

Integrated Traditional Chinese and Western Medicine Treatment of Oral Squamous Cell Carcinoma

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Abstract. The most prevalent of all oral cancers is the oral squamous cell carcinoma (OSCC), and it constitutes over 90 percent of this group. Its occurrence has only been on the rise in recent years, mostly because of the high use of betel nut, tobacco, and alcohol. The traditional treatment procedures mostly consist of approaches relying on Western medicine, as surgery is the dominant form of treatment, and this is complemented by chemotherapy and/or radiotherapy. Though these methods have short-term ability to treat tumors, they fail to treat them effectively due to drug resistance and other side effects, including oral mucositis and bone marrow suppression, which decreases patient therapeutic compliance. Further, the special anatomical position of the mouth cavity, along with the high aesthetic expectations of the face, leads to the fact that inappropriate surgery can become a major physical and psychological liability to the patients. Traditional Chinese medicine (TCM) focuses on holistic control and differentiation of syndromes. The multi-component, multi-target, and multi-pathway action of Chinese herbal medicaments is marked by characteristics and has proven distinct benefits in the case of alleviating toxicity on chemotherapy/radiotherapy, improving immune functions, and slowing down tumor growth. This review is a summary of the recent research to discuss the mechanisms of Chinese herbal medicine in treating OSCC and discuss the clinical feasibility and prospects of integrated traditional Chinese and Western medicine, which may aim to provide theoretical support and reference directions on the clinical management of OSCC.

Keywords: Traditional Chinese medicine, integrated therapy, Oral Squamous Cell Carcinoma.

1. Introduction

The most prevalent malignant tumor of the oral and maxillofacial area is oral squamous cell carcinoma (OSCC), which is diagnosed in more than 90 percent of oral cancers and has high morbidity and mortality. Most patients are diagnosed in middle or advanced stages, and hence the poor treatment results and prognosis due to insidious onset and other nonstereotypic early symptoms. As evidenced currently, it is believed that a combination of factors (including the geographic distribution (higher prevalence in Southeast Asia), smoking, alcohol, betel nut chewing, immune dysfunction, and vitamin deficiency) is related to the occurrence of the OSCC [1, 2]. Clinically, OSCC mainly manifests as oral masses, erythroplakia, and non-healing ulcers.

The treatment of Western medicine is mostly grounded in surgical excision; it is complemented by radiotherapy, chemotherapy, and targeted treatment. Nonetheless, the existing focus on recurrence, metastasis, adverse effects of treatment, and aesthetic impairment is a major problem that most patients struggle to overcome because of the biological peculiarities of OSCC and the body location specifics. It has been demonstrated altogether in numerous earlier studies [3-5] that Chinese herbal medicines do have significant therapeutic effects when used in the treatment of cancer and that they have the ability to offer certain benefits never realized when used singularly with conventional Western pharmaceuticals. To facilitate clinical practice, anticancer Chinese herbal medicines have predominantly been utilized as adjuvant therapy during radiotherapy and chemotherapy and are able to display activity like toxicity mitigation, efficacy advancement, and immunological regulation. Thus, the clinical value of covers concerning the investigation of the strategies of integrated treatment with the application of both traditional and Western medicine is significant.

2. Etiological Factors and Pathogenesis of OSCC

OSCC initiation and progression are due to a combination of environmental risk factors and genetic changes induced internally. The primary etiological triggers are long-time smoking, alcohol use, betel nut chewing, physical and chemical irritability, which may be caused by residual roots, crowns, and sharp dental cusps, as well as human papillomavirus (HPV) infection, a shortage of trace elements, long-term oral inflammation, and poor oral care habits [6, 7].

On the molecular level, OSCC can be linked to inactivation mutations or epigenetic silence of tumor suppressor genes, and the activation or amplification of oncogenes (including EGFR and Cyclin D1), thereby causing cell cycle regulation and an activity/apoptosis imbalance. Moreover, the aberrant expression in several critical signaling pathways, such as EGFR/PI3K /Akt, and NF- κ B, stimulates tumor survival, invasion, and metastasis. Moreover, the OSCC development and progression are caused by immune evasion, epithelial-mesenchymal transition (EMT), and angiogenesis in the tumor microenvironment.

3. Mechanisms and Limitations of Traditional Western Medical Interventions of OSCC

Treatment of OSCC is primarily surgery with radiotherapy, chemotherapy, and targeted therapy as supplements [8, 9]. Pharmacological therapy is the main treatment protocol deployed with patients with advanced or inoperable OSCC, and comprises most notably the use of conventional chemotherapy, EGFR monoclonal antibodies, and PD-1 inhibitors. These three classes present antitumor action by various molecular targets and mechanisms, but each has its own clinical limitations [10].

3.1. Conventional Chemotherapeutic Agents: Non-specific Cytotoxic Antitumor Effects

Platinum (cisplatin and carboplatin) and antimetabolite (5-fluorouracil, 5-FU) agents and taxanes (paclitaxel, docetaxel) are commonly used as chemotherapeutic agents. These agents either cause cell cycle arrest and apoptosis by disrupting the DNA synthesis, replication, or mitosis. Platinum based on cisplatin Platinum-based products create stable platinum-DNA complexes by crosslinking with DNA double strands, disrupting DNA double helix formation, and suppressing replication and transcription, ultimately causing a lack of substrates to synthesize DNA, and additionally, using its metabolites in place of building an RNA strand will inhibit protein synthesis, thus producing a dual inhibitory effect on the proliferation of tumor cells. The taxanes stabilize the microtubule polymerization, inhibit spindle fiber depolymerization, block the metaphase (M phase), and trigger cell death that occurs in mitotic cells.

Although they are effective, traditional chemotherapeutic agents have serious shortcomings. One of the most common causes of treatment failure is drug resistance. As an example, resistance to cisplatin in OSCC could include a decrease in drug uptake, escalation of efflux, augmentation in DNA repair, improved anti-apoptotic signaling circuits, and consequent occurrence and spread of tumors. Additionally, the lack of selectivity by chemotherapy agents causes injury to normal, swiftly growing cells as well as bone marrow hematopoietic cells, gastrointestinal mucosal cells, and hair follicle cells, leading to adverse effects like nausea, vomiting, and bone marrow suppression. Traditionally, under normal conditions, cyclin-dependent kinases (CDKs) phosphorylate p21 at serine 78, which is observed to inactivate it. Nonetheless, experiments have provided evidence that the p21 gene is notably overexpressed due to the damage of DNA in renal cells caused by cisplatin that regulates the CDK activity and prevents the onset of apoptosis. Cisplatin-induced renal tubular cell apoptosis is directly proportional to CDK activity, so acute kidney injury is a frequent occurrence in clinical practice.

3.2. EGFR: Signaling Pathway Inhibitor Antibodies

The receptor Epidermal growth factor receptor (EGFR) is an overexpressed transmembrane tyrosine kinase receptor in OSCC (60%-90). On ligand binding through epidermal growth factor (EGF), EGFR signifies downstream RAS/RAF/MEK/ERK and PI3K/Akt/mTOR, which governs tumor cell growth, anti-apoptosis, angiogenesis, invasion, and metastasis. The initial approved targeted therapies in OSCC were EGFR monoclonal antibodies, and one of them was cetuximab (and the rest were panitumumab). These caused agents exclusively to the extracellular region of EGFR, repressing ligand binding and receptor dimerization and activation to achieve downstream proliferation and inducing tumor cells apoptosis, respectively.

Although EGFR-based monoclonal antibodies are a shift to non-specific to precision therapy, there are significant limitations to their usage. They also differ from non-small cell lung cancer, in which EGFR-sensitive mutations are predictive biomarkers, with EGFR changes that are, in general, restricted to overexpression or amplification of copy number in OSCC, but not to activating mutations. Until now, no molecular markers can be trusted to determine the responsive population of patients, hence the unpredictability in the efficacy of a treatment. Moreover, primary/acquired resistance can still be regarded as one of the severe problems of EGFR-targeted treatment of OSCC.

3.3. PD-1 inhibitors Immunotherapy in the Tumor Immune Microenvironment

Programmed cell death protein 1 (PD-1), an inhibitory receptor, is present in activated B cells and T cells. Its ligand, PD-L1 (B7-H1), has been shown to be expressed both on OSCC tumor cells and dendritic cells and macrophages located in the tumor microenvironment. T cell receptor (TCR) signaling by binding of PD-1 to PD-L1 and T-cell exhaustion is induced to allow tumor immune evasion. Pembrolizumab and nivolumab are PD-1/PD-L1 axis inhibitors that rejuvenate antitumor immune responses and increase T-cell-mediated cytotoxicity.

In spite of the longer survival of a few patients with advanced OSCC in case of PD-1 inhibitors, it has been reported in clinical trials that merely 20%-30% of patients respond to treatment. Besides, responses to treatment are poorly correlated with biomarkers, including but not limited to PD-L1 expression (TPS $\geq$ 1%), tumor mutational load, and microsatellite instability (MSI-H). There are also the immune-related adverse events (irAEs) that have further clinical risk after the disturbance of immune tolerance.

To conclude, the therapeutic options of OSCC in the light of cytotoxicity, targeted signaling inhibition, and immune modulation are conventional chemotherapy, EGFR monoclonal antibodies, and PD-1 inhibitors, respectively. Nonetheless, they all have severe weaknesses. Consequently, combined approaches that merge Chinese and Western medicine might serve as an encouraging trend towards the optimization of OSCC treatment by harmonizing the benefits of improving the efficacy and reducing the toxicity, which would result in better patient survival and increased quality of life.

4. The Chinese Herbal Medicine in OSCC Treatment Mechanisms

Thus, as of now, some 60,000 higher plant species around the world have been found to have a possible anticancer value. The Chinese herbal prescriptions often include several herbs whose efficacy is achieved due to the synergistic action of different components, and it is hard to ascribe efficacy to each chemical component or mechanism. Rather, they attain their actions through multi-target and multi-pathway regulation.

The medical system of the Chinese people does not assign OSCC the name of a disease, but rather falls under classifications like tongue fungus, oral fungus, and tooth rock, in regard to how it presents. The causes of OSCC pathogenesis in TCM theory include emotional disorders, aberrant diet, external pathogenic invasion, lack of essential qi, which provokes dysfunction of zang-fu organs and the imbalance of yin and Yang and qi. These pathological alterations lead to the formation of so-called toxicity, stasis, phlegm, and deficiency in the mouth cavity, which eventually leads to cancerous malignant tumors. In this regard, TCM therapy focuses on disorder differentiation and holistic control,

and the therapeutic principles are as follows: heat-clearing and detoxification, qi tonifying and yin nourishing, and vital qi strengthening [3, 11]. The purpose of Chinese herbal medicine in OSCC management is primarily adjunctive, complementing the action of Western treatment; it can also be used to reduce treatment-related toxicity and to improve prognosis.

To a modern pharmacological approach, the active constituents of the Chinese herbal medicines, including the alkaloids, flavonoids, and terpenoids, have antitumor effects, which work directly on the tumor cells and on the systemic microenvironment. Detoxifying and heat-cleansing herbs, blood-activating and stasis-resolving herbs (e.g., *Hedyotis diffusa*, *Scutellaria barbata*) prevent tumor cell growth and go ahead to induce apoptosis as well as to suppress angiogenesis. Herbs such as *Astragalus membranaceus* and *Codonopsis pilosula*, or qi-tonifying and yin-nourishing herbs, improve the immune system (by increasing the activity of natural killer (NK), promoting cytokines, and increasing the ability of macrophages to phagocytose). Compound herbal formulas can act on different stages of tumor growth, including invasion, regulation of the tumor microenvironment, and reversal of multidrug resistance, and exhibit a multi-component, multi-target, multi-pathway profile [12]. Although there are growing trends in the use of Chinese herbal medicine in oncology globally, its use remains patchy across regions. It lacks sufficient clinical evidence to determine its safety and effectiveness in managing OSCC.

5. Mechanisms of Integrated Traditional Chinese and Western Medicine in the Treatment of OSCC

5.1. *Sophora Flavescens*

Sophora flavescens is a Chinese herbal medicine that is used as an adjunctive treatment of OSCC. The most commonly used (HD) have demonstrated heat-clearing and detoxifying properties, with strong evidence in modern research. This group represents a publication on *Sophora flavescens* that reports a dual antitumor and toxicity-reducing effect of the alkaloid agent. *Sophora flavescens* is the dry root of a leguminous plant. It is also bitter and cold in nature and has been linked to the heart, liver, stomach, large intestine, and bladder meridians in the TCM. It plays its primary role in clearing heat, evaporation of dampness, killing parasites, and diuresis. In the treatment of OSCC, it is primarily applicable in oral inflammation, as well as in tumor prevention; it primarily exerts its effects via its active alkaloids, such as oxymatrine.

Recent pharmacological research has demonstrated that matrine inhibits the PI3K/Akt/mTOR pathway, decreases Cyclin D1 expression in OSCC cells, arrests the cell cycle at the G0/G1 phase, and prevents cell division. Experiments in vitro have demonstrated that OSCC cell lines (e.g., CAL-27 and SCC-15) that are treated with matrine for over 48 hours enhance the percentage of apoptotic cells by 20-30%. Clinical experience shows that OSCC patients who are subjected to matrine with cisplatin chemotherapy show a reduced incidence rate of oral mucositis, which is 75 percent with chemotherapy and 40 percent, and much less severe with chemotherapy. These are related to the antioxidant capacity of matrine in raising the serum level of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reducing the harm of reactive oxygen species (ROS) on oral epithelial cells after chemotherapy, supporting hematopoiesis of bone marrow, elevating the level of leukocytes in the post-chemotherapy period, and preventing infection.

5.2. *Hedyotis diffusa*: Immunomodulatory and Antimetastatic Heat-Clearing Herb

Hedyotis diffusa is a dried herb from a plant of the Rubiaceae family, which is characterized as being bitter and sweet, cool, and associated with the meridians of the stomach, large intestine, and small intestine (TCM). Its key activities are heat clearing, detoxification, and dampness elimination. Its regulatory action on OSCC is mostly concerning antimetastatic action and immune regulation.

A flavonoid such as quercetin in *Hedyotis diffusa* suppresses MMP-9 in OSCC cells, reduces extracellular matrix degradation, and inhibits NF- κ B activation, a major regulator of MMPs, thereby

inhibiting tumor invasion. Quercetin has also been found to increase E-cadherin expression, suppress EMT, and inhibit cell migration, characteristics characteristic of OSCC. In vitro wound-healing assays have shown that Hedyotis diffusa extracts reduce the migration rate of OSCC cells by more than 50%. More so, Hedyotis diffusa polysaccharides increase the macrophage and NK cell performance, which is a vital indicator of the immune functioning.

An analysis of controlled clinical observations of cancer patients at Gansu Provincial Hospital of Traditional Chinese Medicine was conducted by Zhao Yalan et al. [13] during the period from January 2015 to February 2018. The patients who were treated with the combination of Hedyotis diffusa with surgery or chemoradiotherapy had much lower levels of CEA, AFP, and 8 delta-microglobulin as compared with controls ($t = 2.157, 19.985, 3.828$; $p < 0.001$), which indicates that Hedyotis diffusa has antitumor effects, which include regulation of signaling pathways, induction of apoptosis, and stimulation of immune functions, suggesting that it can be used as an integrated

6. Conclusion

Chinese herbal medicine plays an adjunctive regulatory role in the treatment of OSCC, with multi-target antitumor, antimetastatic, and immunomodulatory effects, as well as toxicity-reducing properties, and it also demonstrates benefits in safety, holistic regulation, and therapeutic synergy. Some of the most commonly used herbs include Sophora flavescens and Hedyotis diffusa; however, matrine exhibited antitumor and toxicity-reducing effects, and Hedyotis diffusa showed antimetastatic and immunomodulatory effects. Nevertheless, they both have their weaknesses.

Matrine has a low oral bioavailability (around 10 per cent -15 per cent), and the various processing regimes of Sophora flavescens influence alkaloid content. Besides, the non-normative dosing is a source of inaccuracy in clinical efficacy. In Hedyotis diffusa, there is an absence of studies that examine the effects of this on overall survival (OS) and progression-free survival (PFS) in patients with OSCC. Most literature is based on in vitro or animal models, with no high-quality and large-scale multicentric randomized controlled trials (RCTs) demonstrating its effects in OSCC patients.

The way forward in research should include bettering the bioavailability of active components using various advanced pharmaceutical materials (e.g., nanocarriers and liposomes), conducting well-conducted RCTs to understand the survival benefits better, and integration of TCM syndrome differentiation and Western molecular subtyping to attain personalized therapy. The development of a cooperative traditional Chinese and Western medicine regimen for OSCC could ultimately improve therapeutic outcomes and complement the patient's quality of life.

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