Informed Consent • Informed Notice page

Project Name: Effects of music therapy on anxiety in cancerpatients with cancer: study protocol of a randomised controlled trial

Research Unit: Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine

Principal: Ling Xu Yabin Gong Chenbing Sun

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Dear patient,

Your doctor has diagnosed you with a malignant neoplastic disease.

We will invite you to participate in a randomized controlled trial of the effects of music therapy on anxiety in cancer patients.

Before you decide whether or not to participate in the study, please read the following as carefully as possible to help you understand the study and why it is being conducted, the procedure and duration of the study, and the benefits, risks, and discomfort that may result from participating in the study. If you wish, you can also discuss it with your relatives and friends, or ask your doctor for an explanation to help you make a decision.

1. Research Background:

Current cancer treatments include surgical resection, chemotherapy, targeted therapy and immunotherapy. These treatments, as well as the disease itself, may have adverse psychological effects on patients, including psychological stress reactions and negative emotions such as anxiety and depression, negatively affecting patient quality of life.

Current treatment of cancer-associated anxiety is frequently focused on the primary tumor. Few studies to date have focused on treating anxiety disorders caused by cancer, with even fewer focusing on non-pharmacological treatments. Music therapy has been defined by the American Music Therapy Association (AMTA) as the "clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program". Over the last few decades, music therapy has evolved from a specialized field to a method of treating a wide range of conditions, including perioperative cancer-associated anxiety and anxiety in patients with breast and lung cancer. The pathophysiological basis of anxiety disorders has not yet been determined, although structural brain abnormalities, neurobiochemical abnormalities, and genetic factors are thought to be involved. The primary mechanisms of concomitant anxiety and depression in tumor patients are thought to involve an overactive hypothalamic-pituitary-adrenal (HPA) axis, inflammatory mediators, and immune factors.

2. purpose of research:

This randomized controlled study will assess the ability of individualized music therapy to reduce cancer-related anxiety in patients by analyzing anxiety-related scales after music therapy. In addition, this study will evaluate cytokine

concentrations, gut microbiota and neurotransmitter-related indicators to explore the link their associations in cancer patients. The study will be conducted at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, and 60 participants are expected to participate voluntarily. The Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine has considered that the study is in line with the principles of the "Measures for Ethical Review of Biomedical Research Involving Humans" and the "Declaration of Helsinki", and in line with medical ethics.

3. Inclusion criteria

Subjects will be included if they (1) have a malignant tumor, as confirmed by histopathology or cytology; (2) have been treated for cancer-related anxiety or cancer itself for ≥ 2 months and ≤ 1 year; (2) meet the standard criteria for anxiety, including HAMA scores ≥7 and ≤28 and STAI sores ≥ 20 and ≤ 80; (3) are aged 18 to 74 years, with no gender restrictions; (4) have no history of other mental disorders and do not smoke or drink; (5) are conscious, behave and hear normally, and do not have a professional music background; (6) have normal heart, liver, kidney, and blood test results, with all other vital signs being normal; (7) have not taken anti-anxiety medications within four weeks prior to study entry; (8) have an expected survival time >6 months; and (8) provide written informed consent to study participation.

4. Exclusion criteria

Subjects will be excluded if they (1) are currently participating in other clinical studies or clinical trials; (2) have other serious diseases, such as infection, liver or kidney failure, making them unable, in the opinion of the project leader or researchers, to tolerate the treatment regimen of this study; (3) have primary or metastatic brain tumors, as confirmed clinically or radiologically; (4) are pregnant or lactating women; (5) have received music therapy within 3 months prior to the study; or (6) are taking anxiety medications or medications that can affect anxiety.

5. Rejection, suspension and shedding criteria

Patients will be discontinued from the study if they (1) are found not to meet the above inclusion and exclusion criteria; (2) show poor compliance or fail to follow up as required; (3) have incomplete medical records; (4) withdraw voluntarily from the study; (5) are regarded as unsuitable to continue the study due to serious deterioration of disease, severe complications or special physiological changes; or (6) are regarded by the investigator as unsuitable to continue the study. In addition, patients in the control group will be discontinued if they listen to music during the study period.

6. If you participate in the study, you will need to do the following work:

(1) Before you are enrolled in the study, you will undergo the following tests to determine whether you can participate in the study. Your doctor will ask you, take your medical history, and perform a physical examination. You need to do the cytokines IL-1β，TNF-α, IL-2R, IL-4, IL-6, IL-8 and IL-10, serum concentrations of the neurotransmitters 5-HT, DA, NE, ACTH and GABA, and determination of gut microbiota populations.

(2) If you meet the eligibility criteria, you will be studied according to the following

steps:

At the beginning of the study, a random number will determine whether you will be placed in the control or treatment group. Patients in the study each had a 50% chance of being assigned to one of the two different treatment groups. Neither you nor your doctor can know and choose any treatment in advance. The treatment will last for 1 weeks.

7. Intervention

Patients in the NMT group will receive emotional nursing care but not be allowed to receive any treatment for anxiety. If treatment is required due to worsening anxiety, it will be recorded and excluded. Patients who requested to participate in the music therapy sessions randomly assigned to the NMT group will receive the same music therapy as the MT group after completing the prescribed follow-up time.

Patients in the MT group will receive individualized receptive music therapy supervised by a music therapist, along with routine nursing care as well as required medications. Prior to starting music therapy, patients in the MT group will be introduced to the music therapy process for 5-10 minutes by the music therapist. The treatment room will be soundproofed, with patients in a resting or sitting position with eyes closed and relaxed.

Prior to music therapy, patients in the MT group will be exposed to various types of music to determine their preferences. The repertoire for music therapy which is nature-based sound, lasting 10-15 minutes, will be composed by the Department of Sound Engineering of Shanghai Conservatory of Music. After recording each patient's music preferences during playback, no more than three music clips from each genre will be chosen for individualized music clips of total length about 20 minutes, increasing individual patient comfort and orientation and reducing anxiety. Subsequently, the music therapist will play the personalized music clip created for 20 minutes, once a day for one week. Simultaneously, another music therapist will use a psycho-educational approach in conjunction with verbal instructions. Conditions for music therapy will include: (1) no bright light interference; (2) the patient in a resting or inactive state; and (3) music played through speakers at a volume controlled between 45-65%.

All participants will be required to complete State-Trait Anxiety Inventory (STAI), Distend Thermometer (DT), Hamilton Anxiety Scale (HAMA) and Quality of Life Questionnaire C30 (QLQ-C30) instruments on the day before and the day after treatment, as well as 14 and 28 days after treatment. The total scores of these items will be calculated and their differences in the MT and NMT groups will be compared. Blood samples will be collected for analysis of cytokine levels (serum IL-1β，TNF-α, IL-2R, IL-4, IL-6, IL-8 and IL-10), neurotransmitter levels (5-HT、DA、NE、ACTH and GABA) and gut microbiota on the day after treatment. Changes in primary disease condition will also be recorded.

8. Other matters requiring your cooperation

You must follow your doctor's instructions for treatment. If you need any other treatment, please contact your doctor in advance.

9. Possible benefits of participating in a study

You and society will probably benefit from this research. Such benefits include the possibility that your condition may or may not improve. In addition, this study may help evaluate the effectiveness of music therapy in relieving cancer patients with anxiety, and form a comprehensive music therapy program for tumor patients with anxiety symptoms, which can be used for other patients with similar conditions.

10. Possible adverse reactions, risks, discomfort and inconvenience of participating in the study

The treatment process may have emotional abnormalities and other adverse reactions. We will strictly regulate the treatment process and operation of music therapy to avoid the above things.

If you experience any discomfort during the study, or if you experience any new changes in your condition, or if anything unexpected, whether or not it is related to your treatment, you should inform your doctor promptly and he/she will make a judgment and take medical treatment.

The researchers will do their best to prevent and treat the adverse reactions that may result from this study. If an adverse event occurs during a clinical trial, a committee of medical experts will determine whether it is related to the treatment. As determined by the expert committee, the adverse event is related to the treatment, and the research group will provide the cost of treatment and corresponding financial compensation for the trial-related damage.

During the study period, you need to go to the hospital for follow-up visit on time and do some physical and chemical examinations such as interleukin energy, which may cause you trouble or inconvenience.

11. Qualified tuition and related expenses

The costs of the studies related to this study that you undergo during your study are at your own expense, but these tests themselves are also required for the assessment of your primary disease. Tumor related immune indicators (cytokines and neurotransmitters) and gut microbiota were detected once before and after treatment.

12. Is personal information confidential?

Your medical records (research record / CRF, physical and chemical examination report, etc.) will be completely stored in the hospital, and the doctor will record the results of the laboratory examination in your outpatient medical record. The investigator, sponsor representative, and ethics committee will be granted access to your medical records. 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 data to the extent permitted by law.

Your biological specimen will be kept in the hospital laboratory as required. In addition to this study, it may be used again in other studies in the future. You may now refuse to use your biological specimens for research other than this study.

13. How to get more information?

You may ask any questions about this study at any time. Your doctor will give you his/her phone number so he/she can answer your questions.

Your doctor will inform you if there is any important new information during the study that may affect your willingness to continue participating in the study.

14. You can voluntarily opt in and out of the study

Participation in the study is entirely up to you. You may decline to participate in the study or withdraw from the study at any time during the study without affecting your relationship with your physician or any loss of medical or other benefits.

Your physician or investigator may, in your best interest, discontinue you from the study at any time.

If you do not participate in the study or drop out of the study, there are many alternative treatments, such as anti-anxiety medications. You do not have to choose to participate in this study in order to treat your disease.

15. What should we do now?

It is up to you to decide whether to participate in this study. You can discuss it with your family or friends before making a decision.

Before you make the decision to participate in a study, please ask your doctor as many questions as possible until you fully understand the study. Thank you for reading the above. If you decide to participate in this study, please let your doctor know and he/she will arrange everything for you.

16. The experimental protocol is approved by the Ethics Committee of Shanghai University of Traditional Chinese Medicine. Subjects can directly consult or complain to the Ethics Committee if there is any question or situation during the experiment.

Please keep this information.

Informed Consent · Signature page

Clinical Research Project Name: Effects of music therapy on anxiety in cancer patients：A randomized controlled trial

Sponsor: Ling Xu　Yabin Gong　Sunchenbing

Trial registration number: CTR2000035244

Declaration of consent

I have read the above introduction about this study and fully understand the full contents of the informed consent form, and I have had the opportunity to discuss and ask questions about this study with my doctor. All my questions were answered satisfactorily.

I am aware of the possible risks and benefits of participating in this study. I understand that participation in the study is voluntary, I confirm that I have had sufficient time to consider it, and I understand that:

I can always ask the doctor for more information.

I can withdraw from the study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also know that if I drop out of the study, especially due to side effects, I need to tell my doctor about any changes in my condition and complete the appropriate physical and physical examination, which will be very beneficial to me and the whole study.

If I need to take any other medication due to a change in my condition, I will either consult my doctor beforehand or tell my doctor afterwards.

I allow the Ethics Committee or the sponsor's representative to access my research data.

I consent to or refuse to use my medical records and biological specimens for research other than this study.

I will be provided with a signed and dated copy of the informed consent. In the end, I decided to agree to participate in the study and try to follow the doctor's advice.

Date of subject's signature (handwritten)

Subject's contact Number

Subject's legal guardian's signature (if necessary), (handwritten)　**Date**

Guardian's contact Number

Doctor's statement

I confirm that I have explained the details of the trial, including its powers and possible benefits and risks, and have given the patient a signed copy of the informed consent.

The investigator (informing subject) **signed** (handwritten)　**Date**

Researcher contact Number