Expert consensus statement on diagnosis and treatment of cancer-related depressed mood state based on Chinese medicine

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Abstract This consensus statement is organized into six parts: 1) Definitions: cancer-related depressed mood state is defined as a group of depressive symptoms, rather than major depressive disorder. Thus, “cancer-related depression” or “depressed mood state” is introduced as standard terminology and associated with the Chinese medicine concept of “yu zheng” (depression syndrome). 2) Pathogenesis: factors including psychological stress, cancer pain, cancer fatigue, sleep disorders, surgery trauma, chemotherapy, and radiation therapy are strongly associated with cancer-related depressed mood state. Crucial elements of pathogenesis are cancer caused by depression, depression caused by cancer, and the concurrence of phlegm, dampness, and stasis from constrained liver-qi and spleen deficiency. 3) Symptoms: these include core symptoms, psychological symptoms, and somatic symptoms. Depressed mood and loss of interest are the main criteria for diagnosis. 4) Clinical evaluation: based on the Mini-International Neuropsychiatric Interview and a numeric rating scale, and taking mood changes during cancer diagnosis and treatment into consideration, a questionnaire can be drafted to distinguish between major depressive disorder and cancer-related depression. The aim is to assist oncology clinicians to identify, treat, and refer patients with cancer-related depression. 5) Diagnosis: diagnosis should be based on the Chinese Classification for Mental Disorders (CCMD-3), taking patients’ mood changes during diagnosis and treatment into consideration. 6) Treatment: treatments for cancer-related depression must be performed concurrently with cancer treatment. For mild depression, non-pharmacologic comprehensive therapies, including psychological intervention, music therapy, patient education, physical activity, and acupuncture, are recommended; for moderate depression, classical Chinese herbal formulas based on syndrome pattern differentiation combined with antidepressants are suggested; for severe depressive symptoms that have progressed to major depressive

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Background

During the process of cancer onset, development, diagnosis, and treatment, patients are affected by fear of death, physical and social incapacitation, mental distress, a decline in quality of life, and various depressive symptoms, such as depressed mood, loss of interest, pessimistic thoughts, and guilt. In China, most patients know little about disease diagnosis, treatment, and rehabilitation. As a result, clinicians find it difficult to communicate with their patients freely. Social culture and personality may make patients reluctant to reveal mental and emotional problems. Therefore, as the cancer progresses, there is a dramatic rise in somatic complaints, leading to a concomitant increase in incidence of depression and risk of suicide.

In the clinical setting, more attention is paid to curative effects and survival rates than to the mental wellbeing of patients. Additionally, depressive symptoms, including anorexia, insomnia, and pain, are often obscured by cancer symptoms, making it more difficult for clinicians to recognize cancer-related depressed mood state. Recent data indicate that in China less than 10% of cancer patients with depression are diagnosed and offered mental health counseling and treatment. To help oncology clinicians improve their ability to recognize and treat cancer-related depression, the Hematology Branch of the China Association of Chinese Medicine, Department of Hematology and Oncology, Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine, drafted this consensus guideline on the diagnosis and treatment of cancer-related depression (Chinese medicine version), hereafter referred to the Consensus. The content of the Consensus drew upon the clinical experience and advice of oncology experts throughout China. Based on the concepts of multi-discipline comprehensive treatment, and complying with evidence-based and common practice, as well as practicality, experts in oncology, psychiatry, and neurology discussed and offered recommendations on several aspects of cancer-related depression. The initial symposium addressed definitions, pathogenesis, clinical presentation, screening, diagnosis, and treatment. In the second symposium, psychology experts in counseling and clinical assessment contributed detailed recommendations on the draft created in the first symposium. In the third symposium, experts affirmed the content of the Consensus, agreeing on the definition, clinical presentation, diagnostic criteria, screening instrument, and treatment of cancer-related depression.

Definition of cancer-related depressed mood state

Cancer-related depressed mood state refers to a pathologic depressive state or Chinese medicine syndrome pattern that occurs during the diagnosis and treatment of cancer. It is characterized by depressed mood, loss of interest, fatigue and lack of energy, pessimistic thoughts, guilt, and suicide tendency. Cancer-related depression is defined as a group of depressive symptoms, or depressed mood state, rather major depressive disorder. Thus, “cancer-related depression,” or “depressed mood state,” is hereafter incorporated in the Consensus statement as standard terminology. In traditional Chinese medicine (TCM), the definition of cancer-related depressed mood state as well as its clinical presentation of depressed mood, fullness and oppression in the chest and abdomen, distention and pain in the hypochondriac regions, irritability, and foreign-body sensation in the throat, reflect a Chinese medicine diagnosis of "yu zheng", or syndrome pattern of depression.

Etiology of cancer-related depressed mood state

Risk factors and triggers

Psychological factors

Psychological factors are closely linked with the occurrence depression in persons with cancer. When they are being evaluated and treated for their disease, the emotional stress they experience can elevate levels of stress hormones. The underlying biomedical mechanism may lie in hypothalamus–pituitary–adrenal axis hyperactivity, stimulated by prolonged and intense stressors, leading to alteration in the sympathetic nerve system and peptide and cytokine activity via hypersecretion of glucocorticoid.

Cancer pain

Cancer pain, especially unmanageable severe pain and side effects caused by analgesics, are physical and mental stressors and may induce and exacerbate depressed mood state.

Cancer-related fatigue

Cancer-related fatigue is a common symptom, and its treatment and can last for months or years. Continuous fatigue contributes to depressed mood and decreased quality of life. Fatigue occurs concomitantly and interacts with depressive status.

Sleep disorders

Cancer patients typically have varying degrees of sleep disturbance, which is correlated with anxiety and depression as well as substantial decrease in quality of life.

Surgery

Changes in patients’ emotions before and after surgery, are often related to tumor location and the type of operation.
Alterations in personal appearance can lead to psychological and social dysfunction in patients who undergo head and neck surgery or mastectomy.7

Chemotherapy and radiation therapy
Common side effects from these therapies include nausea, fatigue, hair loss, nerve problems, and bone marrow suppression, and may persist during and following treatment. Thus, the negative emotions elicited by the prolonged stress of treatment-related side effects might develop into depressive symptoms.8–10

Other factors
Tumor staging and progression, treatment success, rehabilitation following treatment, as well as coping style and social support may have a great impact on the incidence and severity of cancer-related depression.

Pathogenesis based on Chinese medicine
In traditional Chinese medicine, the risk factors and triggers described above are highly correlated with emotions such as anger, worry, anxiety, sorrow, and fear. For instance, breast cancer, liver cancer, and lung cancer patients may manifest sorrow, irritation, and sullenness prior to cancer onset. During the development, progression, and treatment of the tumor, negative emotions may increase and grief and fear may develop. Dynamic changes in patients’ emotions correspond to the Chinese medicine assertion that “tumors are caused by depression” and “depression is caused by tumors,” the pathogenesis of which is constrained liver-qi and spleen deficiency combined with the interactions of the pathogenic factors of phlegm, dampness, and stasis. The result is disharmony and restlessness of the spirit and emotional irritation.

Symptoms of cancer-related depressed mood state

Core symptoms
The presence of depressed mood, loss of interest, and lack of pleasure are the key criteria for a diagnosis of cancer-related depressed mood state. Depressed mood refers to feelings of sorrow, helplessness, disappointment, or despair and lack of pleasure from daily activities.

Emotional symptoms
Emotional symptoms include anxiety, self-accusation, guilt, delusions, hallucinations, agitation, reduced attention and memory, suicidal ideas and behaviors, slowed thinking and movement.

Somatic symptoms
Somatic symptoms can include sleep disturbance, headache, loss of appetite, loss of libido, digestive disorder, generalized pain, and muscle tension.

Clinical revaluation of cancer-related depressed mood state
The goal of assessment is to distinguish cancer-related depressed mood state from major depressive disorder to help oncology clinicians recognize, treat, or when needed, refer their patients to psychiatric specialists.

Criteria
Evaluation criteria include: 1) aged between 18 and 75 years; 2) diagnosed with malignant tumor; 3) with normal cognition and able to express intentions (adults older than 75 years should be ruled out for dementia); 4) evaluation should not be conducted at the same time as treatment; 5) patients should be accompanied by an immediate family member.

Screening content
Cancer-related mood changes—evaluation (screening) stage
A screening instrument, or questionnaire, should be used and can be based on the Mini-International Neuropsychiatric Interview (M.I.N.I.)11 and patients’ emotional changes before and after cancer diagnosis and treatment. The questionnaire can consist of 15 items with Yes/No responses. The questionnaire should be self-administered, so that patients complete it without influence from the clinician. Patients with no history of depression episodes, who have been diagnosed with, and treated for cancer for more than 2 weeks, and who manifest 10 of 15 symptoms on the questionnaire are diagnosed with cancer-related depressed mood state.

Depressive episode — diagnosis stage
To diagnose an episode of depressed mood state, a self-administered questionnaire should be used and can be based on the Chinese Classification for Mental Disorders-3 (CCMD-3)12 and patients’ emotional changes during diagnosis and treatment. The questionnaire can consist of 10 items with Yes/No responses. The questionnaire should be self-administered, so that patients complete it without influence from the clinician. Patients with five positive answers out of 10 are diagnosed with cancer-related depressive episodes.

Depressed mood grading
To rate the severity of depression symptoms, a 10-point numeric rating scale can be used: 0 = No symptoms; 1–3 = Mild; 4–6 = Moderate; 7–10 = Severe.

Diagnosis of cancer-related depressed mood state
Tools
A diagnosis of cancer-related depressed mood state can be made based on the aforementioned depressive episode diagnosis. However, mood changes during cancer diagnosis and treatment should be taken into consideration.
 Patients with a cancer diagnosis and treatment background, who display four of the following nine symptoms for a period of more than 2 weeks, are diagnosed with cancer-related depression: 1) loss of interest and pleasure; 2) energy decline and fatigue; 3) psychomotor retardation or agitation; 4) low self-esteem, self-accusation, and guilt; 5) incoherence, retarded thinking; 6) repetitive suicidal thoughts and behavior, self-harm/cutting; 7) sleep disturbances, such as insomnia, early awakening, and hyper-somnia; 8) loss of appetite or body weight; 9) loss of libido.

Referral to psychiatric specialist

In the absence of confirmation from a psychiatric specialist, it is recommended that oncologists make a diagnosis of cancer-related depressive mood state rather than psychiatrists do. Patients with a history of clinical depression or typical/atypical psychiatric symptoms, including a prolonged episode of depression, recurrent depression, bipolar disorder, agitation, fear, and frustration before or after cancer diagnosis, should be referred for psychiatric evaluation.

Treatment of cancer-related depressed mood state

Principles

Treatment of cancer-related depression should be performed simultaneously with cancer treatment. Depression treatment should be given priority only when depressive mood state seriously impedes cancer treatment and its complications. Non-pharmacotherapies are recommended for mild symptoms; for moderate and severe symptoms, medications (including herbs) can be used on advice of the psychiatric specialist and patient preference. Chinese medicine is the preferred treatment if patients are not willing or able to receive antidepressant therapy. If depression symptoms worsen, clinicians should urge patients to receive antidepressant therapy. Once depressed mood state progresses to clinical depression, patients should be referred to a psychiatric specialist.

Non-pharmacotherapy

Non-pharmacotherapies refer to psychological counseling, music therapy, patient education, physical exercise, and acupuncture. These can be recommended alone or in combination depending on the patients’ condition. Massage, physical therapy, acupuncture application, and nutrition counseling may also be beneficial.

Psychological interventions include cognitive behavioral therapy, suggestive therapy and hypnotherapy, and group counseling. Music therapy is a type of expressive therapy in which a music therapist uses music to help patients either cope with or overcome their depression. The type of music used matches patients’ interests receptivity. Music therapy diverts patients’ attention from their depression, relieves psychological tension, and improves mood.

Patient education is aimed at helping patients understand the intense negative emotions caused by cancer. Healthcare providers teach patients about their cancer diagnosis, benefits and goals of treatment and rehabilitation. Patients are also taught strategies for coping with the stress of the disease to elevate their ability and confidence to overcome the cancer.

Physical activity in the form of a prescribed exercise program should be encouraged to improve physical well-being, alleviate depressive mood state, and promote recovery from cancer.

Acupuncture therapy is aimed at clearing the channels and collaterals and regulating qi dynamics. Acupuncture has shown to benefit affective symptoms, such as depression, as well as somatic symptoms. Chinese herbal medicine therapy based on syndrome pattern differentiation

For moderate depressive mood state, when non-pharmacotherapy fails to control symptoms, it is recommended that modified classical Chinese medicine herbal formulas based on syndrome pattern differentiation are used in combination with antidepressants.

Liver-qí stagnation

Symptoms are depressed mood, fullness and stifling sensation in the chest and hypochondrium that causes frequent sighing, restlessness and susceptibility to anger, abdominal distention and fullness, dull pain in the lower abdomen, constipation, and deep yellow urine. Manifestations are dark red tongue with thin yellow coating and a wiry pulse. Treatment principle is to dredge the liver to relieve qí stagnation. The recommended herbal formula is Bupleurum Powder to Dredge the Liver (Chai Hu Shu Gan San). Source: Systematic Instructions on Medicine (Yi Xue Tong Zhi).

Liver constraint and spleen deficiency

Symptoms are depressed mood, pain and stifling sensation in the chest and hypochondrium, abdominal distension and fullness, reduced appetite, limb fatigue, borborygmus and flatus, and loose stools. Manifestations are fat, pale, tongue with thin and white or greasy coating and a wiry and thin pulse. Treatment principle is to dredge the liver and strengthen the spleen. The recommended herbal formula is Rambling Powder (Xiao Yao San). Source: Formulary of the Pharmacy Service for Benefitting the People in the Taiping Era (Tai Ping Hui Min He Ji Ju Fang).

Deficiency of the heart and spleen

Symptoms are depressed mood, palpitations, insomnia and dream-disturbed sleep, fatigue, reduced appetite, and loose stools. Manifestations are a pale tongue with thin and white coating and a thin pulse. Treatment principle is to benefit the heart and spleen. The recommended herbal formula is Restore the Spleen Decoction (Gui Pi Tang). Source: Categorized Essentials for Normalizing the Structure (Zheng Ti Lei Yao).
Phlegm and blood stasis
Symptoms are depressed mood, lumps and stabbing pain, numbness in the limbs, excessive phlegm and stifling sensation in the chest, dizziness, nausea and vomiting, and insomnia and dream-disturbed sleep. Manifestations are a purple and dark tongue with greasy coating, and a taut and rough pulse. Treatment principle is to regulate qi and transform phlegm. The recommended herbal formulas are Four-Substance Decoction with Saflower and Peach Pit (Tao Hong Si Wu Tang; source Golden Mirror of the Medical Tradition: Essential Teachings on Gynecology in Verse; Yi Zong Jin Jian: Fu Ke Xin Fa Yao Jue) combined with Two-Aged Decoction (Er Chen Tang; source Formulary of the Pharmacy Service for Benefiting the People in the Taiping Era; Tai Ping Hui Min He Ji Ju Fang).

Qi stagnation and blood stasis
Symptoms are depressed mood, stabbing pain in the chest with fixed location, fullness and stifling sensation in the hypochondrium, abdominal distention and pain, purple and dark lips, belching and acid regurgitation, and foreign body sensation in the pharynx. Manifestations are a purple and dark tongue with thin and white coating and a wiry pulse. Treatment principle is to regulate the blood and transform phlegm. The recommended herbal formula is Drive Out Stasis from the Mansion of Blood Stasis (Xue Fu Zhu Yu Tang). Source: Correction of Errors Among Physicians (Yi Lin Gai Cuo).

Damp-phlegm internal blockage
Symptoms are depressed mood, heaviness of the head and body, distension and stifling sensation in the chest and hypochondrium, a sticky and greasy feeling in the mouth, abdominal discomfort, reduced appetite, and greasy stools. Manifestations are a pink tongue with white and greasy coating and a soft and slow pulse. Treatment principle is to clear dampness and transform phlegm. The recommended herbal formula is Two-Aged Decoction (Er Chen Tang) combined with Scour Out Phlegm Decoction (Di Tan Tang). Source: Fine Formulas of Wonderful Efficacy (Qi Xiao Liang Fang).

Chinese patent medicines
Chinese patent medicine can be prescribed as adjuvant therapy. The following medicines are recommended based on syndrome pattern differentiation: for depressed mood, Rambling Pill (Xiao Yao Wan) or Modified Rambling Pill (Jia Wei Xiao Yao Wan); for fullness and stifling sensation in the chest, Bupleurum Pill to Dredge the Liver (Chai Hu Shu Gan Wan); for palpitations and fatigue, Emperor of Heaven’s Special Pill to Tonify the Heart (Tian Wang Bu Xin Dan) or Restore the Spleen Pill (Gui Pi Wan); for insomnia and dream-disturbed sleep, Calm the Spirit and Tonify the Heart Capsule (An Shen Bu Xin Jiao Nang) or Jujube Calm the Spirit Extract (Zao Ren An Shen Ye); for fatigue, Ginseng, Poria, and White Atractylodes Pill (Shen Ling Bai Zhu Ke Li/Wan) or Tonify the Middle to Augment the Qi Pill (Bu Zhong Yi Qi Ke Li/Wan).

Injectable medicines
Patients with advanced cancer, especially gastrointestinal malignancies, are unable to receive oral treatment because of reduced appetite or ingestion difficulties. Herbal medicines in injectable form can be considered. The following injectables are recommended based on syndrome pattern differentiation: for anxiety, insomnia, and fatigue, Aidi Injectable (Ai Di Zhu She Ye); for severe insomnia, Acanthopanax Injectable (Ci Wu Jia Zhu She Ye); for fatigue, Codonopsis and Astragalus Injectable to Support the Normal Qi (Shen Qi Fu Zheng Zhu She Ye).

Conclusions
The aims of this consensus statement are to emphasize the mental distress of cancer, guide oncology clinicians in differentiating mood disorders, and in selecting treatment strategies that prevent mortality caused by depression. In addition, the consensus may substantially improve patients’ clinical outcomes and quality of life perceptions. The consensus should be optimized through clinical practice, to provide more evidence for the development of guidelines on the diagnosis and treatment of tumor-related depressive status based on Chinese medicine.

Contributions

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