

Progress in Treatment of Tumor-Related Insomnia with Traditional Chinese Medicine and Western Medicine

Li Tiantian^{1,a}, Ju Feng^{1,b}, Zhang Jinyu^{1,c}, Yang Chenguang^{2,d,*}

¹Shaanxi University of Chinese Medicine, Xi'an, Shaanxi, 712046, China

²Shaanxi Provincial Hospital of Traditional Chinese Medicine, Xi'an, Shaanxi, 710003, China

^alitian8426@163.com, ^b812004375@qq.com, ^c1659594210@qq.com, ^dyang_chenguang@hotmail.com

*Corresponding author

Abstract: Insomnia is one of the most common comorbidities in patients with malignant tumors. Decrease in sleep quality or insufficient sleep time during the onset of the tumor and throughout the treatment process can be categorized as cancer-related insomnia. Lack of sleep will increase the risk of cancer, and even directly or indirectly promote the growth and proliferation of tumors, and may induce other physical symptoms as well as psychological abnormalities to improve the patient's sleep and living conditions. In recent years, the scientific community's interest in CRI has been growing. In this paper, we will review the mechanism of malignant tumor-related insomnia and the different diagnostic and therapeutic options in Chinese and Western medicine, with a view to promoting better treatment of CRI.

Keywords: Malignant tumor; Insomnia; Circadian Rhythms; Treatment Progress

1. Introduction

The Malignant tumor has become one of the most common causes of death. Tumor-related insomnia is one of the most common commodities in patients with a malignant tumor, it is difficult to fall asleep again after waking up, especially in the night more than a dream easy to wake up the most common. Different studies have shown that 30-50% (up to 95%) of patients with cancer have severe sleep disorders, which run through the whole course of cancer treatment, and even cannot return to normal state after the end of treatment, in turn, it can induce some physical symptoms as well as mental and psychological abnormalities, which can aggravate pain and other discomfort, two and more studies have shown that lack of sleep can indirectly increase the risk of People who suffer from insomnia, especially if the disease lasts more than 10 years, has a 24 percent increased risk of cancer compared with the general population [1-3]. This study was to explore the exclusion of other types of sleep disorders (such as restless legs syndrome, obstructive sleep apnea syndrome, etc.) characterized by decreased sleep quality and insufficient sleep hours.

2. Mechanism

The mechanism of CRI is still unclear, but the more common academic explanation is the "3P model", i. e., the three aspects of "quality factors, predisposing factors, and maintenance factors" [4], which suggests that, depending on the individual's constitution, patients with a previous history of insomnia are The model suggests that, depending on individual constitution, patients with a history of insomnia are more likely to have insomnia triggered or exacerbated by cancer diagnosis. Cancer-induced stress can also trigger stress insomnia, and studies have claimed that cancer-induced psychosocial factors (e.g., anxiety, depression, etc.) have become a major causative factor for CRI, with a bidirectional correlation between the two [5-6]. In addition, insomnia can be further exacerbated by the toxic side effects of cancer radiotherapy [7].

Pathological changes in the tumour itself can disrupt the neuro-endocrine system and interfere with normal circadian rhythms, which in turn can trigger and exacerbate insomnia [7]; it has also been shown that sleep disturbances in most cancer patients are related to the activation of inflammatory responses, and that changes in the inflammatory process induced by cancer, as well as its treatment, may trigger

sleep disturbances^[8]. CRI is primarily related to the neural loops controlling the sleep-wake cycle, and the alteration of the circadian rhythm can largely affect the clock genes^[9]. Alteration of circadian rhythm largely affects the expression of clock genes and alters the sleep-wake cycle; on the other hand, genetic mutations also increase the risk of cancer, and the two affect each other, forming a vicious circle^[10-14].

3. Chinese medicine

According to Chinese medicine, insomnia is categorised as "do not sleep", and the earliest record of insomnia can be traced back to the era of "Yellow Emperor's Classic of Internal Medicine", in which it is recorded that "the eyes do not sleep all night", "do not lie down", "do not sleep", and so on. In the *Neijing*, it is written that "the eyes are not dark", "one may not lie down", "one may not sleep", and so on. In "Ling Shu - Great Confusion", it is said that "Wei Qi is not allowed to enter the yin, and often stays in the yang If it is not allowed to enter the yin, the yin Qi will be weak, so the eyes will not be closed", which establishes that the key of the disease mechanism of insomnia lies in the fact that yang is not allowed to enter the yin. In the Han Dynasty, Zhang Zhongjing enriched and developed the classic prescriptions such as "Huanglian and Agaricus Soup" and "Sour Jujube Kernel Soup". In the Tang Dynasty, Sun Simiao proposed the use of dansha and amber to tranquillise the mind and warm the gallbladder soup to treat "insomnia after a serious illness". Extended to the Ming Dynasty, Zhang Jingyue in the "Jingyue Encyclopedia" in the summary, said, "although the disease is not the same, but only to know the evil and positive two words, one is no evil and do not sleep, will be insufficient Ying Qi are treated to raise the nutrient gas, and the second is there is evil and do not sleep, to go to the evil and God from the security", to have evil, no evil, and the division of theory. In Li Zhongzi's *The Golden Book of Medicine*, it is suggested that qi deficiency, yin deficiency and phlegm stagnation can lead to insomnia; in Dai Yuanli's *The Essentials of Politics*, it is suggested that "a person who is old and weak in years will not be able to sleep", suggesting that insomnia is related to yang deficiency. In the Qing Dynasty, Feng Zhaozhang proposed in *Feng's Secret Records of the Golden Pouch* that kidney yin deficiency could lead to insomnia, and in Wang Qingren's *Reform and Error of the Medical Forest*, the treatment of insomnia was based on the treatment of blood-fu and blood-stasis-expelling soup; and Tang Rongchuan pointed out that "there are two kinds of insomnia, one is heart disease, and the other is liver disease", which further enriched the ideas of the identification of insomnia and treatment of insomnia. Based on the specificity and complexity of tumours and the pathogenesis of insomnia in which yang does not intersect with yin, modern medical practitioners have summarized the main causes of insomnia, which are deficiency, phlegm, toxin, and blood stasis, and developed effective clinically specific formulas.

4. Treatment of tumor-related insomnia

4.1. Treatment of Western medicine

For patients with CRI, subjective assessment scales such as the Pittsburgh Sleep Quality Index (PSQI), the Severity Index (ISIS), and objective assessment tools are commonly used clinically, such as polysomnography (SV), polysomnography latency test (MSLT) and wrist movement instrument to assess the degree of sleep disorders in cancer patients^[4]. The Western medicine treatment plan mainly includes drug treatment and non-drug treatment for two aspects:

4.1.1. Drug Treatment

Drug treatments mainly include benzodiazepines (alprazolam, etc.) and Imidazopyridine (zopiclone, etc.). In addition, antidepressants, atypical antipsychotic and Melatonin Care are also used to treat different types of insomnia. Sedative frequency drugs to a certain extent can shorten the time to fall asleep, reduce the time and awakening, increase the total sleep time. The choice of drug and dose should follow the principle of waste, fully consider the tolerance of tumor patients and the interaction with other drugs used in the same period and start the drug at a low dose. The dose gradually increased and the effective dose was maintained^[4]. However, some clinical studies have shown that^[15-16] the effective rate of drugs is less than 80%, and there are many hidden dangers, easy to form drug dependence, arrest reactions and side effects are significant, long-term use of drugs weakened, etc.

Sleep problems are common in psychiatric patients, and there is a two-way relationship between the two. At present, the most representative and clinically applicable antidepressants and antipsychotic

drugs for insomnia promote sleep by inhibiting the activation of other neurons by antagonizing 5-H, thus affecting the activation of the cerebral cortex. There are studies that ^[3] Trazodone in the treatment of insomnia and nightmares has a certain effect. Low doses of sedative Atypical antipsychotic (such as olanzapine) can also improve sleep disorders in patients with CRI, as an initial treatment, on the other hand improving the mental status of patients with cancer, etc. The antipsychotic works by improving sleep efficiency and reducing the number of awakenings. These 2 kinds of drugs in primary insomnia use less, mainly used in case of insomnia combined with mental diseases, so for insomnia-related, less data.

In recent years, melatonin, a hormone secreted by spinal gland with obvious circadian rhythm, has been paid more and more attention as an alternative medicine for insomnia. It can increase the driving force of sleep and change the phase shift of the biological clock and its effect on sleep structure is mainly manifested in the shortening of sleep latency, can affect the circadian rhythm and have a sedative effect ^[17]. Animal studies have found that melatonin can also affect estrogen metabolism, or by increasing the expression of p53 protein, inhibit cell proliferation, thereby affecting the growth and proliferation of tumors. This provides a new way of thinking about the prevention and treatment of breast cancer and so on ^[18]. The causes of insomnia in cancer patients are complicated, and a multi-drug combination is usually used in clinical treatment. Therefore, it is difficult to avoid the potential interaction between drugs, which will cause psychological and physiological burden to patients and affect their quality of life. The ideal hypnotics should be able to quickly absorb, quickly induce sleep, have the best duration, maintain sleep structure and have good safety. This makes non-drug treatment in the clinical increasingly favored.

4.1.2. Non-drug Treatment

Non-drug therapies, also known as complementary and alternative therapies, are increasingly being used clinically to help patients, it mainly includes psychological education (such as cognitive behavioral therapy (CBT-I), individualized sleep programs, mindfulness meditation, deep hypnotherapy, multi-mode aerobic therapy and so on ^[19].

Although most patients with CRI are treated with drugs, there are some limitations because of the obvious side effects on the cancer population. In addition, sleeping health education for patients with cancer is critical and the latest edition of the NCCN has designated CBT-I as the first-line treatment for patients with CRI and CBT can improve the sleep status of patients with cancer. CBT-I can improve sleep significantly and permanently, but it has some limitations. The adherence rate of CBT-I is 32%-52%, therefore, deeper cooperation of patients is needed ^[20].

Mindful therapy has a variety of mindfulness meditation, body yoga, etc. , to alleviate chemotherapy- pain fatigue and other symptoms, improve sleep ^[21]. Hypnotherapy has also been observed to significantly improve severe insomnia ^[22]. Recent studies have shown ^[23] that aerobic exercise training significantly improves symptoms such as dyspnea in patients with advanced lung cancer, thereby improving the quality of life and sleep problems. In order to improve the tolerance of patients with CRI to tumor-related therapy, several interventions combined with drugs are usually adopted to treat the sleeping problems of patients with CRI.

4.2. Treatment of Chinese Medicine

According to Jing Yue quanshu, "Although there are different syndromes of insomnia, you can only know the two words of evil and well. One is that those who do not sleep without evil will not have enough nourishment. Both are treated with nourishing qi and the other is that those who do not sleep without evil will be free from evil and God will be at peace with themselves. ". Based on the particularity and complexity of tumor and the pathogenesis of insomnia, modern doctors have summarized and developed an effective clinical experience in clinical practice.

4.2.1. From the "Virtual" Treatment

Based on the theory of "supporting the positive to cure cancer", Tian Jianhui and others put forward the core pathogenesis of yin and yang imbalance and yang not being able to penetrate into yin due to "positive deficiency and ambush poison", and emphasised on guarding the god to regulate the god in order to keep the god in line with the time. According to Jiang Shiqing, in the late stage of tumour patients, the yin and yang of the five organs are all damaged, the qi and blood are insufficient, and the cold obstructs the middle jiao, which leads to yin and yang disorders and makes it difficult to sleep at night, and according to the clinical experience, it is common to use Semixia Coix Seed Soup combined

with Danggui Sibi Soup with additions and subtractions to warm the yang and dissipate the cold and to nourish the blood and tranquillise the mind [24]. Professor Li Jie used Zuo Gui Wan and Huang Lian A Gao Tang to nourish the kidney essence and communicate with the heart and kidney to treat shallow sleep and dreamy CRI [25]. Duan Yanrui et al. explained CRI from the theory of "yang transforms qi, and yin forms", and proposed two prescriptions for day and night, advocating "warming yang and benefiting qi to disperse tumour evils in the daytime, and relieving depression and tranquillising the mind to cure insomnia in the nighttime", applying warming yang and transforming qi products to smooth qi, warming the yang of the successive heavenly bodies, and the yang of the successive heavenly bodies is in the kidneys, and the yang of the latter is in the spleen and the stomach. In the treatment of CRI, there are many applications of warm kidney yang products such as Cistanchis, Epimedium, Semen, Boneset, Morinda citrifolia, and other warm kidney yang products, and warm spleen and stomach medicines such as ginseng, dried ginger, and Rhizoma Atractylodis Macrocephalae [26].

As the first formula for tranquilising the mind, sour jujube nut soup is a commonly used formula for insomnia caused by deficiency of the heart, liver and blood. Zhang Xinyou et al. combined with network pharmacological methods to obtain that sour jujube nut soup interferes with neurotransmitter regulation and HPA axis function through the 5-hydroxytryptaminergic synaptic pathway, the tumour necrosis factor signaling pathway, the cytokine-cytokine receptor interactions signalling pathway and other related pathways with multi-component, multi-targeted intervention in the treatment of insomnia [27]. The efficacy of Tianwang Xinxindan is mainly to nourish yin and blood, nourish the heart and tranquillise the mind, Zhao Qian et al. simulated the yin deficiency in Chinese medicine by injecting alkylating cytotoxic drugs in animal experiments, and explored that Tianwang Xinxindan could play a sedative-hypnotic efficacy through multiple pathways [28].

4.2.2. From the "Evil" Treatment

Patients with malignant tumours have a long history of illness, which will lead to deficiency and great injury to the origin, forming the phenomenon of "deficiency and stasis". "Stasis is both a disease-causing factor and a pathological product. Stasis leads to poor qi functioning, stagnation and congealment, which in turn leads to more serious stasis, phlegm and stasis intertwine, disturbing the mind and spirit, and the cycle repeats itself, resulting in intractable diseases. Professor Zhou Zhongying believed that in CRI patients, cancer toxin and phlegm and stasis are intertwined with each other, therefore, in the anticancer formulae, drugs that can dissolve phlegm and eliminate stasis and soften and disperse stagnation, such as baked turtle shells, peach kernel, dirong, and lutong, etc., are often added in the anticancer compound formulae [29]. In the clinical treatment of CRI, Professor Li Jie used danshen, peach kernel, safflower, chuanxiong and curcuma to eliminate phlegm and dispel blood stasis [25]; Li Renting, based on his clinical experience, believed that insomnia in patients with tumours is often accompanied by "stasis", and commonly used Haifuyuyuyuzhiyu Tang and Taohongsiwu Tang to eliminate stasis and disperse stagnation, along with tranquilizers, to achieve the goal of elimination of blood stasis and support of the positive to achieve complementarity of therapeutic effects [26]. The therapeutic effects complement each other [30]. It is also pointed out that if the disease is of long duration and deeper, insect medicines such as earthworm can also be added to reach the place of disease and eliminate blood stasis and clear the collaterals.

Haifu yuyu tang is a representative formula for the treatment of activating blood circulation and removing blood stasis. Based on network pharmacology, Shao Jun et al. explored the active components of Haifu yuyu tang, such as quercetin, stigmasterol, and β -sitosterol, which synergistically exerted anti-insomnia effects in a multi-component, multi-target, and multi-pathway manner by regulating neurotransmitters, and then related neural and inflammatory signalling pathways [31]. Jiang Chunqi et al. used the formula of activating blood and removing blood stasis combined with eszopiclone tablets for 40 cases of blood stasis-type insomnia patients in the Department of Oncology, and the results found that the combined method was significantly better than taking eszopiclone tablets alone in relieving CRI, indicating that the formula of activating blood and removing blood stasis Chinese medicine has a better therapeutic effect on blood stasis-type insomnia patients in the Department of Oncology [32].

4.2.3. From the "Cardinal" treatment

Jia Yingjie et al. believed that Chaihu Guizhi Dry Ginger Soup can effectively improve insomnia in cancer patients by turning the pivot of Shaoyang, communicating with the exterior and the interior, and reconciling yin and yang; and the discretionary addition of sour jujube kernel, Yuanzhi, and nightshade to nourish blood and calm the mind in order to help sleep [33]. This is in line with Chen Shunzhong's

idea of using Xiao Chaihu Tang to treat insomnia, suggesting the great potential of Chinese medicine to support positive drugs in the field of tumour prevention and treatment [34]. Professor Lin Yi, in the treatment of insomnia associated with breast cancer, used "Chaihu Shuo Liver San" to treat insomnia by strengthening the liver and spleen [35]. According to the experience of Jiang Shiqing, for the person who is disturbed by liver depression, he chooses Dangdaji Puanxuan to remove liver and clear heat, nourish blood and submerge yang, and it is very effective for the person who suffers from insomnia accompanied by "sweating, five heart-quieting heat, impatience and irritability, and dryness and bitterness of the mouth" [24]. Professor Jia Yingjie used the liver regulation method, and clinically used Chaihu Shuohe San as the base formula, together with medicines to nourish yin and tonify blood to eliminate blood stasis, to ease liver qi to smooth and regulate, so that "the soul returns to the liver, and the spirit is quiet and sleep is obtained" [36].

Chen Zijia et al. found a positive correlation between people with qi-depressed constitution and tumour-related insomnia [37]. Chaihu plus Longbones and Oysters Tang takes Shaoyang as the pivot, which has the meaning of reconciling Shaoyang and tranquilising the mind. Zhuang Genghui et al. found that Chaihu plus Longbones and Oysters Tang can regulate emotional symptoms such as CRI and depression by reversing the HPA axis, and Baicalin in *Scutellaria baicalensis* has anti-tumour effects, which provides the possibility for patients to reduce the dependence on hypnotic drugs, and further improves the quality of life of patients with tumours [38].

4.3. External Treatment of Traditional Chinese Medicine

According to Wu Shi Ji, "The theory of external treatment is the theory of internal treatment, and the medicine of external treatment is the medicine of internal treatment; what is different is the method. " External treatment method and internal treatment method is only different from the method and way of giving medicine, focusing on meridians, guided by the theory of traditional Chinese medicine and the theory of medicinal properties. Commonly used external therapies include acupoints, massage therapy, acupuncture, moxibustion, auricular acupuncture points, and so on.

Acupoints are medicines made into paste directly on the surface of the skin, and the medicines directly reach the lesions through the skin coupling, mostly taking medicines to calm the mind, transport the heart and kidney, and regulate yin and yang, together with the selection of acupoints such as Yongquan and Sanyinjiao, in order to pass the meridian and help sleep. Studies have shown that the "holistic concept of traditional Chinese medicine" as the guidance of the introduction of yang into the yin massage with silent therapy, Tianmen, Yintang, the sun, Baihui, Fengchi and other acupoints for gentle massage, can be achieved to open the meridians and collaterals, open the acupoints, activate the qi and blood, regulate the yin and yang, and calm and tranquillise the role of the spirit [39]. Moxibustion therapy also has obvious efficacy in improving insomnia in tumour patients. Moxibustion has the function of dispelling yin and cold, warming the meridians and collaterals, and selecting Qihai, Guanyuan, Yongquan and several other acupoints for moxibustion, it can achieve the effect of warming luck and blood, warming the yang and helping to sleep [40]. Traditional Chinese medicine gongfu such as eight-duanjin, massage combined with health maintenance gongfu, acupuncture combined with Yi Jin Jing gongfu exercise, guiding, taiji piling gong and other interventions do not sleep, and it was found that these therapies are not only easy to learn and easy to practice for CRI patients without the adverse effects of drugs, but also can improve the psychoemotional problems of patients with malignant tumours to a certain extent [41].

Clinical randomised controlled trials have shown that acupuncture is comparable or even superior to conventional drug or hormonal therapies, and the use of acupuncture for insomnia and through neurobiochemical mechanisms suggests that acupuncture can increase the release of serotonin 5-hydroxytryptophan and decrease glutamate, which has an excitatory effect, and thus triggers sleep [42-43]. Double-blind experiments have shown that electroacupuncture can be used to treat cancer-related insomnia without significant side effects, and even reduce the adverse effects caused by radiotherapy [44]. In addition, the ear, as the convergence of the human body, can be stimulated by stimulating the corresponding acupoints and reaction points to achieve a certain therapeutic effect, and studies have shown that stimulation of acupoints in the ear and stimulation of the corresponding neural nuclei can regulate the function of the central nervous system and the rate of cerebral arterial blood flow in order to improve the state of sleep [45]. Another Meta-analysis showed that qigong and taiji could improve the sleep quality of tumour patients [46].

5. Discussion

Insomnia in patients with malignant tumours is often the result of a variety of factors. Tumour patients are affected by a variety of factors such as the disease itself and therapeutic measures, and often suffer from sleep disorders, which affects patients' quality of life, confidence in treatment, and the development of prognosis. The treatment of short-term insomnia in western medicine lies in the elimination of triggers and self-regulation. For patients with chronic insomnia, it is difficult to maintain the therapeutic effect of long-term medication, and there is a lack of long-term clinical controlled studies. Due to the risk of cancer and the different physique of patients with tumour-associated insomnia, Chinese medicine's idea of "three-cause systematic treatment" reflects the advantages of Chinese medicine, which is based on the principle of diagnosis and treatment and stresses that "the formula follows the method, and the method follows the evidence", and can be flexibly applied according to individual differences and dynamic changes of symptoms at various stages of disease. It can flexibly change the medication according to individual differences and the dynamic changes of symptoms at each stage of the disease, and can also use acupuncture, massage, medicinal baths and health-care techniques to supplement the treatment and regulate the human body as a whole. However, the problem is that most of the clinical studies have small sample sizes and lack of randomised controlled trials with large samples, and there are large differences in individual medication, making it difficult to obtain a consensus and lacking a systematic overview. Therefore, the combination of Chinese and Western medicine in the treatment of tumour-related insomnia, so that the advantages of Chinese medicine treatment and the efficacy of Western medicine treatment can be rapidly combined to jointly reduce the symptoms of CRI patients and improve their quality of life, still needs to be actively explored.

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