Cutaneous Carcinoma Treatments by Topical Chinese Herbal Medicine

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ABSTRACT

In the treatment of malignant skin cancer, topically administered traditional Chinese medicines not only exert dispersing effect directly on the cancerous lesion, but also reduce the cancer-related pain. The common single-ingredient formulations included Toad venom and Rhizoma Bletillae. There were many effective multiple-ingredient formulations for skin cancers. They were Golden powder, Tri-ingredient Spear, Toad venom cream, Xanthium sibiricum Patrin ex Widder cream, Five-smoke pellets and Five-tiger pellets. Topically administered traditional Chinese medicines provides advantages of no scarring and no affect on appearance, when compared to routine surgical treatment. Temporary application on local skin is even safer. The skin cancer lesion is located superficially, and is easily accessible as compared to other tumor tissues, and thus is particularly suitable for topical transdermal dosing. Not only does such application better target the lesion and result in higher tumor cell cytotoxicity, but also avoid the toxic and side effects that could be caused by systemic therapy. In the future, the advanced pharmaceutical techniques, such as nano technology, slow-release and controlled release should be applied to develop topically administered preparations with high efficacy and low toxicity for skin cancer.

Introduction

Skin cancer is a collective term for all malignant dermal tumors, including malignant melanoma, basal cell carcinoma, squamous cell carcinoma, etc. As ozone layer depletion aggravates in recent years, the incidence of skin cancer is increasing year by year over the globe, showing the tendency to involve younger individuals. In China as well as other countries, the incidence is on the rise[1,2]. Therefore, the prevention and management of skin cancer have become a hot topic in the research of skin diseases.

In traditional Chinese medicine (TCM), skin cancer falls into the range of “flower-like sore”, “stone-like condition”, “stone-like induration”, “malignant sore”, “cancerous sore”, etc. In TCM, it is believed that skin cancer is mostly caused by the confliction between “wind” and “poison”, external “fire-related poison”, internal “phlegm”, “Qi” stagnation and “blood stain”, etc. As it is written in Treatise on Causes and Manifestations of Diseases, flower-like sore is mostly caused by the confliction of “wind” and “poison”, and is firstly seen as neoplasm in the shape of a rice grain, and then presenting malignant growth when the neoplasm ruptures, with its root widening. As purulence is discharged, the malignant growth protrudes like a blooming flower, thus it is named as such. In patients with long-term malignant sore without covering, malignant growth also protrudes like a flower-like sore. Topically administered Chinese medicines are directly absorbed via skin and membrane, and exert systemic and topical modulating effects. As one of the topically administered Chinese medicines, they provide solid efficacy, convenient administration, and cost-effectiveness. In Qing dynasty, Xu Ling-tai pointed out that: “when the lesion is well-defined and located between skin and tendons and bones and are palpable, it may be treated with plaster so as to block its “Qi”, and medicine may enter via pore and reach within the skin and open channels, and eventually lift and expel it, or tackle and disperse it. Thus topical administration is more effective than oral administration.” In the treatment of malignant superficial tumors, including skin cancer, topically administered traditional Chinese medicines not only exert dispersing effect directly on the cancerous lesion, but also reduce the cancer-related pain, and are thus worthy of widespread use in clinic.

Single-ingredient formulations

Toad venom

Toad venom is the dried form of the whitish serum secreted by postotic gland and dermal gland of Bufo
bufogargarizan or Bufo melanostictus Schneider. It is pungent and warm, poisonous, ascribed to the “heart” channel, and is effective in detoxicating and killing pain, eliminating swelling and dispersing stagnation, enlightening and restoring consciousness[3]. It is often used to treat ulcer, sore and carbuncle. Toad venom provides extremely strong anti-tumor effect, and has long been used as an anti-tumor agent in clinic. It can be administered orally or topically. As it is written in Treasury of Words on Materia Medica, “it can neutralize all depression and stagnation conditions, and is effective in tackling and removing poison.”[4] In Life-saving Prescriptions, it is written that toad venom treats carbuncle, ulcer and swelling, “a piece of toad venom, preferably in powder form, is mixed with white flour and yellow lead and made into pellet of wheat grain size[5]. Make a rupture on the lesion and insert a pellet. It will produce magical efficacy”. A Collection of Experiences documents a toad cream for treatment of swelling sores: equal amount of toad venom and lime are mixed and made into small piece, which is then applied onto the lesion. The lesion will rupture once it is covered with the cream. Nowadays, this remedy is still in use in some places: skin is peeled from a living toad, then superficial granular glands are pierced and applied directly to the cancerous lesion, as a treatment for superficial tumors[6].

Zhou Ren-xiang et al. formulated a 20% toad venom cream for the topical treatment of skin cancer in a total of 40 patients, of which 19 found their skin tumor disappeared; biopsy found no cancerous cells, with a response rate of 47.50%, and a 5-year cure rate of 22.50%(7]. In addition, toad venom also shows a significant effect in treating the cancer-related pain[8]. Modern studies have shown many active ingredients in toad venom, such as Cinobufagin and Bufalin, have multiple anti-tumor effects, including promoting tumor cell differentiation, inducing tumor cell apoptosis, inhibiting angiogenesis, enhancing radiosensitivity, reversing drug resistance, and modifying immune system[9].

Rhizoma Bletillae

Rhizoma Bletillae is the tuber of Orchids Rhizoma Bletillae[10]. It tastes bitter, sweet and astringent with cold character, and is ascribed to Lung, Stomach, and Liver channels. It has astringent and hemostatic effects, alleviates swelling and promotes skin regeneration. Its earliest documentation traces back to Shen Nong’s Canon of Herbs: “Rhizoma Bletillae tastes bitter with balanced character[10]. It is mainly used to treat carbuncle, malignant wound, gangrene, impairment of Yin, necrotic skin, evil Wind invasion into the stomach, strike by evil spirits, and paralysis”. In Compendium of Materia Medica, it is written that Rhizoma Bletillae is astringent, and can penetrate into the lung and stop hemorrhage, promote regeneration of skin and treat sores[11].

Zhao Shu-ren administered Rhizoma Bletillae topically in a patient with skin cancer, squamous cell carcinoma above the lateral canthus of the right eye[12]. During the therapy, the patient received 100 g Rhizoma Bletillae powder in a plaster over the lesion once daily. After one month of treatment, the lesion became dried, without signs of progression[13]. In clinical application, Rhizoma Bletillae may also be formulated with swelling-alleivating, stagnation-eliminating, Qi-motivating, and weakness-removing herbs, such as Rhizoma Pleionis, Dioscorea Bulbifera, Curcuma Zedoaria, Slender Dutchmanspipe root, Gypsum Rubrum and realgar, as a plaster topically administered on the lesion, so as to enhance the effect[14]. Furthermore, Rhizoma Bletillae is also commonly used in treatment of lung, hepatic and gastric cancers. In addition to its direct anti-tumor effect, Rhizoma Bletillae contains a Rhizoma Bletillae gel, which is an ideal vascular embolization agent and may act as an intervention therapy against tumor. Modern pharmacology studies have suggested mucus contained in Rhizoma Bletillae has inhibitory effect on sarcoma, and a main active ingredient contained in Rhizoma Bletillae shows significant inhibitory effect in animals bearing tumors induced by dimethyl aminobenzene[15].

Multiple-ingredient formulations

Golden powder

The formulation was created by Chen Shi-gong, and was first documented in Orthodox Manual of External Medicine. The formulation includes turmeric, rheum officinale, golden cypress, Radix Angelica dahuricae, Rhizoma atracylodis, Mangnolia officinalis, dried tangerine skin, licorice, and unprocessed Rhizoma Arisaematis[16]. Chen Shigong stated: “it can treat all refractory and malignant sores in external diseases”. A modern approach of administration is as follow: first sterilize a container and then let it air dry; place some Golden powder into the container, mix with strong tea or edible vinegar and make into a plaster, and apply onto the lesion. The area of the plaster should be larger than the lesion. Change the plaster 3 - 4 times daily.

Golden powder is indicated for the skin cancer patients who presents hyperactive heat and poison with local redness, swelling, heat and pain[17]. Fang Qing et al used Ruyi Golden powder as topical therapy in 36 patients with acute sore and ulcer of Yang syndrome, of which 10 had skin cancer-related ulcer. Topical therapy was given once daily on average in 5-day cycle, with a total of two cycles. Treatment outcome was cure in 13 patients (36.11%), improvement in 18 patients, and no response in five (5) patients. The overall response rate was 86.11%. In addition, Golden powder may be mixed with water and applied onto painful lesion as a remedy for cancer-related pain[18].

Tri -ingredient Spear

The formulation is documented in Orthodox Manual of External Medicine, and includes white arsenic, alums, realgar and unprocessed frankincense at the ratio of 1:2.0.2:0.1. First of all, place the white arsenic and alums in a pot and roast until it stops producing green smoke and starts to produce white smoke; add realgar and frankincense, and grind it into fine powder for subsequent use. Before administration, take some powder and scatter over the lesion; or prepare a Tri-
ingredient pastille and place into the lesion, and cover the lesion with a black plaster; use one pastille every 2 - 4 days. Liu Shen et al treated 19 patients with skin cancer using the Tri-ingredient Spear, of which 12 had squamous cell carcinoma and 7 had basal cell carcinoma[19]. They found one patient who had been suffering from squamous cell carcinoma for 25 months was cured after merely two doses; two patients were cured after less than 10 doses; three patients were cured after 10 - 20 doses. Gao You-fen et al. used this remedy to treat 14 patients with squamous and basal cell carcinoma without regional nodal metastasis, and found that all patients achieved short-term cure; 3 patients were followed for five years, and no recurrence was seen[20]. Liu Shen et al believed the formulation exhibited established efficacy in superficial skin cancer with no nodal metastasis or bone destruction; however, it was not as effective in skin cancer with deep infiltration, longer course of disease or bone destruction[19].

**Toad venom cream**

The toad venom cream formulation includes croton, frankincense, castor bean kernel, toad venom, realgar and borneol. Before administration, take a cotton cloth of proper size, smear the ointment onto the cloth and apply onto the lesion once daily. When changing the ointment, discharge from the lesion must be cleaned[21]. Zhang Shao-run selected 128 patients with skin cancer as subjects for clinical observation, and 72 of them achieved significant efficacy at Day 6 - Day 15[22]. Liu Jia-xiang et al suggested toad venom cream was formulated based on knowledge on tumor formation in TCM, and borneol in the formulation dissolved and destroyed structure around the tumor and aggregated fibrin within the tumor, relieving chemical stimulation and physical oppression caused by the tumor to pain-sensitive locus[23]. In addition to treating skin cancer, toad venom cream reliefs skin cancer-related pain. Clinical trials have confirmed in patients with moderate to severe pain that most patients could significantly reduce or discontinue use of analgesics (Dolantin, Tramadol or Dihydroetorphine hydrochloride) after pain management with toad venom cream. Toad venom cream can be conveniently administered, and may be adjusted according to size of tumor and range of pain, with no addiction or any toxic or side effects on heart, lung, liver, kidney and gastrointestinal tracts[22].

**Xanthium sibiricum Patrin ex Widder cream**

Xanthium sibiricum Patrin ex Widder cream is made of tender stems and leaves of Xanthium sibiricum Patrin harvested in summer in addition to borneol. First rinse it thoroughly and grind into powder, stew it over intense heat to a high concentration and then remove the dregs; add moderate amount of borneol that has been grind into fine powder, and mix well. Smear the resulted cream onto a piece of gauze, and apply to the lesion. Change the gauze once every 1 - 2 days in an averagely 2-month cycle.

Ma Ze-li et al used this remedy to treat 38 patients with skin cancer, of which 34 had squamous cell carcinoma and four (4) had basal cell carcinoma[24]. Treatment outcome was cure in 23 out of 38 patients and improvement in 15. The shortest treatment course was 57 days, and the longest 19 months[25]. Zong Yu-ying et al conducted an anti-tumor study on 90% ethanol extraction of Xanthium sibiricum Patrin and found it had established anti-tumor effect. Cumanda suggested sesquiterpene lactone might be the major active ingredient responsible for the cytotoxicity and anti-tumor activity[26]. Therefore, Mu Ze-li et al believed Xanthium sibiricum Patrin ex Widder acted as poisonous agent against the vicious tumor in the treatment of skin cancer, and when combined with borneol its effects in dispersing phlegm and stagnation, and eliminating toxin and weakness were enhanced; on the other hand, borneol mitigated the irritation caused by Xanthium sibiricum Patrin ex Widder, thus promoting the cure of skin cancer[25].

**Five-smoke pellets**

The formulation is formulated by a renowned external medicine expert Zhang Yan-ting and is consisted of chalcanthite, cinnabar, realgar, aluminate and magnetite. Before application, rinse the lesion with a rinsing formulation for skin cancer, and select method of administration based on shape of the tumor. For example, the pellets may be applied from the top of the lesion in case the tumor has a larger base, and from the base in case of a smaller base; if there is necrosis and liquidation in the tumor, preferably the pellets should be applied by inserting into the tumor. Dosing frequency was once every 1 - 2 days.

Hu Hui-mung used this formulation to treat four patients with skin cancer of the head, including one patient with cancerated papilloma, and three with squamous cell carcinoma; after treatment all 4 patients were cured[27]. Li Chang-xin used this formulation to treat 16 patients with skin cancer, of which 11 had squamous cell carcinoma, 3 melanoma, 1 basal cell epithelioma, and 1 had synovial sarcoma; treatment outcome showed cure in 10 patients, and improvement in 6 patients[28]. Jing Ai-chen et al suggested that five-smoke pellets provided some advantages, such as alleviating pain, enhancing local blood circulation without causing local bleeding, having no harm to healthy tissue around the lesion, promoting healing of the lesion, and showing no tendency toward recurrence after healing[29]. In clinical application, dosage must be carefully monitored, and the maximum dosage per dose was 6 mg. With repeating dosing, the application range and the tensity must be carefully controlled, that is, when the lesion is adequately treated and is in check, terminate the dosing and let the lesion exfoliate[27].

**Five-tiger pellets**

The formulation is consisted of mercury, alum, green vitriol, and mirabilite. The ingredients are made into pellets
using sublimation method before use. Meanwhile, yellow lead, radix Astragali, medlar and sesame oil are used to prepare the Fairy plaster for future use. Select method of administration based on the severity of tumor necrosis. If there is no ulceration in the tumor, grind the pellets into powder, mix well with rice milk and make it in the shape of a nail, and let it air dry before use. During dosing, pierce into the lesion by 1 - 2 cm using a three-edge needle. If the lesion is already ulcerated, grind the pellets into fine powder, mix well with rice milk and make it in a pasta form. Apply onto the lesion, with thickness of pasta of approximately 0.2 cm[30].

Xiao Yi-liang selected 162 patients with skin cancer as subjects, of which 84 had squamous cell carcinoma, 68 basal cell carcinoma, and 10 melanoma[30]. They were followed up for three years, and cure was achieved in a total of 126 patients, response in 28 patients, and no response in eight patients. Thus the efficacy was quite remarkable. Zhu Bo-fang used the pellets to treat nine patients with melanoma; seven patients were cured, and no recurrence or relapse was noticed after three years of follow-up; one patient showed response, while another showed no response; however, the quality of life was significantly improved as compared to that before treatment in all patients[31]. Xiao Zhi-rong used the pellets to treat 115 patients with malignant skin tumors, and found an overall response rate of 79.10%; these included six (6) patients with malignant melanoma, and all of them achieved favorable efficacy[32]. Xiao Yi-liang believed that the pellets were significantly effective for basal and squamous cell carcinoma, and were somehow effective in melanoma[30].

In clinical application, the formulation contains mercury ion, which may sensitize some patients. Patients may show signs of chronic mercury poisoning after long-term administration[30]. The pellets must be discontinued immediately once similar signs are seen, and meanwhile start an oral antidote therapy: unprocessed mung bean 30 g, Juncus 10 g, and raw licorice stewed in water, and administer the juice orally.

**Issues and prospect**

A large number of clinical reports confirms that topically administered traditional Chinese medicines show well-established efficacy in treatment of superficial tumors, and are easy to administer and cost-effective. In the treatment of malignant superficial tumors, especially skin cancer, topically administered traditional Chinese medicines provides advantages of no scarring and no affect on appearance, when compared to routine surgical treatment. Many traditional Chinese medicinal herbs have significant anti-tumor effects and are very potent. However, some of them are poisonous and sometime highly toxic, for example, arsenic, toad venom, mercury, and realgar, which have been mentioned above, are associated with toxic and side effects to various extents. In anti-tumor treatment, these medicines exert anti-tumor effect by poisoning the cancer, but we should be aware that the application will be limited by their significant toxicity, and by the fact that effective dosage and toxic dosage are not clearly defined. Therefore, with traditional oral administration, they are prone to causing poisoning. When administered by parenteral routes, such as intra-tumor injection, arterial intervention and intra-cavity dosing, they will cause significantly less toxic and side effects. In particular, temporary application on local skin is even safer. While in superficial malignant tumors including skin cancer, the lesion is located superficially, and is easily accessible as compared to other tumor tissues, and thus is particularly suitable for topical transdermal dosing. Not only does such application better target the lesion and result in higher tumor cell cytotoxicity, but also avoid the toxic and side effects that could be caused by systemic therapy.

Although there have been a large number of clinical reports on the topically administered Chinese medicines for the treatment of malignant superficial tumors, including skin cancer, there are quite some issues in current research. First of all, the studies are mainly clinical, without much laboratory investigation. There are many clinical reports of TCM therapies for skin cancer, these are mostly case studies, while large-sample, multi-center studies are missing. Also experimental studies are quite rare. Secondly, the studies mainly involve single-ingredient or multi-ingredient formulations, but barely involve well-defined molecules or groups of molecules. The formulation studies are also short. Thirdly, many studies demonstrate that the medicine or the formulation is effective, but fails to explain the underlying mechanism; there has not been adequate thorough research into this regard.

Concerning the issues mentioned above, the authors believe, while digging deep into the treasury of traditional Chinese medicines, we should preferably screen some of the most effective medicines or formulations, so as to optimize clinical prescription. Secondly, according to the nature of skin cancer and of the medicine, suitable dosage form should be identified by applying the advanced pharmaceutical techniques, such as nano technology, slow-release and controlled release, in order to develop topically administered TCM (Tranditional Chinese Medicine) preparations with high efficacy and low toxicity for skin cancer.

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