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Treatment of Triple Negative Breast Cancer by Compound Matrine Injection Combined with Paclitaxel

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Abstract: Objective triple-negative breast cancer was described, and the newly published treatment status of the compound matrine injection combined with paclitaxel for triple-negative breast cancer was briefly described. Methods "Triple-negative breast cancer, compound the matrine injection, paclitaxel, treatment" were used as Chinese keywords. Using "Triple Negative Breast Cancer, compound Kushen injection, Paclitaxel PTX and treatment" as English keywords, a systematic search was conducted on CNKI and PubMed databases. Inclusion criteria: (1) Basic overview of triple-negative breast cancer; (2) basic treatment methods of triple-negative breast cancer; (3) Exclusion criteria for the treatment of breast cancer by compound the matrine injection combined with paclitaxel: the literature with obsolete data and low credibility were finally included in 21 pieces of literature for analysis.

Keywords: Triple-negative breast cancer, Compound the matrine injection combined with paclitaxel, Combination therapy, Review literature.

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1. Introduction

Breast cancer (CB) is a phenomenon of uncontrolled proliferation of breast epithelial cells under the action of various carcinogenic factors [1]. There are no obvious symptoms in the early stage of the disease. Then it can be manifested as breast lumps, breast skin abnormalities, such as "orange peel sign" or "dimple sign", and nipple discharge during non-pregnancy or breastfeeding, etc. With the deterioration of the disease, cancer cells invade the surrounding lymphatic tissue, liver, lung, seriously threatening the life and health of patients [2]. It is estimated that there will be 2.26 million new breast cancer cases worldwide in 2020 and about 680,000 deaths from breast cancer. Among them, the number of new breast cancer cases in China has reached 410,000, accounting for about 1/5 of the global total, and since 1990, the incidence rate of breast cancer in China has increased by more than twice the global rate [3]-high morbidity and mortality.

Clinical treatments for breast cancer include surgery, endocrine therapy, adjuvant chemotherapy, radiation therapy and targeted therapy [4]. However, there are still many difficulties, the same stage of disease, the same treatment, but the prognosis is very different, indicating the heterogeneity of the tumor and different biological characteristics. Surgical indications for radical breast cancer were in TNM stage 0, stage I, stage II and stage III without surgical contraindications. Indications for breast-conserving surgery are ① Patients with early breast cancer and breast preservation needs. ② Patients in clinical stage I and stage II with maximum tumor diameter ≤3 cm, and suitable breast volume and good breast shape can be retained after surgery. ③ Patients in clinical stage III (except inflammatory breast cancer) who meet the criteria for breast preservation after the neoadjuvant chemotherapy can also be carefully considered. General surgical treatment of breast cancer has developed to the middle stage, and patients are relatively weak, may have metastases, and easy to relapse after surgery; once recurrence it will give patients greater psychological pressure and treatment difficulty. At present, endocrine therapy is only suitable for some breast cancer patients with positive expression of hormone receptors, and its therapeutic effect is also closely related to the positive expression rate of hormone receptors. The treatment cycle is longer, even taking five years, and some even more than ten years [5]. The disadvantages of adjuvant chemotherapy are more obvious. Breast cancer chemotherapy is very harmful to the body, and chemotherapy drugs will kill normal cells while killing cancer cells, resulting in various complications such as low white blood cells, bone marrow suppression, nausea and vomiting, and weight loss in patients [6]. The survival rate after treatment is unsatisfactory and can not reach the ideal level. At present, early diagnosis is still the primary means to prevent the malignant transformation of breast cancer. Still, due to the influence of various reasons, the detection rate of in-situ cancer in China is low, and most of the cases develop rapidly after being diagnosed with breast cancer.

Traditional Chinese medicine has developed rapidly in recent years and has gradually occupied a certain proportion in cancer treatment. Some drugs with clear inhibitory effects on tumor cells gradually enter the clinic, and drug dosage forms are constantly enriched. Although most studies of Chinese medicine mainly focus on postoperative intervention, the treatment of any disease is not only the treatment process but also the prognosis of the disease, which also reflects various inhibitory effects of Chinese medicine on cancer cells in the process of postoperative intervention. These include relieving upper limb edema, relieving nausea and vomiting, preventing cardiotoxicity caused by chemotherapy, improving immune function, attenuated and synergistic effects, and anti-recurrence and metastasis effects [7]. It can be seen that the application of traditional Chinese medicine in the treatment of breast cancer is worthy of affirmation and further study.

This article introduces the mechanism of action of compound matrine injection combined with paclitaxel in treating triple-negative breast cancer, and regulates triple-negative breast cancer by acting on specific targets and specific pathways.

2. Treatment of triple-negative breast cancer by compound the matrine injection combined with paclitaxel

2.1 Compound Kushen injection

Compound Kushen injection (CKI) comprises matrine and pia coia extract, which can clear heat and dampness, cool blood, detoxify, and relieve pain [8]. Modern studies have shown that CKI is a compatible chemotherapy drug, and oxymatrine, with high content and anti-tumor activities, can interfere with the cell cycle of breast cancer and induce apoptosis. Its pharmacological complexity is of great significance for effectively blocking tumor migration and invasion [9], and can enhance the therapeutic effect in clinical tumor treatment, enhance the body's immunity and improve cancer pain. Enhance chemotherapy tolerance, etc. [10]. Compound the matrine injection has different effects on different tumors. According to the analysis of modern molecular biology techniques[7], in the treatment of gastric cancer, compound the matrine injection can inhibit the proliferation of gastric cancer cells SGC-7910 in a time-concentration dependent manner and can induce the apoptosis of human gastric cancer cells SGC-7901. The mechanism of action is enhanced regulation of Bak and Caspase-3 protein expression [12]. In treating liver cancer, compound the matrine injection can inhibit the growth of BEL27402, SMMC-7721, HepG2 and other liver cancer cells and directly kill liver cancer cells. Studies have shown that after using compound the matrine injection in liver cancer patients, the alanine aminotransferase level will significantly decrease, which plays a role in protecting liver cells. It can reduce the effect of chemotherapy drugs on normal liver cells [13]. Therefore, compound the matrine injection has been widely used in the adjuvant treatment of cancer, which can be combined with conventional analgesics, chemotherapy, and radiotherapy to relieve pain, reduce side effects, and improve patients' quality of life.

2.2 Paclitaxel

Paclitaxel is a crucial anticancer drug in highly toxic diterpenoid natural products called taxoid alkaloids. Paclitaxel was first isolated from a plant called California evening primrose in the Pacific Northwest, and later found to also be present in the bark of the spruce tree, is a tricyclic diterpenoid drug with anti-cancer activity, and was listed in the Chinese Clinical Oncology Society (CSCO) Breast Cancer Diagnosis and Treatment Guideline 2022. Paclitaxel has been the grade I recommendation for neoadjuvant therapy for HER-2 positive breast cancer, and combined with paclitaxel chemotherapy has become the basic program of neoadjuvant therapy for HER-2 positive breast cancer. As a new drug in chemotherapy, it can prevent cell mitosis by disrupting the spindle formation in normal mitosis. To a certain extent, it can effectively control the spread and metastasis of tumor cells [14]. Paclitaxel has a broad spectrum of anti-tumor activity, especially for breast, ovarian, lung, gastric, and other malignant tumors. It also blocks cancer development in vitro and in vivo by inhibiting the proliferation of tumor cells, preventing carcinogenic stimulation, activating cell cycle arrest, and inducing apoptosis through different signaling pathways.

Paclitaxel is commonly used in chemotherapy regimens and can be used alone or in combination with other chemotherapy agents. It can be administered intravenously or delivered to the tumor site through interventional perfusions, local injections, etc. The dose and treatment regimen will depend on the tumor type, stage, and patient's condition. The application of paclitaxel may bring some side effects, such as myelosuppression (resulting in decreased platelet, red blood cell, and white blood cell), neurotoxicity (causing peripheral neuropathy and paresthesia) , digestive system reaction, skin reaction, etc. [15]. Therefore, before using paclitaxel, doctors assess the patient's physical condition and closely monitor and manage potential side effects.

Paclitaxel binds to microtubules, rather than tubulin dimers, and stabilizes microtubules (polymerization) by promoting the assembly of the microtubule's building units, alpha and beta microtubule subunits. The drug reduces the critical concentration of tubulin required for its assembly, thus promoting the elongation of the tubulin polymer. Moreover, the therapeutic effect of paclitaxel on breast cancer depends on its concentration, and the mechanism of PTX cytotoxicity is highly dependent on the concentration of the drug in cells, which has been confirmed in vitro studies. Giannakakou et al. showed that after treatment with PTX concentrations higher than 12 nM, the proliferation of lung cancer cell line A549 and breast MCF-7 cells was reduced, leading to G2/M block, and lower concentrations of PTX (3 to 6 nM) had similar potential to inhibit cancer cell proliferation, leading to programmed cell death.

Apoptosis plays an important role in the development and treatment of the tumor. Cancer is a condition of apoptosis dysfunction, which leads to the non-death of malignant cells. The mechanism of apoptosis is complex and involves multiple pathways. A large number of literature has shown

that targeting the apoptosis of tumor cells is feasible [16]. Among them, many proteins are related to apoptosis of tumor cells, including c-myc (proto-oncogene c-myc encodes a transcription factor c-myc, which plays a vital role in controlling cell growth and vitality. Several mechanisms tightly control the amount of c-Myc, and interactions with other regulatory proteins regulate the action of its inducing and inhibiting genes [17]. Pharmacological inhibitors of CDK4/6 (cyclin-dependent kinases 4 and 6 (CDK4/6)) have recently entered the therapeutic domain of clinical oncologists. The main mechanism of action is inhibition of retinoblastoma (RB) protein phosphorylation, thereby inducing cell cycle arrest, with which CDK4/6 inhibitors alter cancer cell biology in other ways [18], RB1 (recent studies have highlighted the importance of RB1 tumor suppressor as a cancer therapeutic target. RB1 regulates cell cycle progression, represents the downstream target of clinically used cyclin-dependent kinase (CDK) 4/6 inhibitors, affects tumor immune properties and microenvironment, and can enhance susceptibility to immunotherapy [19]), TP53 (the main purpose of TP53 protein is tumor inhibition，the tumor inhibition function may be mediated through multiple synergistic functions, rather than through a single pathway or a single transcriptional target [20]), PTEN (the protein encoded by the PTEN gene has protein phosphatase and lipid phosphatase activity, and is the first tumor suppressor gene with phosphatase activity. PTEN is the main negative regulator of PI3K/Akt pathway) and PIK3CA (PI3K/AKT signal transduction pathway is an important intracellular signal transduction pathway. HER-2 overexpression can lead to the activation of PI3K/AKT signaling pathway, and PIK3CA gene is an important proto-oncogene in the PI3K pathway [21], and KRAS (KRAS gene is a GDP/GTP binding protein. KRAS is activated when it binds to GTP and turns off when it binds to GDP. KRAS can be temporarily activated by growth factors or tyrosine kinases (such as EGFR), and the activated KRAS can activate the downstream signaling pathway, such as PI3K-AKT-mTOR, which controls cell generation. As well as the RAS-RAF-MEK-ERK signaling pathway that controls cell proliferation, mutant KRAS will be continuously activated without activating kinases such as EGFR, resulting in continuous cell proliferation and cancer [22]).

3. Discussion

cck-8 method was used to detect the killing activity of combination drugs on breast cancer cells, scratch test to explore the migration ability of breast cancer cells, Western Blot test to detect protein expression, immunohistochemical test to determine intracellular antigens (polypeptides and proteins), and to locate, qualitatively and relatively quantitatively. The protein expression related to breast cancer cell apoptosis was determined to provide a new theoretical basis for the clinical application of the matrine injection compound combined with paclitaxel.

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