
Herbal Medicines as Adjunctive Therapy for Oral Squamous Cell Carcinoma Management: a Case Report

Obat Herbal sebagai Terapi Tambahan untuk Manajemen Karsinoma Sel Skuamosa Oral: Laporan Kasus

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Abstract

Oral Squamous Cell Carcinoma (OSCC) is the most frequent oral cancer. The management for OSCC are surgery, chemotherapy, and radiotherapy. Chemotherapy and radiotherapy have high toxicity and side effects, therefore effort are needed to reduce them. Several studies show that herbal medicines have anticancer effects with lower toxicity and side effects. The objective is to discuss about management of OSCC using chemotherapy and anticancer herbal medicines as adjunctive therapy. A 59-year-old man came to the oral medicine clinic complaining a painful ulcer on the right tongue since 8 months ago. The ulcer had been enlarged in the last 3 months and the tongue was difficult to be moved. He used pain relievers and aloe vera gel but there was no improvement. He smoked one pack a day since 40 years ago. Intraoral showed an irregular indurated endophytic mass with an ulcer on the right lateral of the tongue. An incisional biopsy was performed and the histopathological diagnosis was poorly differentiated OSCC. The patient was referred to the oncology department and advised for chemotherapy 6 cycles per 3 weeks. He also used herbal medicines containing *Panax ginseng radix*, *Panax pseudoginseng radix*, *Ophiopogonis japonicus*, *Ganoderma lucidum*, *Ligusticum wallichii rhizoma*, and *Atractylodes macrocephala rhizoma*. The content of these herbal medicines have anticancer and immunomodulatory effects. After the second cycle of chemotherapy, there was a significant improvement. OSCC management with chemotherapy combined with anticancer herbal medicines can increase the success of therapy and reduce the side effects of chemotherapy.

Keywords: oral squamous cell carcinoma, herbal medicine, adjunctive therapy, OSCC management

Abstrak

Oral Squamous Cell Carcinoma (OSCC) adalah keganasan rongga mulut yang paling umum. Penatalaksanaan OSCC adalah pembedahan, kemoterapi, dan radioterapi. Kemoterapi dan radioterapi memiliki toksisitas dan efek samping tinggi sehingga diperlukan upaya untuk menguranginya. Beberapa studi menunjukkan bahwa obat-obatan herbal memiliki efek anti kanker dengan efek samping dan toksisitas yang lebih rendah. Tujuan studi kasus ini adalah untuk membahas mengenai manajemen OSCC menggunakan kemoterapi dan obat-obatan herbal anti kanker sebagai terapi tambahan. Seorang laki-laki 59 tahun datang ke klinik penyakit mulut dengan keluhan sariawan yang sakit pada lidah kanan sejak 8 bulan lalu. Sariawan membesar dalam 3 bulan terakhir dan lidah sulit digerakkan. Pasien menggunakan penghilang rasa sakit dan gel lidah buaya tetapi tidak ada perbaikan. Riwayat merokok satu bungkus sehari sejak 40 tahun yang lalu. Intraoral menunjukkan massa endofitik berindurasi tidak teratur dengan ulser di lateral kanan lidah. Biopsi insisional dilakukan dan diagnosis histopatologi adalah *poorly differentiated OSCC*. Pasien dirujuk ke departemen onkologi dan disarankan untuk kemoterapi 6 siklus per 3 minggu. Ia juga menggunakan obat herbal yang mengandung *Panax ginseng radix*, *Panax pseudoginseng radix*, *Ophiopogonis japonicus*, *Ganoderma lucidum*, *Ligusticum wallichii rhizoma*, dan *Atractylodes macrocephala rhizoma*. Kandungan obat herbal ini memiliki efek anti kanker dan imunomodulator. Setelah kemoterapi siklus kedua, terdapat perbaikan yang signifikan. Penatalaksanaan OSCC dengan kemoterapi yang dikombinasi obat herbal anti kanker dapat meningkatkan keberhasilan terapi dan menurunkan efek samping kemoterapi.

Kata kunci: karsinoma sel skuamosa oral, obat herbal, terapi tambahan, manajemen OSCC

INTRODUCTION

Oral Squamous Cell Carcinoma (OSCC) is the most frequent neoplasm and contribute for more than 90% of all oral cancers. OSCC is more prevalent in men, develops during the fifth and seventh decades of life, tongue is the most commonly affected.¹ OSCC is a malignant tumor of epithelial cells with squamous differentiation defined by the development of keratin and the involvement of intercellular bridges.² Some types of OSCC are conventional, basaloid, spindle cell, verrucous, papillary, mucoepidermoid, adenosquamous, acantholytic and cuniculatum.³

The etiology of OSCC is idiopathic. Several risk factors are associated with OSCC. OSCC risk factors have been discovered in a wide range of lifestyle and environmental variables. Tobacco, alcohol, and HPV are the most common risk factors.⁴ Standards of care should follow National Comprehensive Cancer Network guidelines whenever possible and depend on the stage of the patient. The management for OSCC are surgery, chemotherapy, and radiotherapy.⁵

Herbal medicine is a plant product that is used as traditional medicine and food additive. Recent years several herbal medicines have been studied for their anticancer effects including ginger, curcumin, saffron, and cinnamon.⁶ This herbal medicines can cause cell death by promoting apoptosis and interrupting the cell cycle, allowing it to be utilized to treat oral cancer with less toxicity and side effects. Some of the therapeutic compounds that have showed promising efficacy against OSCC and other malignancies including curcumin, lycopene, ginseng, anthocyanins, and artemisinin.⁷

This article discusses a case report related to OSCC of the tongue. The purpose of this case report is to inform about management of OSCC using anticancer herbal medicines as adjunctive therapy that could increase the success of therapy and reduce the side effects of chemotherapy.

CASE REPORT

A 59-year-old male patient came to the Oral Medicine clinic complaining of ulcer on the right tongue since 8 months ago. The ulcer had been developing since the last 3 months and the tongue was difficult to be moved. The patient used self-purchased pain relievers including ibuprofen, mefenamic acid, and aloe vera gel three times a day for the past 1 month but there was no improvement. He smoked one pack per day since 40 years ago. No abnormalities at the extra-oral. Intraoral examination showed an irregular indurated endophytic mass with

ulcer on the right lateral of the tongue. The ulcer was deep, single, yellowish white surrounded by erythematous area, irregular border, 1x2 cm in size (Figure 1a).

The diagnosis was confirmed by incisional biopsy (Figure 1b). The results of histopathological examination (Figure 2) showed that the mucosa was lined with stratified squamous epithelium that grew hyperplastic, parakeratosis which partially had been turn into a tumor mass consisting of oval-shaped cells that grew hyperplastic, condensed, and clustered. There were polymorphic, hyperchromatic, partially vesicular, mitotic cell nuclei. Subepithelial showed connective tissue stroma filled with inflammatory cells of lymphocytes accompanied with blood vessels dilatation. The conclusion from the histopathological examination was poorly differentiated squamous cell carcinoma.

The patient was referred to the oncology department and was advised for surgery, but he refused it and chose chemotherapy. The patient was scheduled to get 6 cycles of chemotherapy for 3 weeks. He also consumed herbal medicines containing *Panax ginseng radix*, *Ganoderma lucidum*, *Ophiopogonis japonicus*, *Panax pseudoginseng radix*, *Ligusticum wallichii rhizoma*, and *Atractylodes macrocephala rhizome*. The patient bought this herbal medicine on the advice of his sister who has ovarian cancer and have consulted an oncologist. The content of these herbal medicines had anticancer and immunomodulatory effects. After the second cycle of chemotherapy in 2 months, there was significant improvement.

DISCUSSIONS

The diagnosis of the patient in this case was Oral Squamous Cell Carcinoma (OSCC). Management for OSSC including surgery, chemotherapy, radiotherapy or combination of those therapies. Surgery is often recommended for the initial management in early-stage OSCC patients, but many of them cannot be resected or refuse it because of speech impairment after resection. The patient was referred to the oncology department and advised for chemotherapy. Chemotherapy with high-dose cisplatin every 3 weeks can reduce the risk of local recurrence by 42% in patients with inoperable oral cancer.⁸ Chemotherapy medications not only destroy cancer cells, but they can also harm healthy cells and induce a variety of side effects including exhaustion, nausea, hair loss, and vomiting. More than 70% of patients have side effects. Mucositis, dry mouth, and numbness are among the other side effects.⁹

Before and after the chemotherapy cycle, the patient consumed Chinese herbal medicines. The herbal medicine contains *Panax ginseng radix*, *Ganoderma lucidum*, *Ophiopogonis japonicus*, *Panax pseudoginseng radix*, *Ligusticum wallichii rhizoma*, and *Atractylodes macrocephala rhizoma*. The patient felt that the pain was decreasing after he consumed the herbal medicine and he could eat better. No side effects due to chemotherapy after undergoing two cycles.

Panax ginseng (Figure 4a) is one type of ginseng which is the most widely used and originate from several countries especially China and Korea. *Panax ginseng* was initially grown around 11 BC and has a more than 5000-year medicinal history.¹⁰ The main active compounds in ginseng are ginsenosides or ginseng saponins.¹¹ Other ingredients such as polysaccharides and polyacetylenes are also found in ginseng root.¹² Pharmacological studies show that ginseng has many bioactive effects, such as antiaging, anti-stress, anticancer, anti-inflammatory, and antidiabetic.¹³

Ganoderma lucidum (*G. lucidum*) (Figure 4b) is a form of fungus that has been exploited in Chinese medicine for over 2000 years. *G. lucidum* is also known as Reishi, Ling-zhi, the “mushroom of immortality”, and “spirit plant”.¹⁴ The surface of the fungus is like a bright, dark red wood texture. Polysaccharides, triterpenoids, nucleotides, sterols, steroids, fatty acids, and proteins/peptides are among the 400 bioactive compounds found in *G. lucidum*. Polysaccharides from *G. lucidum* have been discovered as a major bioactive component, which exhibit pharmacological effects, such as anticancer, immunomodulating, antioxidant, and hypoglycemic.¹⁵ Several studies have found that *G. lucidum* can improve response to standard treatments, regulate immunity, or relieve certain side effects caused by cancer or cancer treatment.¹⁶

Ophiopogonis japonicus (*O. japonicus*) (Figure 4c) is a popular traditional Chinese medicine that has been utilized for thousands years and is widely distributed in Southeast Asia.¹⁷ *O. japonicus*'s essential components including steroidal saponins, homoisoflavonoids, and polysaccharides, which have a variety of pharmacological properties such as cardiovascular protective, anti-inflammatory, anticancer, antioxidant, immunomodulating, antimicrobial, and antidiabetic.¹⁸ One study proved that *O. japonicus* acts by suppressing p38 MAPK activation, inflammatory cytokines, and reactive oxygen species.¹⁹

Around 1500 BC, minority ethnic groups in southwest China used the root of *Panax pseudoginseng* or *Panax notoginseng* (Figure 4d) that also known as Sanqi, Sanchi, or Tianqi.²⁰ Saponins, amino acids, and essential oils have been discovered as active

components in notoginseng. The saponins in *Panax notoginseng* (notoginsenosides) are most commonly found in the roots and their content is higher than that contained in ginseng.^{21,22} Notoginsenosides have been found to improve blood circulation, eliminate blood stasis, and reverse cancer multidrug resistance. An animal study found that notoginsenosides protect against cisplatin-induced nephrotoxicity by reducing blood urea nitrogen and serum creatinine.²³

Ligusticum wallichii (*L. wallichii*) (Figure 4e) is a Chinese herbal medicine that has also been widely used for more than 2000 years. The primary bioactive compounds in this plant's rhizome including ligustrazine, ferulic acid, cnidilide, and ligustilide.²⁴ *L. wallichii* has been tested on various cancers, such as leukemia, lung cancer, ovarian carcinoma, liver cancer, glioma, osteosarcoma, chemotherapy-resistant breast cancer, and prostate cancer. This herbal medicine's mechanism of action including anti-inflammatory and promoting apoptosis.²⁵

Atractylodes macrocephala (*A. macrocephala*) (Figure 4f) is an herbaceous perennial that has been grown for over 700 years in subtropical region. In traditional Chinese medicine, the rhizome of this plant is known as Baizhu. Sesquiterpenoids, triterpenoids, polyacetylenes, coumarins, phenylpropanoids, flavonoids and flavonoid glycosides, steroids, benzoquinones, and polysaccharides are all found in the rhizome of this plant.²⁶ Several studies have shown that *A. macrocephala* has been investigated to have antioxidant, antimutation, antitumor, antiaging, growth promotion and cell differentiation effects.²⁷

Panax ginseng radix, *Ophiopogonis japonicus*, *Ligusticum wallichii rhizoma*, and *Atractylodes macrocephala rhizome* have anticancer effects by promoting cancer cell apoptosis. In addition, these herbal medicines have antioxidant effects by reducing oxidative stress. Oxidative stress that occurs before chemotherapy is caused by free radicals released by cancer cells and will continue during chemotherapy, thereby increasing the occurrence of chemotherapy side effects. The use of *Ganoderma lucidum* and *Panax pseudoginseng radix* can mitigate chemotherapy side effects. *Panax pseudoginseng radix* can prevent nephrotoxicity which is one of the adverse effects of cisplatin-based chemotherapy. *Ganoderma lucidum* can also increase the effectiveness of chemotherapy drugs used.

Herbal medicines which was consumed by the patient could speed up the healing process because they have anti-cancer effects and increase the effectiveness of chemotherapy. In addition, the content of these herbal medicines can reduce the side effects of chemotherapy. Chemotherapy combined with herbal

medicines that have anti-cancer effects can be an option for OSCC treatment.

In conclusion, chemotherapy for OSCC, is an option treatment for patients who refuse surgery. Patients with chemotherapy can use herbal medicines as adjunctive therapy. Herbal medicine such as *Panax ginseng radix*, *Ophiopogonis japonicus*, *Ligusticum wallichii rhizoma*, and *Atractylodes macrocephala rhizome* has anticancer effect. *Ganoderma lucidum*

and *Panax pseudoginseng radix* can eliminate certain side effects caused by chemotherapy.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the patient for accepting to be a part of this case report.

FIGURES



Figure 1. a. Lesion on the right lateral of the tongue at first visit. b. After incisional biopsy of the lesion.

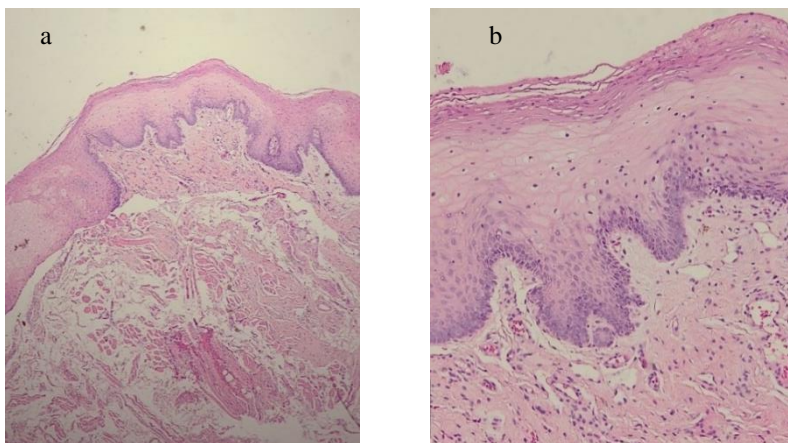


Figure 2. Histopathological appearance of OSCC on the tongue at 20x (a) and 100x (b) magnification. The mucosa was lined with stratified squamous epithelium that grew hyperplastic and there were polymorphic, hyperchromatic, partially vesicular, mitotic cell nuclei.



Figure 3. A significant improvement after two months of therapy.

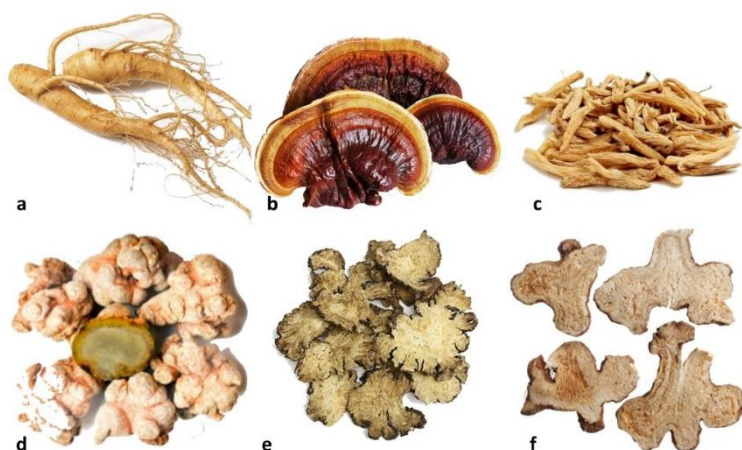


Figure 4. a. *Panax ginseng radix*¹⁰, b. *Ganoderma lucidum*¹⁵; c. *Ophiopogonis japonicus*¹⁸; d. *Panax pseudoginseng radix*²⁰; e. *Ligusticum walichii rhizoma*²⁸; f. *Atractylodes macrocephala rhizoma*²⁹

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