Study Protocol

The effect of cognitive behavioral therapy on chemotherapy-induced side effects and immune function in colorectal cancer patients undergoing chemotherapy: study protocol for a randomized controlled trial

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Background: Colorectal cancer (CRC) was one of the most widely diagnosed cancers in the United States in 2021. CRC patients may experience significant psychological stress and are susceptible to depression and anxiety. Previous studies have shown that cognitive behavioral therapy (CBT) can reduce fatigue and improve quality of life among breast cancer patients. However, as a non-pharmaceutical treatment, it remains unclear whether CBT improves chemotherapy-induced side effects and immune function in CRC patients. In this study, we will conduct a randomized controlled trial (RCT) among CRC patients undergoing chemotherapy to determine whether CBT can reduce the side effects of chemotherapy and improve the immune function of CRC patients.

Methods: The study will be a single-center RCT. CRC patients undergoing chemotherapy will receive either eight sessions of group-based CBT (every 2–3 weeks) or usual care (usual oncology care). Each participant will undergo assessments at baseline (T0), immediately post-intervention (T1), 3 months post-intervention (T2), and 6 months post-intervention (T3). The primary outcome will include chemotherapy-induced side effects in CRC patients. The secondary outcome will be immune function (measured by levels of inflammatory cytokines). Other outcomes will include the levels of tumor markers, assessments of psychological status (perception of stress, depression and anxiety, self-efficacy, sleep quality, quality of life, social support condition, and cognitive function), and necessary laboratory examinations (biochemical index and blood cell counts) among CRC patients undergoing chemotherapy.

Discussion: Our study will provide clinical evidence regarding whether CBT should be generalized in clinical treatment and the extent to which CBT reduces chemotherapy-induced side effects for CRC patients.

Trial Registration: ClinicalTrials.gov registration number NCT04741308.

Keywords: Cognitive behavioral therapy (CBT); chemotherapy; immune function; colorectal cancer (CRC)

Submitted Jul 27, 2023. Accepted for publication Aug 22, 2023. Published online Aug 30, 2023.
doi: 10.21037/jgo-23-625
View this article at: https://dx.doi.org/10.21037/jgo-23-625

Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies (1). It was the third most diagnosed cancer and the second most common cause of cancer-related death in the United States in 2020 (2). At present, the incidence of colorectal cancer ranks second among all malignant tumors in China (3). The number of CRC patients worldwide has more than doubled over the last 30 years (4). The number of new cases in 2022 is estimated to exceed 590,000 (3). Although the survival time of CRC patients has significantly increased (5), several studies suggest that the mental status of CRC patients is associated with more severe chemotherapy-induced side effects and poorer prognoses (6-8).

Increasing evidence suggested that CRC patients have a high risk of psychological disorders (9). Anxiety and depression are the most common psychological disorders in cancer patients (10). Among patients with CRC, approximately 20.4% and 31.8% of patients were diagnosed with depression and anxiety, respectively (11). The incidence of depression and anxiety has been shown to increase during the chemotherapy (12,13). Moreover, the risk of mental disorders remains higher 10 years after cancer treatment (14).

Depression and anxiety disorders among CRC patients could lead to more interruptions in tumor treatment (15,16), thus decreasing the quality of life (17) and leading to a higher mortality rate (18,19). In addition, CRC patients with depressive and/or anxiety disorders were reported to suffer from more side effects of chemotherapy (20). Bonhof *et al.* [2019] found that CRC patients with more severe adverse effects, such as chemotherapy-induced sensory peripheral neuropathy, reported more fatigue, anxiety, and depressive symptoms (21). Psychological intervention is one of the most important treatments for depression and anxiety in patients with CRC. Cognitive behavioral therapy (CBT) has been demonstrated to be effective in reducing depressive and anxiety symptoms in cancer patients (22,23), and alleviate fatigue in cancer patients (24). In theory, CBT can reduce the side effects of chemotherapy by reducing the level of depression and anxiety.

Moreover, previous studies have suggested that depression and anxiety are associated with immune function (25,26). Depression and anxiety have been associated with the immune response [e.g., lower natural killer cell counts (27)] and proinflammatory factors [e.g., interleukin-1β, interleukin-6, interleukin-8, and tumor necrosis factor-α (28)] in CRC patients. Psychological interventions (including CBT) can improve immune function in cancer patients (29).

However, whether CBT is associated with fewer chemotherapy-induced side effects and the improvement of immune function in CRC patients remains unclear. Therefore, we plan to conduct a randomized controlled trial (RCT) among CRC patients undergoing chemotherapy to determine whether CBT can reduce the side effects of chemotherapy and improve the immune function of CRC patients. We also try to explore the underlying biological mechanism of CBT. We hypothesize that CBT will reduce side effects related to chemotherapy and improve the immune function of CRC patients. We present this article in accordance with the SPIRIT reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-625/rc).

Methods

Study design and setting

This study is a single-center RCT that has been ongoing since March 1, 2021, at the Colorectal Cancer Center of Shanghai 10th People's Hospital. Eligible patients will be enrolled and randomly assigned to receive either CBT or usual care (1:1). The overall study design is illustrated in *Figure 1*.

Study population

We plan to recruit 100 CRC patients who are undergoing chemotherapy.

Participants will be screened for inclusion if they meet the following criteria:

- Age ≥18 years and ≤75 years;
- Have an education of junior high school or higher;
- Be able to complete psychological condition assessment;
- Willing to participate and competent to provide informed consent;
- Have normal cognitive function at enrollment, indicates by a score greater than 23 on the Chinese version of the Mini-Mental State Examination (CMMSE) (30);
- Speak Chinese Mandarin as their native language;
- Have a CRC in stage IV going for first-line chemotherapy.

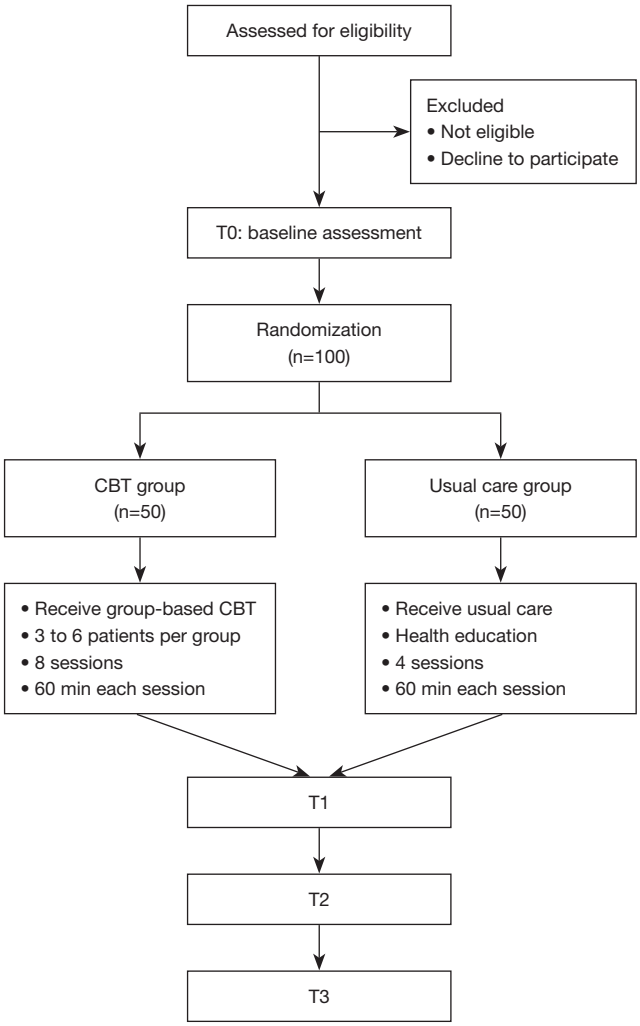

Figure 1 Flowchart of the study design. CBT, cognitive behavioral therapy; T1, immediately post-intervention; T2, 3 months post-intervention; T3, 6 months post-intervention.

Participants who meet any of the following criteria will be excluded:

- ❖ History of malignancies;
- ❖ History of mental disorders (e.g., major depressive disorder and schizophrenia) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V; American Psychiatric Association, 2013);
- ❖ History of brain trauma or neurologic diseases (e.g., epilepsy, stroke) according to the International Statistical Classification of Diseases and Related Health Problems, 11th Revision (ICD-11-version, 2022);
- ❖ Severe or untreated medical disorders (e.g., advanced cardiac or respiratory disease, severe liver, kidney, or metabolic disease);
- ❖ Receive adjuvant chemotherapy, neoadjuvant chemotherapy and immunotherapy;
- ❖ Alcohol dependency or drug abuse;
- ❖ Participation in other clinical studies.

Purpose of the study

The primary goal is to determine the effect of CBT on chemotherapy-induced side effects in CRC patients. We hypothesize that CRC patients who receive CBT will report fewer chemotherapy-induced side effects during chemotherapy.

The second goal is to determine the effect of CBT on the immune function of CRC patients during chemotherapy. We hypothesize that CRC patients who receive CBT will have lower levels of certain plasma inflammatory cytokines during chemotherapy.

Other goals are to examine (I) the effect of CBT on the level of tumor markers; (II) the effect of CBT on psychological status (including perception of stress, depression and anxiety, self-efficacy, quality of life, and sleep quality); and (III) other laboratory examinations (e.g., biochemical index and blood cell counts).

Intervention group: CBT group

The intervention will be performed in the ward's post-operative recovery room each time the patient comes in for chemotherapy. Patients randomly assigned to the CBT group will receive usual oncology care (including nutrition assessment, stoma care, observation of chemotherapy drug adverse reactions, etc.) in addition to 8 sessions of group-based intervention (3–6 participants per group). Group is open because patients have different chemotherapy regimens and it is difficult for patients in the same group to be hospitalized for chemotherapy at the same time every time. Specifically, the CBT manual incorporates education, relaxation training, self-awareness of stress and how to deal with it, encouragement of stress expression, development of self-confidence, self-regulation training, identification of maladaptive coping, and encouragement of adaptive coping. Every intervention section will last for 60 minutes (45 minutes for CBT and 15 minutes for relaxation training)

and will be conducted every 2–3 weeks within the period of each chemotherapy course.

Control group: usual care group

Patients randomly assigned to the usual care group (usual oncology care) will receive four sessions of health education monthly. Each session will last for 60 minutes, including lectures and question-and-answer segments. These four sessions will focus on (I) diagnosis and treatment of CRC; (II) adverse reactions and management of chemotherapy; (III) nutritional support; and (IV) physical exercise during chemotherapy.

Training

Two well-trained psychotherapists will conduct the CBT. They will receive professional training before the start of this study and will be regularly supervised by a senior clinical psychologist throughout the study.

Data collection

The data will be collected by trained research assistants and recorded on case report forms. The data will be stored in a secure database, and patients will be numerically coded to anonymize data. The data to be collected include the following.

Population characteristics

Demographic characteristics such as age, sex, body mass index (BMI), years of education, marital status, annual income, smoking, alcohol consumption, exercise, hobbies, Charlson comorbidity index (CCI), tumor grade, and number of chemotherapy courses will be collected at enrollment.

Baseline assessment (T0)

Clinical baseline data will be collected at enrollment approximately one week before chemotherapy.

Chemotherapy-induced side effects

Chemotherapy-induced side effects will be evaluated using the M.D. Anderson Symptom Inventory-Gastrointestinal Cancer Module (MDASI-GI), which includes 13 core symptom items, five gastrointestinal cancer-specific symptom items, and six interference items (31). The Chinese version of the MDASI-GI has demonstrated good reliability and validity among the Chinese population (32). The MDASI-GI will be assessed on the last day of each chemotherapy cycle.

Immune function

Inflammatory cytokines: C-reactive protein (CRP), IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ).

Other outcomes

(I) Psychological condition

Perception of stress. Perception of stress will be assessed using the 10-item Perceived Stress Scale (PSS-10), one of the most widely used psychological instruments, developed by Cohen *et al.* in 1983 (33). The scale involves 10 items scored from 0 to 4 with a total possible score of 40. Higher scores indicate greater perceived stress. The 10-item version has been confirmed to have good reliability and validity in the Chinese population (34).

Depression. Depression will be assessed using the Patient Health Questionnaire-9 (PHQ-9). It involves nine items scored from 0 to 3 with a total possible score of 27. The total score of the PHQ-9 ranges from 0 to 27 points, and the severity of depression increases as the total score increases. The scale has well-established reliability and validity in the Chinese population (35).

Anxiety. Anxiety will be assessed using the Generalized Anxiety Disorder-7 (GAD-7). It involves seven items scored from 0 to 3, with a total possible score of 21. The total score of the GAD-7 ranges from 0 to 21 points, and the severity of anxiety increases as the total score increases. The reliability and validity of this scale has been well established in the Chinese population (36).

Self-efficacy. The level of self-efficacy will be assessed using the General Self Efficacy Scale (GSES). The GSES was published in 1981 by Ralf Schwarzer and translated into Chinese in 1995 (37). It involves 10 items scored from 10 to 40. The final score is the sum of all items divided by 10, rated 1–4. Higher scores indicate greater self-efficacy. The Chinese version if the GSES has good reliability and validity (38).

Social support. Social support conditions will be assessed using the Social Support Rating Scale (SSRS). The scale was developed by Chinese scholar Shuiyuan Xiao in 1987 (39). It contains 10 items across three dimensions: objective support, subjective support, and utilization of social support. The total score is the sum of the 10 items. A higher score indicates greater social support. The scale has good reliability and validity in the Chinese population (40).

Quality of life. Health-related quality of life (HRQoL) will be measured using the European Organization for

Research and Treatment of Cancer (EORTC), Quality of Life Questionnaire, Core 30 (QLQ-C30), and EORTC diagnosis-specific modules for colorectal cancer (QLQ-CR29). The two scales have been shown to have satisfactory reliability and validity (41,42).

Sleep quality. Sleep quality will be assessed using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) (40). It is a 9-item self-rating scale with a total summed score ranging from 0 to 21. Higher scores indicate lower sleep quality. The scale has good reliability and validity (43).

(II) Tumor markers

The following tumor markers will be measured: alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), carbohydrate antigen 72-4 (CA 72-4), and carbohydrate antigen 242 (CA242).

(III) Laboratory examinations

- The following biochemical indices will be measured: liver and renal function, blood glucose, and lipid profile.
- Blood cell counts will be assessed.

Follow-up assessments

Time points: immediately post-intervention (T1), 3 months post-intervention (T2), and 6 months post-intervention (T3).

Contents: all baseline measures except SSRS.

Sample size estimation

Sample size calculation was based on the results of a previous RCT conducted among breast cancer patients to determine the effect of cognitive therapy on immune function (44). For the current study, we determined the effect size of Cohen's d=0.67 for the group difference in the change in interleukin-1 (IL-1) between the intervention group and control group. With a type I error of 5% and a power of 90%, we needed a total of 72 patients (36 per group). Anticipating a dropout rate of approximately 20%, we plan to enroll a total of 100 patients (50 per group) to ensure that we can include 72 participants in the final analysis.

Randomization and blinding

A researcher who is independent of the study will be responsible for randomization and allocation of participants at the beginning of the study. Participants will be randomly assigned to either a CBT group or a usual care group at a 1:1 ratio.

The therapists performing the intervention cannot be blinded to the allocation because they will need to use the psychotherapy manual during intervention. Another research assistant who is blinded to the allocations will perform psychological assessments and conduct clinical examinations of the participants.

Statistical analysis

Descriptive data will be reported as the mean ± SD (standard deviation) for continuous variables and counts or percentages for categorical variables. The Kolmogorov-Smirnov test will be used to test the normality of all variables. An independent t-test and a chi-squared test will be used to compare general characteristics, psychological conditions, and immune function between the two groups. The changes in psychological conditions and immune function at different time points will be examined using linear mixed models.

Statistical analysis of the data will be performed using SPSS version 26.0 (IBM, Armonk, New York, USA). A two-sided P value less than 0.05 was considered statistically significant for all analyses.

Patient and public involvement

Neither patients nor the public will be involved in identifying the research question or the design of the study. The results of the study will be disseminated to the public at the completion of the trial.

Data and safety monitoring board and interim analysis

Electronic data will be securely stored, while all remaining data will be documented on paper case report forms and later transcribed into electronic format. Regular monitoring of the data will be conducted, and the principal investigators or their representatives will perform interim data analyses to ensure data quality, such as identifying and excluding any data errors resulting from technical issues.

Handling of missing data

The respective analyses will involve the imputation of missing data. In the case of data missing completely at random, the expectation-maximization (EM) algorithm will be utilized for replacement. However, if the missing data

is not completely at random, multiple imputation will be employed.

Trial status

The trial has been ongoing since March 1, 2021. We expect data collection to be completed by December 31, 2023.

Ethics and dissemination

Written informed consent documents will be obtained from all the participants. Participants will be informed of the purpose of the study, the voluntary nature, the risks and benefits, and the right to refuse or withdraw from the study. CBT is an intervention that will not cause any physical or psychological harm to the participants. However, if any other unanticipated problem is reported or the participants feel discomfort during the assessment, participants may choose not to answer any questions or terminate the assessment. Participants will be asked to sign two copies of the consent form, one of which will be kept by the participants, and the other will be retained by the researcher. All information collected without personal identifiers will be stored safely in a locked file cabinet in the principal investigator's office. Electronic data will be kept in a computer secured with a password. The principal investigator of the study will have access to the final trial dataset. The results will be published in peer-reviewed journals. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Shanghai 10th People's Hospital (No. SHSY-IEC-4.1/20-268/01). In addition, the principal investigator will submit research progress reports to the ethics committee regularly.

Discussion

This is a single-center RCT. In this study, we will conduct CBT for CRC patients undergoing chemotherapy. CRC patients face a higher incidence of depression and anxiety during chemotherapy treatment (45). In addition, one study showed that after controlling for cancer characteristics, every one-standard deviation (1-SD) increase in anxiety or depression symptoms was associated with 17% and 20% increased in the risk of mortality, respectively (18), indicating that anxiety and depression are significantly related to elevated mortality risk in CRC patients. Other studies have demonstrated that the degree of chemotherapy-induced side effects is affected by multiple factors, including depression and anxiety (46-48).

Many tumor treatment guidelines advocate for the inclusion of psychosocial intervention as a crucial component of therapy throughout the entirety of tumor treatment (49-52). Cognitive Behavioral Therapy (CBT) emerges as a significant psychological treatment modality that offers noninvasiveness, convenience, and safety for patients with colorectal cancer (CRC). Substantial evidence supports the efficacy of CBT in significantly ameliorating anxiety and depression among individuals diagnosed with cancer (53,54). Moreover, some studies have examined the positive impact of CBT on fatigue reduction in cancer patients (24,55). Therefore, CBT maybe a promising method that has the potential to reduce the side effects of chemotherapy. In addition, CBT has been shown to improve immune function in other patients, such as human immunodeficiency virus (HIV) and sleep disturbance (56,57), but there have been few studies in CRC patients.

In this study, we will focus on the effect of CBT and determine the differences in chemotherapy-induced side effects and immune function between CRC patients who receive CBT and those who do not receive CBT. We expect that the outcomes of this RCT will provide clinical evidence regarding whether CBT should be generalized in clinical treatment and the extent to which CBT reduces chemotherapy-induced side effects for CRC patients.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-625/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-625/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-625/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study will be conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Shanghai 10th People's Hospital (No. SHSY-IEC-4.1/20-268/01) and informed consent will be taken from all the patients.

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Cite this article as: Wang M, Xu Y, Shi J, Zhuang C, Zhuang Y, Li J, Cashin PH. The effect of cognitive behavioral therapy on chemotherapy-induced side effects and immune function in colorectal cancer patients undergoing chemotherapy: study protocol for a randomized controlled trial. J Gastrointest Oncol 2023;14(4):1869-1877. doi: 10.21037/jgo-23-625

