voluntary and having the right to withdraw from the study at any time without discrimination or retaliation, medical treatment and benefits; and agreeing access to the study materials by MFDA, EC or the Sponsor. Represents a voluntary participation in the study.

I will obtain a copy of the signed and dated informed consent form.

Finally, I decided to consent to participate in this study.

Patient signature: Date: _ _ _

Patient contact phone number:

Signature of the legal agent (if applicable)

Relationship with patients: Contact number:

The Investigator Statement:

I have conscientiously fulfilled my informed notification obligation, explaining to the subject the details of the trial, including its powers and the possible benefits and risks, and giving her a copy of the signed informed consent form.

Doctor's signature: Date: _ _ _

Doctor work number:

If you have any complaint, you can contact the Ethics Committee of

.0Version Number: 2 Version Date: 2024.07.01

Guang'anmen Hospital of Chinese Academy of Chinese Medical Sciences at 010-88001552