Journal of Pharmaceutical and Medical Research
Print ISSN: 2663-1954
Online ISSN: 2663-1962
DOI: https://doi.org/10.61784/jpmr3068

THEORETICAL EXPLORATION OF YIQI HUAYU JIEDU THERAPY COMBINED WITH TRASTUZUMAB AND CHEMOTHERAPY IN THE TREATMENT OF ENDOMETRIAL CANCER

MengXin Xu, Lei Liu*
College of Integrated Chinese and Western Medicine, Jining Medical University, Jining 272067, Shandong, China.
**Corresponding Author: Lei Liu*

Abstract: Endometrial cancer is a common female reproductive system malignancy with rising morbidity and mortality annually. Trastuzumab combined with paclitaxel and carboplatin chemotherapy is the standard regimen for HER2 - positive endometrial cancer, exerting anti - tumor effects by blocking HER2 signaling, inhibiting JAK/STAT pathway activation, and downregulating PD - L1 expression. However, it has limitations such as severe adverse events and acquired drug resistance. According to TCM theory, endometrial cancer is related to "beng lou" and "zheng jia", with a core pathogenesis of vital qi deficiency and retention of damp - heat, blood stasis, and toxin in the uterus. Yiqi Huayu Jiedu therapy, a classic TCM anti - tumor regimen, can regulate the tumor microenvironment, reduce inflammatory mediator levels, and reverse drug resistance with few adverse reactions. This review summarizes the mechanisms and limitations of trastuzumab plus chemotherapy, analyzes the synergistic effects of combined TCM and Western medicine treatment, and shows that Yiqi Huayu Jiedu therapy can alleviate treatment - related toxicities and enhance anti - tumor sensitivity. This combined regimen integrates TCM holistic concepts with modern precision medicine, offering a novel strategy for HER2 - positive endometrial cancer, which is of great value for improving patient survival and quality of life.
Keywords: Endometrial cancer; Yiqi Huayu Jiedu therapy; Trastuzumab; Chemotherapy

1 INTRODUCTION

Endometrial cancer is one of the most common malignant tumors of the female reproductive system, with its morbidity and mortality increasing year by year. Statistics show that the incidence of endometrial cancer ranks second among all gynecological malignancies, second only to cervical cancer [1]. Approximately 70% of patients are diagnosed with lesions confined to the endometrium, with a favorable prognosis and a 5-year survival rate of 80-90% [2]. However, for patients with recurrent or metastatic endometrial cancer, the prognosis is significantly worse, with a 5-year survival rate of less than 20% [3]. The treatment of recurrent and metastatic endometrial cancer is challenging, mainly due to poor tolerance to traditional treatments (such as surgery, radiotherapy, and chemotherapy) and high incidence of multidrug resistance. With the rise of tumor immunotherapy, immune checkpoint inhibitors (such as PD-1/PD-L1 inhibitors) have demonstrated significant efficacy in the treatment of various cancers. However, their response rates and durability as monotherapy still require improvement.Although existing treatment methods have extended patient survival to some extent, their efficacy remains limited and accompanied by significant side effects. Surgery is typically suitable for early-stage localized endometrial cancer, but its effectiveness is often unsatisfactory for advanced recurrent or metastatic cases. Radiotherapy and chemotherapy serve as the primary treatment modalities, yet they induce severe side effects, including myelosuppression, gastrointestinal reactions, neurotoxicity, and others, leading to a marked decline in patients' quality of life [4]. Traditional Chinese medicine (TCM)for replenishing qi, resolving stasis, and detoxifying can exert anti-tumor effects through multiple pathways such as regulating immune function and improving blood circulation. This paper theoretically explores the combined therapeutic effects and mechanisms of the qi-replenishing, stasis-resolving, and detoxifying method in conjunction with the immune checkpoint inhibitor trastuzumab and chemotherapeutic agents (paclitaxel and carboplatin) in endometrial cancer, aiming to provide new insights and approaches for integrated traditional Chinese and Western medicine in clinical treatment.

2 APPLICATION OF TRASTUZUMAB IN ENDOMETRIAL CANCER TREATMENT

In recent years, immune checkpoint inhibitors have achieved significant progress in the treatment of various malignant tumors. Among them, pembrolizumab and nivolumab, as inhibitors of the PD-1/PD-L1 pathway, have been widely used in clinical practice, particularly demonstrating remarkable efficacy in patients with endometrial cancer exhibiting microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR) [5,6]. Immune checkpoint inhibitors block the binding of PD-1 to PD-L1, thereby relieving suppression of T cells and restoring and enhancing the body's antitumor immune response. However, the response rate of immune checkpoint inhibitors as monotherapy remains low, with some patients developing treatment resistance and potential severe immune-related adverse events (irAEs), such as inflammatory reactions in the skin, gastrointestinal tract, liver, and endocrine system. These side effects limit their

clinical application [7]. Combining immune checkpoint inhibitors with other therapeutic approaches, such as targeted therapy and chemotherapy, can improve efficacy and reduce side effects. Additionally, exploring biomarkers to predict patient response to immune checkpoint inhibitors and optimizing patient selection can enable more personalized treatment strategies [8].

Trastuzumab is a monoclonal antibody targeting HER2, widely used in the treatment of HER2-positive breast cancer and gastric cancer, and has also shown certain efficacy in HER2-positive endometrial cancer in recent years [9]. It inhibits tumor cell proliferation by blocking the HER2 receptor. After treatment, tumor shrinkage and disease control are achieved in some patients, leading to improved prognosis [10]. However, trastuzumab may cause cardiotoxicity and is associated with high treatment costs [11]. Paclitaxel and carboplatin are common chemotherapeutic agents, which inhibit the growth of cancer cells by interfering with microtubule assembly and binding to DNA, and are widely used in the treatment of endometrial cancer [12]. They exert highly efficient anti-cancer effects through synergistic action, but have significant toxic and side effects, such as myelosuppression, gastrointestinal reactions and neurotoxicity, resulting in poor tolerance in patients, and some patients even develop drug resistance [13]. In addition, abnormal activation of the JAK/STAT and PD-L1/PD-1 pathways is closely related to the occurrence and progression of endometrial cancer [14]. Lailler et al. found that the combination of paclitaxel and carboplatin significantly improved the therapeutic effect in patients with head and neck squamous cell carcinoma by inhibiting the abnormal activation of the JAK/STAT pathway [15]. A study by Rojkó et al. showed that the combination of paclitaxel and carboplatin significantly improved the therapeutic outcome of lung cancer by reducing PD-L1 expression on the surface of tumor cells and enhancing T cell activity [16]. Therefore, exploring the combination strategy of trastuzumab and drugs regulating these pathways may improve the therapeutic effect of HER2-positive endometrial cancer, reduce the side effects of chemotherapeutic drugs, and improve patient tolerance.

3 YIQI HUAYU JIEDU THERAPY FOR ENDOMETRIAL CANCER

Traditional Chinese medicine (TCM) posits that the primary pathological factors of tumors are deficiency, phlegm, stasis, and toxin. Among these, deficiency of vital energy (Zheng Xu) is the fundamental pathological factor underlying the occurrence and progression of tumors, while phlegm and stasis are the direct pathological factors contributing to tumor formation. Carcinogenic toxin, specifically parazacco spilurus subsp. spilurus, is the unique pathological factor that drives the development and progression of tumors. On the basis of vital energy deficiency, dysfunction of the internal organs disrupts the normal flow of qi, blood, and body fluids. This leads to the congelation of fluids into phlegm and the stagnation of blood into stasis. The intermingling and binding of phlegm and stasis gradually form accumulations, which over time undergo pathological changes, giving rise to endogenous carcinogenic toxins. This process ultimately results in the occurrence and progression of tumors.Pattern differentiation and treatment is one of the fundamental principles in TCM for tumor management. The etiology and pathogenesis of tumors are complex, influenced by multiple factors including innate predisposition, external causes, internal factors, and therapeutic interventions. Patients' clinical manifestations become increasingly intricate and diverse as the disease progresses. Accurate pattern differentiation enables the identification of key pathogenic mechanisms from a TCM perspective, facilitates the summarization of diagnostic and therapeutic patterns, and supports prognosis assessment. Proper pattern differentiation and treatment are crucial for improving clinical efficacy.

TCM does not have a specific disease name for "endometrial cancer," which bears resemblance to the descriptions of "metrorrhagia and metrostaxis," "multicolored vaginal discharge," and "female abdominal masses (women's abdominal masses)" in ancient TCM medical texts. It is primarily caused by the dysfunction of the spleen, liver, and kidneys, leading to qi stagnation and blood stasis, meridian blockage, and the accumulation of damp-heat, stasis, and toxins in the uterus. Modern clinical studies have found that most patients with endometrial cancer exhibit a deficiency of vital qi due to postoperative conditions, radiotherapy, or chemotherapy, resulting in a pathological mechanism characterized by a combination of dampness, heat, stasis, and toxins with underlying deficiency and superficial excess. TCM adopts a holistic approach to syndrome differentiation and treatment, with herbal medicine demonstrating minimal adverse reactions in treating endometrial cancer. It holds certain advantages in preventing cancer progression, recurrence, and metastasis of endometrial cancer, as well as in comprehensive treatment during perioperative, radiotherapy, and chemotherapy periods[17-18]. The commonly used Chinese herbs in the method of replenishing qi, resolving stasis, and detoxifying mainly include Astragalus membranaceus, Pseudostellaria heterophylla, Dioscorea opposita, Curcuma zedoaria, Persicae Semen, Moutan Cortex, white peony root, Red Peony Root, Coix Seed, Poria, Aconitum carmichaelii, Fritillaria thunbergii, Scutellaria baicalensis, Hedyotis diffusa, Paris polyphylla, and Phellodendron amurense.Studies have found that Yiqi Huayu Jiedu therapy for endometrial cancer can reduce the levels of postoperative tumor markers and inflammatory mediators, and improve the clinical remission rate [19-20].

4 APPLICATION OF COMBINATION THERAPY IN CANCER TREATMENT

Combination therapy plays a critical role in cancer treatment. By integrating the advantages of traditional Chinese medicine (TCM) and Western medicine, it can significantly improve therapeutic efficacy, reduce drug toxicities, and enhance patient tolerance and quality of life [21]. Trastuzumab, as a monoclonal antibody targeting the HER2 receptor, precisely targets tumor cells, and in combination with the chemotherapeutic effects of paclitaxel and carboplatin, further inhibits tumor cell proliferation and metastasis, demonstrating synergistic therapeutic effects. A meta-analysis showed

that Huangqi (Astragalus membranaceus), a qi-invigorating Chinese herb, combined with platinum-based chemotherapy, has favorable efficacy and safety in the treatment of advanced gastric cancer [22]. Huangqin (Scutellaria baicalensis), a heat-clearing and detoxifying Chinese herb, combined with immune checkpoint inhibitors (such as PD-1 or PD-L1 inhibitors) plus paclitaxel and carboplatin chemotherapy, has shown significant efficacy in the treatment of non-small cell lung cancer [23]. Through its main active components baicalin and baicalein, Scutellaria baicalensis enhances the immune system's recognition and attack on tumor cells, while alleviating chemotherapy-induced inflammatory responses and oxidative stress [24]. Immune checkpoint inhibitors relieve tumor-mediated immunosuppression, enabling immune cells to attack tumors more effectively. When combined with chemotherapeutic agents paclitaxel and carboplatin, they can significantly improve tumor response rates and patient survival [25]. These studies indicate that the combination of TCM and modern therapeutic modalities has significant synergistic effects. In summary, Yiqi Huayu Jiedu therapy combined with trastuzumab and chemotherapy may have great potential in the treatment of endometrial cancer.

5 CONCLUSION

There is an urgent need for novel therapeutic strategies for endometrial cancer to improve clinical efficacy, prolong patient survival, and reduce treatment-related adverse events. Yiqi Huayu Jiedu therapy, as a classic TCM anti-tumor treatment principle, exerts anti-tumor effects through multiple pathways and represents an effective adjuvant treatment modality. The combination regimen of Yiqi Huayu Jiedu therapy, trastuzumab and chemotherapeutic agents is expected to significantly improve the therapeutic efficacy and quality of life of patients with endometrial cancer.

The cognitive differences between TCM and Western medicine have permeated the entire history of medicine and the transformation of medical paradigms, from theoretical foundations to clinical thinking, each forming distinct diagnostic and therapeutic models. Relatively speaking, TCM focuses on holistic and macroscopic perspectives, while Western medicine emphasizes localized and microscopic aspects. The integration of these two approaches complements their respective strengths, thereby enhancing cancer prevention and treatment, which exemplifies the distinctive features of integrated TCM-Western medicine in cancer management.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

FUNDING

Shandong Provincial Key Traditional Chinese Medicine Discipline Construction Project (Lu Wei Traditional Chinese Medicine Science and Education Document [2022] No. 4).

REFERENCES

[1] Crosbie E J, Kitson S J, Mcalpine J N, et al. Endometrial cancer. The Lancet, 2022, 399(10333): 1412-1428.
[2] Berek J S, Matias‐Guiu X, Creutzberg C, et al. FIGO staging of endometrial cancer: 2023. International Journal of Gynecology & Obstetrics, 2023, 162(2): 383-394.
[3] Rütten H, Verhoef C, Van Weelden W J, et al. Recurrent endometrial cancer: local and systemic treatment options. Cancers, 2021, 13(24): 6275.
[4] Restaino S, Dinoi G, La Fera E, et al. Recurrent endometrial cancer: which is the best treatment? Systematic review of the literature. Cancers, 2022, 14(17): 4176.
[5] Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. New England Journal of Medicine, 2021, 385(20):1856-1867.
[6] Cascone T, Awad M M, Spicer J D, et al. Perioperative Nivolumab in Resectable Lung Cancer. New England Journal of Medicine, 2024, 390(19):1756-1769.
[7] Zhao B, Zhao H, Zhao J. Serious adverse events and fatal adverse events associated with nivolumab treatment in cancer patients: Nivolumab-related serious/fatal adverse events. Journal for ImmunoTherapy of Cancer, 2018, 6:1-12.
[8] Larroquette M, Domblides C, Lefort F, et al. Combining immune checkpoint inhibitors with chemotherapy in advanced solid tumours: A review. European Journal of Cancer, 2021, 158:47-62.
[9] Ahn E R, Rothe M, Mangat P K, et al. Pertuzumab plus trastuzumab in patients with endometrial cancer with ERBB2/3 amplification, overexpression, or mutation: results from the TAPUR study. JCO Precision Oncology, 2023, 7: e2200609.
[10] Kreutzfeldt J, Rozeboom B, Dey N, et al. The trastuzumab era: current and upcoming targeted HER2+ breast cancer therapies. American journal of cancer research, 2020, 10(4): 1045.
[11] Dempsey N, Rosenthal A, Dabas N, et al. Trastuzumab-induced cardiotoxicity: a review of clinical risk factors, pharmacologic prevention, and cardiotoxicity of other HER2-directed therapies. Breast Cancer Research and Treatment, 2021, 188: 21-36.

[12] Yang S-T, Chang W-H, Chou F-W, et al. Front-line chemoimmunotherapy for treating epithelial ovarian cancer: Part II promising results of phase 2 study of paclitaxel-carboplatin-oregovomab regimen. Taiwanese Journal of Obstetrics and Gynecology, 2024, 63(1): 10-16.
[13] Miller D S, Filiaci V L, Mannel R S, et al. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). Journal of Clinical Oncology, 2020, 38(33): 3841.
[14] Yamashita H, Nakayama K, Ishikawa M, et al. Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. Oncotarget, 2018, 9(5): 5652.
[15] Lailler C, Lamuraglia M, Racine F, et al. DNA damage response-and JAK-dependent regulation of PD-L1 expression in head and neck squamous cell carcinoma (HNSCC) cells exposed to 5-fluorouracil (5-FU). Translational Oncology, 2021, 14(8): 101110.
[16] Rojkó L, Reiniger L, Téglási V, et al. Chemotherapy treatment is associated with altered PD-L1 expression in lung cancer patients. Journal of cancer research and clinical oncology, 2018, 144: 1219-1226.
[17] Qimeige, Prunus salicina Li, Qilin, et al. Clinical analysis of Wan Dai Tang in the treatment of postoperative patients with endometrial cancer . Chinese Journal of Experimental Traditional Medical Formulae, 2019, 25(14): 130-135.
[18] Sun Xiaohe, Prunus salicina willow, Cheng Haibo. Discussion on the Diagnosis and Treatment of Endometrial Cancer Based on the Theory of Cancer Toxin Pathogenesis. Modern Chinese Clinical Medicine, 2023, 30(05): 94-97.
[19] He Fengyi, Wang Yi, Luo Yanhua, et al. Preliminary Study on the Pharmacological Effects and Mechanism of Guizhi Fuling Decoction on Endometrial Cancer . Chinese Journal of Comparative Medicine, 2019, 29(03): 43-47.
[20] Wang Xiaoqing, Zhang Bei, Qi Yu, et al. Effects of Guizhi Fuling Capsule on Postoperative Recovery and Inflammatory Mediator Levels in Early Endometrial Cancer Patients After Laparoscopic Surgery. World Chinese Medicine, 2024, 19(03): 373-376+382.
[21] Bai X, Ta N, Gong G H, et al. Effects of integrated Chinese traditional medicine and conventional western medicine on the quality of life of breast cancer patients: a systematic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine, 2022.
[22] Cheng M, Hu J, Zhao Y, et al. Efficacy and safety of astragalus-containing traditional Chinese medicine combined with platinum-based chemotherapy in advanced gastric cancer: A systematic review and meta-analysis. Frontiers in oncology, 2021, 11: 632168.
[23] Boța M, Vlaia L, Jîjie A R, et al. Exploring Synergistic Interactions between Natural Compounds and Conventional Chemotherapeutic Drugs in Preclinical Models of Lung Cancer. Pharmaceuticals, 2024, 17(5): 598.
[24] Dinda B, Dinda S, Dassharma S, et al. Therapeutic potentials of baicalin and its aglycone, baicalein against inflammatory disorders. European journal of medicinal chemistry, 2017, 131: 68-80.
[25] Heinhuis K, Ros W, Kok M, et al. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Annals of Oncology, 2019, 30(2): 219-235.