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Research Progress on Taxol-Induced Acute Pain Syndrome

Yajing Li[1], Xiaoyan Zhou[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China
**Correspondence Author*

Abstract: ***Taxane-induced acute pain syndrome is an adverse reaction that occurs during the use of taxane-based drugs, which has a great impact on patients' quality of life and can lead to treatment interruption, thereby affecting the overall treatment effect. This article aims to review the pathogenesis, clinical manifestations, and treatment strategies of taxane-induced acute pain syndrome, providing reference for clinical treatment and being of great significance for improving the treatment effect and quality of life of cancer patients.***

Keywords: Taxane-induced Acute Pain Syndrome, Muscle and joint pain, Modern medical treatment, Traditional medical treatment**.**

1. Introduction

As a crucial chemotherapeutic agent, taxanes are extensively used in clinical treatment for various solid tumors including lung cancer, ovarian cancer, breast cancer, and head and neck cancers due to their remarkable biological activity and unique antitumor mechanisms [1]. Currently marketed taxane-based anticancer drugs include paclitaxel and docetaxel, along with derivatives such as liposomal paclitaxel, albumin-bound paclitaxel, and the emerging polymerized paclitaxel colloid beads [1]. These medications may cause adverse reactions affecting multiple systems and organs, including hematological, neurological, cardiovascular, digestive, and skin systems [2]. Cumulative neurological adverse reactions encompass peripheral neuropathy (Chemotherapy-induced peripheral neuropathy, CIPN) and taxane acute pain syndrome (TAPS). Notably, TAPS—a specific neurological complication also termed paclitaxel-associated acute pain syndrome (PAPS)—not only compromises patients' quality of life but may also lead to treatment discontinuation and diminished therapeutic outcomes. Therefore, comprehensive understanding of TAPS holds significant clinical importance.

2. Pathogenesis of TAPS

The exact pathogenesis of TAPS remains unclear. Current research indicates that the occurrence of taxane acute pain syndrome (TAPS) is primarily associated with neurotoxicity and inflammatory immune responses induced during taxane drug administration.

Taxanes disrupt microtubule protein polymerization and depolymerization, impairing normal neuronal function and leading to neuropathy and pain. An observational study involving 18 patients confirmed that TAPS originates from nociceptive dysfunction in the nociceptor system or spinal thalamic pain pathways. Subsequent animal models revealed detectable cellular injury markers in peripheral nerves shortly after paclitaxel administration [4]. Additionally, taxanes may exacerbate pain symptoms through inflammatory and immune responses. A foreign study demonstrated that interleukin-1β (IL-1β) released by microglia initiates enhanced glutamatergic activity in the spinal dorsal horn during taxane-related acute pain syndrome. As a key molecule mediating TAPS development, IL-1β activates microglia-like receptor 4 (TLR4) to modulate astrocyte and neuronal functions. Targeting the signaling pathway regulating microglial IL-1β production and function represents a potential therapeutic strategy for developing analgesics against TAPS [3].

3. Clinical Manifestations of TAPS

According to statistics, the incidence rate of TAPS ranges from 2.8% to 72% [1]. The primary manifestation is muscle and joint pain, which presents as a diffuse pattern throughout the body, particularly more pronounced below the knees. This adverse reaction typically occurs within 1-3 days after medication administration and generally lasts 5-7 days [5], with symptoms subsiding within a week. A 2024 report on acute pain syndrome caused by paclitaxel injection mentioned a case of cervical squamous cell carcinoma metastasis patient who developed TAPS during a 4-cycle chemotherapy regimen (specific medications: paclitaxel 300mg ivd d1 + cisplatin 30mg ivd d1, 50mg ivd d2 + camrelizumab 200mg ivd d1, q21d). The patient reported diffuse pain in both lower limbs 3 days after the second cycle of chemotherapy, persisting for one week. Notably, this symptom exclusively occurred after paclitaxel administration. The case noted that TAPS may not exclusively manifest as peripheral neuropathy and does not exhibit cumulative dose effects, typically recurring with subsequent treatments [6]. Peripheral neuropathy differs from paclitaxel acute pain syndrome (CIPN), a common neurotoxicity of taxanes with an incidence rate of 70%-80%. Clinically, symptoms predominantly involve sensory and reflex abnormalities in hands and feet, such as numbness, pain, and weakness [7]. Peripheral neuropathy typically shows cumulative dose effects, worsening with increased dosage and prolonged treatment duration, with a drug threshold of approximately 1000mg/m² [1]. Different drugs in the purple stannane class exhibit varying rates of peripheral neuropathy depending on their chemical structures and administration methods. Preventive measures for peripheral neuropathy include cryotherapy (such as ice gloves or socks) or compression gloves, while therapeutic options may involve antidepressants like duloxetine [8]. However, current medical research still lacks effective treatment methods and targeted preventive strategies for TAPS, failing to adequately address patients 'and families' urgent needs for pain relief and risk

reduction.

4. Current Treatment Status of TAPS

4.1 Modern Medical Approaches

4.1.1 Preventive Medications

To reduce the incidence and severity of TAPS, clinicians routinely use nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids as preventive measures. NSAIDs primarily inhibit cyclooxygenase (COX) to disrupt arachidonic acid metabolism, thereby reducing prostaglandin (PG) synthesis and suppressing pain and inflammatory responses [9]. A randomized controlled trial demonstrated that preventive oral etoricoxib significantly decreases docetaxel-induced TAPS incidence and severity while improving patients' quality of life and neurotoxicity [10]. Etoricoxib, a selective COX-2 inhibitor, works by targeting COX-2 activation induced by inflammatory mediators, which promotes PG synthesis [9]. Its high selectivity and inhibitory effect on COX-2 enable precise antipyretic, analgesic, and anti-inflammatory effects, showing proven efficacy in managing acute and chronic pain [11]. Furthermore, a 2019 retrospective study demonstrated that continuous dexamethasone administration for three days after chemotherapy could prevent TAPS, particularly effective in high-dose albumin-bound paclitaxel-treated patients [12]. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), dexamethasone not only suppresses inflammatory responses but also alleviates pain by modulating the neuroendocrine system.

In summary, NSAIDs and glucocorticoids contribute critical strategies for preventing TAPS through their distinct mechanisms and pathways, while providing valuable references for optimizing preventive measures. When chemotherapy patients receive paclitaxel-based regimens, preemptively using these medications can serve as preventive interventions against acute pain syndrome. This approach reduces patient discomfort, facilitates treatment progression, creates favorable conditions for recovery, and offers a practical clinical strategy to advance the prevention and management of chemotherapy-related complications.

4.1.2 Therapeutic Management

For patients with established TAPS, symptomatic treatment remains the primary approach to relieve pain. Following acute pain syndrome onset, NSAIDs such as diclofenac sodium enteric-coated dual-release capsules may be administered based on patient tolerance without paclitaxel discontinuation [13]. However, since taxanes often cause gastrointestinal discomfort and other side effects, it is particularly important to choose NSAIDs with fewer gastrointestinal side effects, such as celecoxib. Additionally, patients 'pain levels should be assessed, and analgesics should be administered according to the WHO's "three-step" analgesia principle based on varying pain severity. When using weak opioids and strong opioids, strict control of morphine dosage is essential, along with close monitoring and follow-up care.

However, in TAPS treatment, Western medical approaches have certain limitations due to the scarcity of available medications. Traditional medicine, however, possesses unique theoretical systems and diverse treatment methods that emphasize syndrome differentiation and holistic concepts. Through TCM regulation, acupuncture, massage, moxibustion, and other approaches, it focuses on restoring internal balance and enhancing the body's self-regulation and repair capabilities. Therefore, combining traditional and modern medical approaches can be adopted in treatment. TCM not only compensates for the shortcomings of Western medical treatments but also provides patients with more comprehensive, integrated, and personalized therapeutic plans.

4.2 Traditional Medical Treatment

4.2.1 Syndrome Differentiation

TAPS patients primarily present with knee joint pain, which traditional medicine categorizes under the TCM syndrome "Bi Shi". In traditional Chinese medicine (TCM), arthralgia typically manifests as limb pain, numbness, and restricted mobility [14]. The pathogenesis of this condition is primarily attributed to "pain from obstruction" and "pain from malnutrition". TCM theory posits that qi and blood serve as vital nourishment for human tendons, vessels, and joints. When their circulation becomes obstructed or weakened, these tissues fail to receive adequate nourishment, ultimately leading to arthralgia-a classic example of "pain from obstruction" [15]. Cancer patients often experience prolonged internal struggles between pathogenic factors and body's defenses. Over time, this leads to deficiency of vital energy (zhengqi), yang qi depletion, and yin blood insufficiency. Additionally, most require multiple treatments like surgery, radiotherapy, and chemotherapy to alleviate symptoms, which further weaken the body's defenses and deplete qi-blood reserves [13], creating vulnerabilities for pathogenic invasion. Professor Huang Jinchang, building on TCM principles, identifies TAPS (Therapeutic Arthralgia Syndrome) through two mechanisms: spleen-stomach deficiency and cold-dampness obstruction in meridians. He proposes therapeutic strategies focusing on regulating spleen-stomach functions to eliminate dampness and nourish tendons. He emphasizes that cancer patients already have weakened spleen-stomach systems, making them prone to dampness accumulation. Since taxane drugs are predominantly cold-natured, their use exacerbates yang qi deficiency in these systems. This deficiency disrupts fluid metabolism and distribution, generating cold-dampness that obstructs meridians and impairs qi-blood circulation, ultimately causing joint pain [16]. A randomized controlled trial in 2021 demonstrated that combining Guizhi Fuzi Decoction with three-step analgesic therapy significantly outperformed monotherapy for taxane-induced acute pain syndrome [17]. In a 2023 study, Pu Huali and colleagues further confirmed through randomized controlled trials that combining Ren Shen Baidu San with diclofenac sodium enteric-coated dual-release capsules not only improved TAPS pain relief rates but also effectively shortened the duration of discomfort [13]. These combined treatment regimens collectively reveal that oral administration of traditional Chinese herbal decoctions shows remarkable efficacy in managing acute pain syndrome caused by taxane medications. This new treatment method brings hope to patients and provides new ideas and

methods for clinical treatment.

4.2.2 Traditional Chinese External Therapies

In the evolution of TCM theory, acupuncture and moxibustion comprise two primary treatment modalities. The needle technique originates from "penetrating with a sharp point," while moxibustion stems from "warming through direct application" [18]. This therapeutic approach is characterized by safety, efficacy, painlessness, and minimal side effects, with extensive clinical studies demonstrating its remarkable analgesic properties [19]. The mechanism of acupuncture can be summarized as three key aspects: unblocking meridians, harmonizing yin-yang balance, and strengthening vital energy to expel pathogens [20]. Therefore, acupuncture effectively regulates qi flow and mental states, achieving pain relief by addressing both the source of discomfort and its manifestation [21]. Xu Shengyan et al. proposed three additional dimensions for acupuncture's pain management: first, identifying root causes through syndrome differentiation to eliminate pain triggers; second, disrupting pathological mechanisms by promoting qi circulation and blood flow to achieve "smooth flow without pain"; and third, providing symptomatic relief through calming techniques to soothe the mind [22]. When selecting acupoints, practitioners should integrate proximal and distal acupoints based on syndrome differentiation, strategically applying "Wushi points," Yuan points, and Shu points to maximize analgesic effects [22]. Modern medicine attributes acupuncture's pain-relieving mechanism to its regulation of neural pathways, humoral systems, and enzymatic functions [21]. When applying TAPS therapy, Professor Huang Chang strategically selects acupoints that warm and tonify spleen yang while strengthening bones and generating marrow. For instance, the Zhongshu point achieves dual therapeutic effects by harmonizing bodily functions and promoting bone health. The Liangqiu point fortifies the spleen and stomach, providing effective warming and tonification for the middle energizer. The Ashi point alleviates discomfort at pain sites while facilitating meridian energy flow [16]. Additionally, combining moxibustion at the Zhongwan point enhances meridian warming and cold-dampness elimination [16]. Through these multidimensional acupoint selection and therapeutic approaches, comprehensive TAPS treatment can be achieved from various therapeutic angles.

5. Summary

Taxane acute pain syndrome (TAPS) is a common toxic side effect of taxane chemotherapy drugs, significantly impacting patients 'quality of life. Through comprehensive approaches including preventive medication, therapeutic interventions, and traditional therapies like herbal decoctions and acupuncture, we can effectively control the occurrence and progression of TAPS. However, numerous challenges and unresolved issues remain. First, the exact pathogenesis of TAPS has not been fully elucidated. Second, there is currently a lack of specific therapeutic agents and methods targeting TAPS, necessitating the development of new treatment strategies and medications to meet clinical demands. Additionally, we should truly integrate traditional Chinese and Western medicine to provide precision treatment tailored to individual patient conditions. With ongoing advancements in TAPS research and technological progress, we are confident that more breakthroughs will be achieved in TAPS prevention, diagnosis, and treatment, ultimately improving cancer patients' therapeutic outcomes and quality of life.

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