Review

Advances in TCM Treatment for Metastasis of Tumors

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As one of the basic biologic features of malignant tumors and a major cause leading to failure of treatment and even death, metastasis has aroused a great interest among the medical researchers. To date, convincing evidence is still lacking as to whether metastasis could be controlled by surgery, radio- or chemotherapy. However, TCM measures have proved to be advantageous in improving the survival quality and prolonging the survival period by decreasing the rate of distant metastasis of tumors. The following is a brief summary on the advances in this field.

Therapeutic Principles

1. Strengthening the body resistance:

Metastasis of the malignant tumors is positively correlated to the inhibitory degree of the immune functions. Recent studies have demonstrated that immune surveillance of the host could eliminate most of the cancer cells in the whole process of metastasis, and a sound immune system could raise the survival rate in patients with tumors by inhibiting the distant metastasis. The previous experiments have proved that illness of the deficiency type is often characterized by decreased immune functions, especially the decrease of the cellular one, while TCM drugs could enhance the immune function of patients with tumors. With carcinoma of esophagus as an example, Shen Weixi et al. studied the relations between TCM deficiency syndromes and such biological behaviors as the degree of metastasis and infiltration as well as the TNM staging, and found that the infiltrating degree of the cancer cells was much severer with a late TNM staging in patients of the deficiency type than those with no signs of deficiency, which was of significant statistical difference.

Jiang Ping et al., based on TCM differential typing, X-ray findings and pathological examinations, treated 38 in-patients with carcinoma of esophagus, and found that the highest rate of metastasis fell into in the type of qi-deficiency with yang-weakness in the late stage. Based on the clinical experience, Liu Jiaxiang et al. summarized that yin-deficiency and deficiency of both qi and yin occupied 80% of carcinoma of lung, and the compound recipes for supplementing qi and nourishing yin could mobilize the immune function to resist the metastasis.

2. Promoting blood circulation and removing blood stasis:

Clinical practice of many years have proved that blood stasis did exist in patients with cancers. However, whether promoting blood circulation and removing blood stasis could prevent metastasis is still open for arguments. Liu Yonghui et al. studied the changes of blood rheology in 77 cases with pulmonary cancers (27 with metastasis and 50 without metastasis), and found that there existed a significant difference in the indices between cancer patients and normal subjects, while the plasma viscosity and fibrinogen content was also significantly different between those who had metastasis and those without metastasis. They
concluded that the high coagulability of blood in cancer patients played an important role in metastasis, and metastasis was very closely related to the micro-blood stasis syndrome.

Wu Shuisheng et al.\(^4\) supported the conclusion that the high coagulability of the blood was related to metastasis of the carcinoma of esophagus. They observed the blood rheologic changes in 63 cases of different stages, and found that all the indices in patients with carcinoma of stomach were apparently higher than those in the normal subjects, while the whole blood viscosity and plasma specific viscosity in patients with metastasis to the regional lymph nodes (35 cases) and distant area(s) (20 cases) were significantly higher than those with no metastasis. Zhao Yujuan et al.\(^5\) also found that the activity of tissue-type plasmin activator and profibrinolysin activating factor in 30 cases with malignant tumors of the blood stasis type was at least twice higher (more than two fold) than that of the normal middle-aged and senile subjects (28 cases), while the activity of profibrinolysin activator inhibitor did not show any significant changes. They, therefore, suggested that for hyperactivity of fibrinolysis and decrease of blood viscosity, it should be preferably treated with the principle of strengthening the body resistance to eliminate the pathogenic factors. The principle of promoting blood circulation to remove blood stasis should be adopted very cautiously to avoid further infiltration and metastasis.

Xu Decheng et al.\(^6\) reviewed the correlation between the intensity of promoting blood circulation to remove blood stasis in the recipe(s) of reinforcing qi and engendering blood and the rate of metastasis of gastric cancer of dual deficiency of qi and blood type. They found that the rate of metastasis was directly proportional to the activity of promoting blood circulation to remove blood stasis. They also urged that doses of such drugs should be lowered gradually to avoid metastasis when the amount of platelets, as well as the rate of platelet aggregation, is decreased markedly, the coagulation time is prolonged, and the level of fibrin degradation product is increased.

**Clinical Treatment**

Local recurrence and distant metastasis are the direct causes leading to death. The distinguishing feature of tumor-bearing survival in TCM therapy of tumors infers that inhibition of its distant metastasis would be one of the mechanisms to treat them effectively. In recent years, the studies were focused on the survival rate and the rate of distant metastasis in carcinoma of the lung, stomach and intestine.

1. Carcinoma of the Lung:

The 5-year survival rate of primary bronchogenic carcinoma was about 13%, and the distant metastasis was the cardinal factor. Kotlyarov et al.\(^7\) reported that the rate of hematogenous metastasis after radical resection was about 55.2%, and 88.7% of them occurred within one year.

With Meta method, Chen Zhifeng et al.\(^8\) made a quantitative analysis on the median survival period of non-small cell lung cancer treated purely with TCM method (according to the data in 7 literatures published in China), and found that the survival period in TCM group was 335.4 days, significantly longer than that of the control group treated with chemotherapy (231.8 days). They concluded that the longer median survival period was contributed not only to killing the tumor cells in situ, but also to inhibiting metastasis to the distant area(s).

Liu Jiaxiang et al.\(^9\) administered TCM drugs for strengthening the body resistance as the main measure assisted by softening the hard masses and removing the toxins to treat 171 cases of middle or late stage carcinoma of the lung. The 1-, 2-, 3- and 5-year survival rate was respectively 60.94%, 36.77%, 31.68% and 24.22%, and the median survival period was 417 days. The actions of the drugs for strengthening the body resistance were nourishing yin,
invigorating qi, and warming yang. The drugs for nourishing yin consisted of Nan Sha Shen (南沙参 Radix Adenophorae), Bei Sha Shen (北沙参 Radix Glehniae), Tian Dong (天冬 Radix Asparagi), Mai Dong (麦冬 Radix Ophiopogonis), Xuan Shen (玄参 Radix Scrophulariae), Bai He (百合 Bulbus Lilii), Di Huang (地黄 Radix Rehmanniae) and Bie Jia (鳖甲 Carapax Trionycis); the drugs for invigorating qi included Ren Shen (人参 Radix Ginseng), Huang Qi (黄芪 Radix Astra galii) Dang Shen (党参 Radix Codonopsis), Tai Zi Shen (太子参 Radix Pseudostellariae), Bai Zhu (白术 Rhizoma Atractylodis Macrocephalae), Fu Ling (茯苓 Poria); and the drugs for warming yang were composed of Bu Gu Zhi (补骨脂 Fructus Psoraleae), Yin Yang Huo (淫羊藿 Herba Epimedi), Rou Cong Tong (肉苁蓉 Herba Cistanche), Tu Si Zi (菟丝子 Semen Cuscutae), Suo Yang (锁阳 Herba Cynomorii), and Bi Li Guo (薜荔果 Receptaculum Fici Pumilae). The 1-, 2-, 3-, and 5-year survival rate in the control group (133 cases treated with chemotherapy only) was respectively 36.67%, 26.79%, 24.56% and 0%, and the median survival period was 265 days. The difference was of great significance in statistical analysis.

Liu et al.21 treated 85 cases of stage III non-small cell lung cancer (neither radio-, chemo-therapy nor surgical operations were performed) by administration of Yi Fei Kang Liu Yin (益肺抗癌饮), 30ml, t.i.d for 60 days. The distant metastasis rate was 23.52% (20/85), which was significantly lower than that of 35.71% (15/42) in the control group (42 cases treated with chemotherapy only). The recipe of Yi Fei Kang Liu Yin: Huang Qi (黄芪 Radix Astra galii), Bei Sha Shen (北沙参 Radix Glehniae), Tian Dong (天冬 Radix Asparagi), Nü Zhen Zi (女贞子 Fructus Ligustri Lucidi), Shi Shang Bo (石上柏 Herba Selaginellae Doederleinitii), and Chong Lou (重楼 Rhizoma Paridis).

Lin Hongsheng et al.22 reported the effect of Fei Liu Ping No. II (肺瘤平Ⅱ号 20g/time, bid). It was administered for a long period (≥6 months in a year) in 25 cases of carcinoma of the lung. The 1-year survival rate was 28% (7/25) significantly higher than that of 10% (1/10) in the control group (10 cases treated with chemotherapy, 2-3 courses in a year). The results confirmed that TCM treatment could prolong the survival period. The recipe of Fei Liu Ping No. II: Huang Qi (黄芪 Radix Astra galii), Xi Yang Shen (西洋参 Radix Panacis Quinquefolii), Chong Lou (重楼 Rhizoma Paridis), Bai Hua She She Cao (白花蛇舌草 Herba Hedyotis Diffusae), Tao Ren (桃仁 Semen Persicae) and San Qi (三七 Radix Notoginseng).

2. Carcinoma of the Colon:

Although most carcinoma of the colon was treated surgically, the recurrence rate and distant metastasis is still as high as 40%-70% even a radical resection is performed.23

Guo Yong et al.24 designed a basic recipe called Chang Liu Ping (肠瘤平), and administered it in combination with surgery and/or chemotherapy to treat 31 cases of middle or late stage carcinoma of the colon. The 1-, 3-, and 5-year survival rate was respectively 100% (31/31), 80.6% (25/31) and 64.5% (20/31), apparently higher than those who were not treated with the recipe. Composition of the basic recipe: Dang Shen (党参 Radix Codonopsis) 12g, Bai Zhu (白术 Rhizoma Atractylodis Macrocephalae) 12g, Fu Ling (茯苓 Poria) 12g, Gan Cao (甘草 Radix Glycyrrhizae) 6g, Teng Li Gen (藤梨根 Radix Actinidiae Chinensis) 30g, Shui Yang Mei (水杨梅 Radix Adinae) 30g, Hu Zhang (虎杖 Radix Polygoni Cuspidati) 30g, Shan Zha (山楂 Fructus Crica ti) 30g, and Ji Nei Jin (鸡内金 Endothelium Cornuem Gigeriae Galli) 6g. Modification: For deficiency of the spleen and qi stagnation, 12g of Mu Xiang (木香 Radix Aucklandiae), 12g Tian Xian Teng (天仙藤 Herba Aristolochiae) and 15g Da Fu Pi (大腹皮 Pericarpium Arecae) were added. For downward flow of damp-heat, 30g Yi Yi Ren (意苡仁 Semen Coicis), 15g of Bai Tou Weng (白头翁 Radix Pulsatillae) and
15g Feng Wei Cao (凤尾草 Herba Pteridis Multifidae) were added. For depletion of liver- and kidney-yin, 15g Gou Qi Zi (枸杞子 Fructus Lycii), 12g Di Huang (地黄 Radix Rehmannia) and 12g Shan Zhu Yu (山茱萸 Fructus Corni) were added.

Pan Mingji et al. 25 treated 260 cases of carcinoma of the colon (stages II, III, and IV), who had undergone surgery and then treated with Fu Zheng Jian Pi Tang (扶正健脾汤) during chemotherapy, Fu Zheng Yang Yin Tang (扶正养阴汤) during radiotherapy, and Fu Zheng Jie Du Tang (扶正解毒汤) during intermittent and convalescent stages. The recipes were administered with modifications according to the morbid state of the patients. Composition of Fu Zheng Jian Pi Tang (Body Resistance-strengthening and Spleen-invigorating Decoction): Huang Qi (黄芪 Radix Astragali) 30g, Dang Shen (党参 Radix Codonopsis) 15g, Bai Zhu (白术 Radix Atractylodis Macrocephalae) 12g, Fu Ling (茯苓 Poria) 12g, Gan Cao (甘草 Radix Glycyrrhizae) 3g, Shu Di Huang (熟地 黄 Radix Rehmannia) 15g, Gou Qi Zi (枸杞子 Fructus Lycii) 12g, He Shou Wu (何首乌 Radix Polygoni Multiflori) 12g, Huang Jing (黄精 Rhizoma Polygonati) 10g, Nü Zhen Zi (女贞子 Fructus Ligustri Lucidi) 15g, Sha Shen (沙参 Radix Glehniae seu Adenophorae) 10g, Mai Dong (麦冬 Radix Ophiopogonis) 10g, Ji Xue Teng (鸡血藤 Caulis Spatholobi) 25g, Qian Shi (柴胡 Radix Bupleuri) 15g, Shan Yao (山药 Rhizoma Dioscoreae) 12g. Composition of Fu Zheng Yang Yin Tang (Body Resistance-strengthening and Yang-nourishing Decoction): Huang Qi (黄芪 Radix Astragali) 30g, Dang Shen (党参 Radix Codonopsis) 15g, Fu Ling (茯苓 Poria) 12g, Bai Zhu (白术 Radix Atractylodis Macrocephalae) 12g, Gan Cao (甘草 Radix Glycyrrhizae) 3g, Tai Zi Shen (太子参 Radix Pseudostellariae) 15g, Ren Shen (人参 Radix Ginseng) 8g, Mai Dong (麦冬 Radix Ophiopogonis) 10g, Sha Shen (沙参 Radix Glehniae seu Adenophorae) 10g, Yu Zhu (玉竹 Rhizoma Polygonati Odorati) 1g, Bai Hua She She Cao (白花蛇舌草 Herba Hedyotis Diffusae) 15g, Dan Shen (丹参 Radix Salviae Miltiorrhizae) 10g. Composition of Fu Zheng Jie Du Tang (Body Resistance-strengthening and Toxin-resolving Decoction): Dang Shen (党参 Radix Codonopsis) 15g, Bai Zhu (白术 Rhizoma Atractylodis Macrocephalae) 12g, Fu Ling (茯苓 Poria) 12g, Gan Cao (甘草 Radix Glycyrrhizae) 4g, San Qi (三七 Radix Notoginseng) 1.5g, Huang Qi (黄芪 Radix Astragali) 30g, Bai Ying (白英 Herba Solani Lyrati) 20g, Bai Hua She She Cao (白花蛇舌草 Herba Hedyotis Diffusae) 15g, Ban Zhi Lian (半枝莲 Herba Scutellariae Barbatae) 15g, Huang Jing (黄精 Rhizoma Polygonati) 15g, Nü Zhen Zi (女贞子 Fructus Ligustri Lucidi) 15g, Xian He Cao (仙鹤草 Herba Agrimoniae) 15g. The decoction was given one dose daily or every other day in the first year, 3 doses every week in the second year, and 2 doses weekly from the third year.

The 5-year survival rate for patients at stage II, III, and IV was respectively 80.6%, 56.1% and 21.7% (mean, 50.4%)26.

Guo Zhixiong27 reported that 38 patients with carcinoma of the colon had undergone surgery, and then treated with the basic recipe Fu Zheng Yi Ai Tang (扶正抑癌汤) he designed. The 1-, 3-, and 5-year survival rate was respectively 100%, 82.4% and 65.7%, and the median survival period was 31.4 months, significantly higher than the control group treated with chemotherapy only (89.7%, 61.2%, 41.3% and 18.0 months). The results supported the conclusion that TCM measures have a synergistic effect with chemotherapy. Composition of Fu Zheng Yi Ai Tang (扶正抑癌汤 Body Resistance-strengthening and Tumor-inhibiting Decoction): Yi Yi Ren (薏苡仁 Semen Coicis) 60g, Ren Shen (人参 Radix Ginseng) 10g, Ling Zhi (灵芝 Ganoderma Lucidum) 10g, San Qi (三七 Radix Notoginseng) 10g, Huang Qi (黄芪 Radix Astragali) 15g, Bai Zhu (白术 Rhizoma Atractylodis Macrocephalae) 15g, Ku Qiao Tou (苦荞麦 Radix et Rhizoma Fagopyri Dibotrydis) 15g, Wu Hua Guo (无花果 Receptaculum Fici
Caricae) 15g, Zhu Ling (猪苓 Polyporus) 15g, Shan Ci Gu (山慈菇 Pseudobulbus Cremasae seu Pleiones) 15g, Shan Dou Gen (山豆根 Radix Sophorae Tonkinensis) 15g, Dan Shen (丹参 Radix Salviae Miltiorrhizae) 30g, Bai Jiang Cao (败酱草 Herba Patriniae) 30g. The decoction was given one dose a day for 2 courses (2 months each).

3. Carcinomas of the Stomach:

Though surgical operation is the main measure for carcinoma of the stomach, its recurrence and metastasis are still unavoidable. It has been proved that a combined therapy is the only way to improve the prognosis. Shen Hongxun et al. reported that combination of administration of Fu Fang Shen San Qi Gao (复方参芪膏 Composite Ginseng and Notoginseng Paste) with chemotherapy had produced a 5-, 8-, and 10-year survival rate (35 cases) of 80.0% (16/20), 60.0% (9/15) and 57.1% (8/14). The remote therapeutic effect was superior to that treated with chemotherapy only (35 cases), the survival rates for the latter was 58.6% (17/29), 40.0% (4/10) and 14.3% (1/7) respectively. The composition of the Fu Fang Shen San Qi Gao included San Qi (三七 Radix Notoginseng), Ren Shen (人参 Radix Ginseng), Huang Qi (黄芪 Radix Astragali), Dang Gui (当归 Radix Angelicae Sinensis), Chen Pi (陈皮 Pericarpium Citri Reticulatae), Mu Xiang (木香 Radix Aucklandiae), Chuan Wu (川乌 Radix Aconiti), Ban Zhi Lian (半支莲 Herba Scutellariae Barbatae) and Ban Bian Lian (半边莲 Herba Lobeliae Chinensis). The decoction was given one dose a day starting from 3 weeks after the operation for 2 courses (3 months each) in the first 2 years, and one course in the third year.

Yang Jiquan et al. reported that in his series of 69 cases of middle and late stage carcinoma of the stomach treated with a basic recipe, the number of cases with a rate (%) of survival period over 6 months, and over 1, 3 and 5 years was respectively 47 (85.4), 42 (84), 31 (56.4) and 25 (45.4), and the median survival period was 2.45 years. The effect was superior to that in the control group of 33 cases treated with the recipe and chemotherapy, the figures for the latter were 25 (83.3), 23 (76.7), 16 (53.3), 13 (43.3) and 1.73 years, respectively. Although the difference was not significant in statistical analysis, it did show that the recipe had a great impact on the remote survival. Composition of the basic recipe: Huang Yao Zi (黄药子 Rhizoma Dioscoreae Bulbiferae) 15-30g, Rou Gui (肉桂 Cortex Cinnamomi) 10g, Gan Jiang (干姜 Rhizoma Zingiberis) 10g, Huang Qi (黄芪 raw Radix Astragali) 30g, Dang Shen (党参 Radix Codonopsis) 15g, Xu Duan (续断 Radix Dipsaci) 15g, Sha Yuan Zi (沙苑子 Semen Astragali Complanati) 15g, Chen Pi (陈皮 Pericarpium Citri Reticulatae) 10g, Zhe Shi (赭石 Haematitum) 30g, Teng Li Gen (藤梨根 Radix Actinidae Chinensis) 30g, Bai Hua She She Cao (白花蛇舌草 Herba Hedyotis Diffusa) 30g, Bing Lang (槟榔 Semen Arecae) 20g, E Zhu (艾术 Rhizoma Curcumae) 10g, Sheng Jiang (生姜 Rhizoma Zingiberis Recens) 5g, Da Zao (大枣 Fructus Jujubae) 10g.

The basic recipe recommended by Bo Ping et al. for strengthening the body resistance and removing blood stasis was composed of Huang Qi (黄芪 Radix Astragali) 15g, Bie Jia (鳖甲 Carapax Trionycis) 12g, She Liu Gu (蛇六谷 Rhizoma Arismatidis) 12g, Bi Hu (壁虎 Gecko Domestica) 12g, Bai Zhu (白术 Rhizoma Atractylodis Macrocephalae) 12g, Yi Yi Ren (益智仁 Semen Coicis) 30g, Dang Gui (当归 Radix Angelicae Sinensis) 10g, Fu Ling (茯苓 Poria) 18g, and Bai Hua She She Cao (白花蛇舌草 Herba Hedyotis Diffusa) 30g. Modifications: For insufficiency of stomach-yin, 10g Di Huang (地黄 Radix Rehmanniae), 10g Xuan Shen (玄参 Radix Scrophulariae), and 10g Mai Dong (麦冬 Radix Ophiopogonis) were added. For accumulation and obstruction of phlegm-dampness, 10g Ban Xia (半夏 Rhizoma Pinelliae), and 10g Dan Nan Xing (胆南星 Arisaema cum Bile) were added. For exuberance of
heat-toxin, 30g Ban Zhi Lian (半支莲 Herba Scutellariae Barbatae), 10g Shan Ci Gu (山慈姑 Pseudobulbus Cremastreae seu Pleiones) and 10g Long Kui (龙葵 Herba Solani Nigri) were added. And for apparent accumulation of blood stasis, 10g Shui Zhi (水蛭 Hirudo) and 10g Chuan Xiong (川芎 Rhizoma Chuanxiong) were added. This recipe was used to support 36 post-operative cases of stomach carcinoma during chemotherapy. The number of cases with metastasis to the regional lymph nodes or remote area(s) was 10, and no recurrence and metastasis was found in 22 cases, with 4 undefined cases in a one-year follow-up period. The figures in the control group of 32 cases treated only by chemotherapy were respectively 18, 11 and 3. The results indicated that the recipe combined with chemotherapy could inhibit metastasis to the remote areas.

There are also some clinical studies on the effects of TCM drugs on metastasis of the mammary carcinoma and tumors of the head and neck. Cao Yang et al31 adopted Cox proportional hazards model to study the prognosis of postoperative survival of squamous carcinoma of the head and neck, and found that administration of TCM decoctions would be the leading factor that affects the survival function. Qiu Weiliu et al32 also found that Shen Yang Fang (参阳方) could prolong the survival period for patents with squamous carcinoma of the oral cavity in their prospective study. Liu Yanhong et al33 reported that no metastasis was found during a 3-year follow-up period in 40 postoperative cases of mammary carcinoma undergone radio- and/or chemotherapy and given TCM herbal decoctions.

Zhuo Bin34 treated 36 cases of mammary carcinoma who underwent surgery, and radio- or chemotherapy, combined with oral administration of Ru Kang Tang (乳康汤). 34 cases (94.4%) were free from recurrence and metastasis in 3-5 years, and the 5-year survival rate was 69.4%. Composition of Ru Kang Tang: Tai Zi Shen (太子参 Radix Pseudostellariae), Bai Shao (白芍 Radix Paeoniae Alb), Huang Qi (黄芪 Radix Astragali), Gou Qi Zi (枸杞子 Fructus Lycii) and Ban Zhi Lian (半支莲 Herba Scutellariae Barbatae), etc. Chang Zeling et al35 reported that chemotherapy combined with administration of the circulation-promoting and blood stasis-removing drugs could markedly decrease the rate of distant metastasis in cases of nasolaryngeal cancer, and Li Lianhua et al36, 37 stated that TCM decoctions might raise the survival rate.

**Summary**

The above therapeutic results show that TCM drugs have excellent effects in counteracting the metastasis of tumors. They can produce a synergistic effect when used together with surgery, radio- and chemotherapy. In analyzing the relationship between the factors that affect the distant metastasis, the authors strongly recommend that the FDM-survival rate be used, i.e. the survival rate free from distant metastasis as suggested by Hong Minghuang et al38 in their article. An analysis based on FDM-survival rate in a duration of three or five years with the data treated with the Kaplan-Meier and/or Life Table would be rational and convincible.

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