Journal of Pharmacopuncture

ISSN 2093-6966(Print), ISSN 2234-6856(Online)
Journal of Pharmacopuncture 2013;16(1):012-020
DOI: http://dx.doi.org/10.3831/KPI.2013.16.005

Review Article

Review of Tumor Dormancy Therapy Using Traditional Oriental Herbal Medicine

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Key Words
cancer dormancy, dormancy therapy, traditional Oriental herbal medicine

Abstract

Objective: Standard cancer therapy prolongs survival, but can be detrimental to the quality of life, compromise the immune system, and leave residual disease that can cause recurrence years or decades in the future. Tumor dormancy therapy is a novel therapeutic approach that may improve these shortcomings, promote quality of life, and prolong survival. The aim of this study was to analyze studies on dormancy therapy, especially studies using traditional Oriental herbal medicine, so as to evaluate the efficacy of dormancy therapy with traditional oriental herbal medicine.

Methods: We conducted a systematic literature review using Scientific and Technical Information Integration Services (NDSL), PubMed, and RISS. We searched for clinical reports, papers, and books related to tumor metastasis, recurrence, immunotherapy, tumor dormancy, and traditional oriental herbal medicine with anticancer effects. Seventy-nine (79) experimental and clinical articles in both Korean and English were reviewed. This study was conducted from March 1, 2012 to May 31, 2012.

Results: This approach, Tumor dormancy therapy, rather than seeking to remove the tumor, includes combination of low-dose chemotherapy, immunotherapy, immunosurveillance, and other methods to stabilize tumor growth and to enhance the host is immunity against disseminated tumor cells and thus to manage cancer as a chronic disease while maintaining quality of life. In particular, integrative use of Oriental herbal medicine has been shown to induce or maintain tumor dormancy, increase the effectiveness of conventional chemotherapy, improve quality of life, and prolong survival.

Conclusion: Tumor dormancy therapy is a promising novel therapeutic approach that may be especially effective with Oriental herbal medicine. Further research is needed to determine its potential mechanisms and therapeutic applications.

Received: Oct 30, 2012 **Accepted:** Jan 18, 2013

1. Introduction

According to the National Health Insurance Corporation, Korea, in 2010, the total number of cancer patients was estimated to be 290,000. Last year, the incidence of newly-developed cancer cases was

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110,000 and between 1999 - 2008, the number of cancer-related deaths in Korea increased from 114.4 to 116.1 per every 100,000 people [1]. Because of this increase in the number of cancer-related deaths, economic and social losses have also increased. The cumulative national cost of cancer treatment is approximately 2.2 trillion won per year, and direct and indirect costs total 14.1 trillion won per year, or 1.75% of the GDP in Korea [2].

Recently, tumor research has made great strides, but life extension effects have not met the level of technological development. Conventional cancer treatments reduce tumor size and kill tumor cells directly, but can have negative side effects. In addition, even if the primary treatment for tumors is successful, local or distal metastasis can still occur after many years. This shortcoming necessitates further tumor treatment research. Tumor dormancy is the period when the tumor does not progress and does not present symptoms [3-5], it is found occasionally [6-8]. Tumor dormancy therapy utilizes this state and aims to suppress and stabilize cancerous cell growth after removal of the primary tumor. Tumor dormancy therapy reduces the side effects of chemotherapy and improves, the relative quality of life [9-11], and can thus improve the efficacy of standard treatment by reducing dose delays and reductions [10].

Many studies have been reported that Oriental herbal medicine promotes apoptosis in a tumor, increases immunity, and relieves the side effects of chemotherapy or hormone therapy. Thus, Oriental herbal medicine with a particular mechanism can be supposed to lead to tumor dormancy.

In this study, we review literature related to both chemotherapy and tumor dormancy therapy, with emphasis on the potential benefits of utilizing traditional Oriental herbal medicine integrated with tumor dormancy therapy.

2. Methods and materials

2.1. Data sources

The main databases used for the electronic searches were 'Scientific and Technical Information Integration Services (NDSL)', 'www.pubmed.com' and 'www.riss.kr'. Copies of relevant papers and electronic files from this search were downloaded or requested from the library or institute. Bibliographies of relevant papers were also searched by purchasing books and other publications on related themes and were summarized and extracted in the required range. In addition, authoritative Internet sources (www.kosis.kr, www.fda.gov, www.cancer.gov) were included in the data collection. This study was conducted from March 1, 2012 to May 31, 2012.

2.2. Study selection

Searches were limited to domestic and international clinical reports, discussion papers related to tumor metastasis and recurrence reporting significant anti-cancer effects, and books on immunotherapy and tumor dormancy therapy. For internet sources, tumor treatment standards and guidelines were referenced.

2.3. Data extraction

We searched for clinical reports, papers, and books with the terms "tumor metastasis, recurrence, immunotherapy, tumor dormancy, traditional, oriental and herbal medicine. Seventy-nine experimental and clinical articles in both Korean and English were reviewed.

3. Results and Discussion

3.1.Background and concept of dormancy therapy

Cancer treatments consist of surgical tumor resection, systemic chemotherapy, and local radiotherapy. In cancer therapy, surgery is the most obvious way to remove the tumor, but as an invasive treatment, includes the side effects of pain and weakness. Ironically, surgery activates cyclooxygenase (COX) -2 inhibitor and β,-adrenerigic blocker, which cause immune suppression and prostaglandin and stress hormone release, thus increasing the risk of infection and micrometastasis. Chemotherapy shrinks the primary tumor, but also inhibits active bone marrow and stem cell regeneration as well as tumor cell growth, leading to suppressed immunity, weakness, hair loss, nausea and other side effects. Short-term tumor inhibition with chemotherapy also weakens immunity, eventually decreasing overall fitness and predisposing the patient to future metastasis.

Reports indicate that the decrease in tumor size with chemotherapy does not directly lead to prolonged survival time. Even when the tumor is effectively reduced, life extension is not clinically substantiated. Current chemotherapy is considered valid when it reduces the tumor size by 50%. However, a successful 50% reduction in tumor size only prolongs survival an average of about two months. A 90% tumor size reduction increases survival time by almost a year, but few patients attain this clinical outcome [10]. Radiation therapy causes side effects such as hair loss, organic brain disorders, oral mucositis, xerostomia, radiation pneumonitis, and radiation enteritis. It may effectively shrink tumors, but degrades the quality of life of patients [12].

Conventional chemotherapy cannot remove disseminated tumor cells (DTCs), which means it cannot prevent the tumor cells from having proliferating or dormant cancer cells from activating in the future [13-15]. Adjuvant chemotherapy for breast cancer patients does not completely remove DTCs located in the bone marrow, and in fact, studies suggest that achieving complete cancer remission through chemotherapy impossible [16]. Rather, malignant cancer cells can develop a resistance to chemotherapy, further complicating complete removal. Studies have shown that micro-environments are degraded during chemotherapy, which promotes the growth of DTCs [17].

Anticancer drugs were not originally designed to be cancer-specific, but to act upon all differentiated cells. They affect not only cancer cells but also bone marrow; the gastrointestinal tract, the liver, and actively dividing cells. Because of this, chemotherapy side effects are severe and can include cachexia, fatigue, and overall reduced quality of life.

Cancer micrometastasis might not proceed and might not be harmful in itself. In the 1990s, a new approach called tumor dormancy therapy drew attention for its clear effects on prolonged survival and possible inducibility. Tumor dormancy therapy was proposed by Dr. Yutaka Takahashi of Japan's Kanazawa University Cancer Institute and seeks not to kill tumor cells or reduce tumor size, but to stabilize tumor cell growth while maintaining the patient's quality of life. In contrast to conventional cancer therapy which treats and removes cancer cells, tumor dormancy therapy is patient-centered and aims to maintain quality of life while reducing side effects.

Cases in which patients with malignant tumor cells have lived the rest of their lives with no evidence of disease have been reported. In one clinical case, kidneys transplanted from a donor who had been treated for invasive melanoma 16 years earlier and in whom no residual tumors had been found, rapidly metastasized in the organs of the immuno-suppressed recipients [18]. In such cases, possible genetic, cellular, immune environments that promote or suppress tumor growth and induce tumor dormancy evidently exist. Examining current available clinical and experimental findings on tumor stem cells, immune therapy, and tumor suppressor genes may elucidate a more comprehensive understanding of tumor dormancy, its mechanisms, and its very exciting clinical applications for reducing recurrence and increasing patient survival rate.

3.2. Mechanism of tumor dormancy

The mechanisms of inducing and maintaining tumor dormancy are unclear. Homeostatic controls, such as anti-angiogenesis despite active proliferation and immunological condition, are known to contribute to tumor dormancy that can then lead to years of minimal residual disease [19]. Meanwhile, the identified mechanisms are as follows: Cellular dormancy includes two states, static and dynamic dormancy. Static dormacy is growth arrest in the G0-G1 phase of the cell cycle. In some studies, this arrest of tumor cells is directly linked to tumor dormancy [3, 20-23]. Dynamic dormancy is a state of balance between cell proliferation and apoptosis. In spite of active micrometastasis, cancer cells are destroyed at the same rate, so a dynamic equilibrium state is achieved. By regulating internal mechanisms that determine the cell cycle, cellular dormancy may be achieved.

Tumors metastasize through angiogenesis [24-28], which can be described in five stages. First, cells mutate and then become angiogenic and proliferate easily. Next, growing cells destroy the cell membrane and enter blood vessels. By overcoming the flow of blood and immune cells, cancer cells reach blood vessels throughout the body, finally increasing angiogenesis and metastasizing in distal organs. Therefore, angiogenesis plays an important role in tumor metastasis. During tumor dormancy, anti-angiogenesis factors are activated, while angiogenesis factors are inhibited [29-33]. If this protective mechanism is broken by external factors, angiogenic factors are activated, anti-angiogenesis factors are suppressed, and tumors quickly form new blood vessels. Therefore, anti-angiogenesis therapy may suppress tumor growth and promote tumor dormancy [34]. The development of angiogenesis-inhibiting drugs has the promising potential to inhibit metastasis.

Controlled trials have studied the effects of immunotherapy on induced tumor growth and have shown that mice treated with immunotherapy have inhibited tumor growth compared to active controls. These studies show evidence that tumor growth is affected by the host's learned immune system which can promote or inhibit tumor growth [35-37]. This immune mechanism is associated with cytokine secretion by the white blood cells that induce various immune responses. White blood cells consist of lymphocytes, such as T lymphocytes, B lymphocytes, NK cells, monocytes such as macrophages, and granulocytes such as neutrophils.

Cytokines secreted by these cells have several types and mediate cell interaction. Cytokines such as interferon and tumor necrosis factor inhibit proliferation of cancer cells. Interferons activate cytotoxic T-lymphocytes, NK cells and macrophages, and suppress the tumor cell by inhibiting angiogenesis. Tumor necrosis factor (TNF)

consists of TNF-α and TNF-β. TNF-α from activated macrophages and TNF-β from active T-cells are secreted to kill tumor cells. In addition, reports have indicated that activated T cells inhibit tumor growth by surrounding tumor cells. In particular, CD8 + T cells inhibit the proliferation of tumor cells, which then induced inhibits the growth of DTCs [38].

Other proteins known to be associated with tumor dormancy are urokinase receptor (uPAR), Epidermal growth factor receptor (EGFR), Extracellular signal-regulated kinases (ERK), and genes p38, p53, myc, and ras. uPAR inhibits inflammation by disabling the uPA, regulating protein degradation, and activating many intracellular signaling pathways to inhibit tumor growth. Overexpression of EGFR is associated with tumor genesis. From the identification of EGFR as an ocogene, anticancer agents such as gefitinib, erlotinib, and cetuximab have been developed. The ERK pathway concluding ERK protein is a chain of proteins in the cell that communicates a signal from a receptor on the cell. In tumor cells, irregularity of ERK causes disruption of ERK pathway. The p38 gene is involved in cellular cytokine secretion, cell apoptosis, and cell differentiation. Tumor dormancy is associated the inhibition of p38 which produces therapeutic effects in case of inflammation and autoimmune disease. p53 is a tumor suppressor gene that prevents mutation of cells during the cell cycle. Myc and ras are involved in tumor formation and play a role in modulating tumor dormancy. Myc is a gene that modulates transcription and is overexpressed in many carcinomas while Ras is known to be a regulator of myc activity. Inhibition of Ras expression is associated with tumor recurrence, endometrial apoptosis of tumor cells and vascular collapse of tumor cells. In addition, tumor dormancy may be modulated by hormone regulation [5]. In general, the incidence of ER/PR+ breast cancers is known to be increased by estrogen exposure, but therapeutic exposure to high doses of estrogen is also said to lower the incidence of gastric cancer [39]. Tumor dormancy is also influenced by diet [40]. Various mechanisms are involved in tumor dormancy, but many aspects that need further research still exist.

3.3. Tumor dormancy therapy

Angiogenesis is required for a tumor to grow beyond a certain size. Experimental results show that anti-angiogenic medicine can extend tumor dormancy and even remove spread cancer cells [41]. Normal cells undergo a cell cycle in which they are repeatedly destroyed and regenerated. Tumor cells bypass this balance of apoptosis and proliferation. Chemotherapy not only inhibits angiogenesis, but also causes apoptosis of tumor cells. For example, mice with induced colorectal cancer treated with UFT (oral 5-FU) had observed tumorcell apoptosis and inhibited of angiogenesis [42].

Hormone-dependent tumors treated with hormone therapy have reduced proliferation of micro tumor cells. In fact, it is a standard of care for patients with ER+ breast cancer to be treated with anti-estrogen therapy such as tamoxifen. Conventional chemotherapy has severe side effects in proportion to its dosage. High dose chemotherapy has a high intensity of side effects while low-dose oral chemotherapy has a lower intensity of associated side effects, making it possible to take chemotherapy medication continuously long-term. One report indicates that long-term, low-intensity treatment is more effective than high-dose chemotherapy for elderly patients and cancer patients with faster growth rates. Research in Japan has shown that low-dose combinations of 5-FU and cisplatin are effective in promoting anti-angiogenesis, immune system maintenance, immune function resurrection, and cachexia improvement. Also, in a comparison of 16 cases treated with low-dose Irinotecan to 17 cases treated with high-dose Inrinotecan, side effects were less intense in the low-dose group compared to 11 out of 17 patients experiencing side effects in the high dose group. In most cases in which tumor dormancy therapy is administered, stopping the proliferation of tumors is possible. Long-term chemotherapy has also been shown to be possible because of its low intensity of side effects [9].

Recent studies show that immune status and tumor dormancy are closely related. Especially, mushroom polysaccharides have been shown to induce differentiation of cytokine-secreting cells, thus improving anticancer effects. Animal studies suggest the presence of a tumor suppressor gene that may induce tumor dormancy and inhibit tumor growth. Based on the results of those studies, p53 gene therapy for thyroid carcinomas has been carried out to inhibit angiogenesis and has been observed to have an effect on tumor dormancy [43]. uPAR, EGFR, and ERK have been associated with tumor growth. Agents that block signaling associated with receptors and receptor precursors, and so induce tumor dormancy, have been studied [44-46]

3.4. Oriental herbal medicine therapy in tumor dormancy therapy

Oriental herbal medicine can relieve the side effects associated with low-dose chemotherapy or hormone therapy and can boost quality of life by regulating biological rhythm. In addition, long-term use of Oriental herbal medicine can moderate anticancer activity and

promote apoptosis, making it faster than the rate of tumor proliferation. It can also inhibit angiogenesis and increase immunity. Because of these benefits, the cancer can maintain dormancy. In the principle of Oriental medicine 扶正祛邪 (reinforce the healthy qi and eliminate the pathogenic factors), considering overall health, as well as the treatment of illness is important. This concept is similar to tumor dormancy therapy in that it suppresses a tumor by activating the host's immune function. This is especially beneficial for elderly cancer patients for whom chemotherapy leads to no change in life expectancy, but can profoundly affect quality of life, necessitating an approach that will allow such patients to live with their cancer rather than actively remove it. Clinical cases of Oriental medicine therapy have shown significant results.

In China, nasopharynx cancer, advanced gastric cancer, colorectal cancer, liver cancer, pancreatic cancer and lung cancer patients treated with herbal medicine have a good progress compared to such patients treated only treated with chemotherapy. One report said that a combination of radiation therapy and Oriental medicine is more effective than radiation therapy only. Another report said that a combination of chemotherapy and Oriental medicine had a good prognosis, increasing the effectiveness of chemotherapy, relieving symptoms, and side effects for bone marrow and the digestive system, and ultimately improving the quality of life and immunity [9]. Although the mechanism is unknown, because of these positive results, we can assume that herbal medicine inhibits tumors effectively. We think that treating tumors with Oriental medicine leads to static or dynamic dormant tumors. These mechanisms are slowly being revealed through study, as detailed belows:

When advanced colorectal cancer patients took PHY906 ablets pharmaceutically developed from Oriental herbal medicine 黃芩湯 (*Scutellaria baicalensis Georgi* decoction) during chemotherapy, antitumor effects were increased with no increase in toxicity or inhibition of antitumor effects [47]. *Aconitum koreanum R. Raymund* extracts (supercritical fluid extraction with CO, SFE-CO2) increases active oxygen levels that induce reduction of mitochondria cytoplasm. It increases intracellular calcium concentrations of SMMC-7721 cells in cancerous liver cells and inhibits the Bcl-2 gene, promotes Bax expression, and increases caspase-3 and caspase-9 protease activity. Through this process, cancer cells enter apoptosis [48]. In renal cancer treatment, *Orobanche coerulescens* has a synergistic effect with 5-FU, which inhibits tumor metastasis. According to an analysis, *Orobanche coerulescens* deactivates nuclear factor-kβ. This reduces the expression of ICAM-1 (786-O cell adhesion factors) so that apoptosis is promoted by its synergistic effect. It seems to also inhibit metastasis through this mechanism [49].

Sophora flavescens Ait. extract has been shown to inhibit MCF-7 SP cells in both in-vitro and in-vivo studies. When mice received injections of the 10000 SP cell, were randomly assigned to groups receiving either *Sophora flavescens Ait.* extract, cisplatin, or saline, and were compared after 7 weeks of treatment, the *Sophora flavescens Ait.* extract group had nearly a 90% reduction in SP cells and a downregulation of important gene signaling mechanisms of Wnt. The mechanism of Wnt signaling is upregulated in tumors that are derived from SP cells compared to tumors not derived from SP cells. The tumor formation rate of the *Sophora flavescens Ait.* extract group was 33%, that of the cisplatin group was 50%, and that of the saline group was 100%. These results show that *Sophora flavescens Ait.* extract downregulates the Wnt / beta-catenin pathway, so that it seems to inhibit tumor growth. *Sophora flavescens Ait.* extract may have a valid effect on tumor cells, but more research is needed [50].

Ganoderma lucidum extract inhibits invasive breast cancer cells. Ganodermanontriol (GDNT) inhibits CDC20, which are cell-cycle regulatory proteins. CDC20 is overexpressed in the tumor and in tumor precursors. GDNT also inhibits the secretion of urokinase-plasminogen activator (uPA), the activity of the uPA receptor, and invasive activities like cell adhesion, cell metastasis, and cell invasion [51]. Research has shown that officinalis extracts have an anti-proliferative effect on estrogen receptor-positive breast cancer cells [52].

According to research on ovarian cancer, *Ganoderma lucidum* extract decreased cyclin D1 expression, and inhibited the cell cycle and, in turn, cell growth. In addition, it has antioxidant activity. Because it promotes health by suppressing carcinogenic activity, it can be beneficial as an adjuvant therapy for chemotherapy [53]. Celastrol contained in *Celastrus orbiculatus* has been reported to promote apoptosis and to inhibit tumors in cervical, lung, and prostate cancer [54]. Berberine acid contained in *Coptis chinensis* and *Phelledendron amurense* has been found to reduce drug-resistance and to increase the sensitivity of multi-drug chemotherapy. This improves the quality of life of patients and introduces new insight into the field of cancer-cell metabolism and future nanoparticle treatment [55].

Furanodiene in *Clematis manshurica* extracts has been shown to have an anti-angiogenic effect by inhibiting microtubule formation through PI3K pathway regulation and control of endothelial cell growth, invasion, and

metastasis [56]. The apoptotic effect of *Bufonis Venenum* has been observed in in-vitro studies with T24 bladder cancer cells. In the G2/M phase, the cell cycle did not progress because it accumulated chromatin and cell bodies in the G1 phase. *Bufonis Venenum* induces apoptosis by protease activation of caspase-3, caspase-8, and caspase-9. In addition, it is related to the downregulation of ADP-ribose polymer synthesis and mitochondrial cytoplasm collapse. *Bufonis Venenum* also inhibits the secretion of inhibitor of apoptosis proteins (IAP) which is the protein that inhibits the Bax/Bcl-2 ratio and reduces apoptosis [57].

Pseudotsuga menziesii is one kind of pine, in which B-type procyanidin is the major component, and is known to prevent the proliferation of tumor cells. Experimental results with *pseudotsuga menziesii* extract showed no significant effect for HeLa cell (cervical cancer cell) adhesion, but it did show strong metastasis inhibition [58]. *Oldenlandia diffusa* extracts prevent proliferation and angiogenesis of human umbilical vein endothelial cells (HUVEC) in the G1 to the S phase of the cell cycle. Furthermore, it also decreases the expression of mRNA and HUVEC's VEGF-A. In other words, *Oldenlandia diffusa* extracts have anticancer effects through anti-angiogenesis [59].

3.5. Future of tumor dormancy therapy

New studies of carcinogenesis and tumor metastasis have spurred the development of new anticancer medicines. These agents have promising effects, but share the limitations of conventional chemotherapy in that they cannot induce complete remission of the cancer. This shortcoming strengthens the case for tumor dormancy therapy whose goal is not complete remission, but survival that does not differ significantly from that with chemotherapy while maintaining the quality of life. This approach maintains quality of life because it focuses on the treatment of the patient, not the disease.

Oriental medicine, in particular, seems to be useful in tumor dormancy therapy. Through research, we have identified some of the mechanisms that suppress tumors and prevent metastasis and proliferation. Certain Oriental herbal medicines induce anti-angiogenesis, promote apoptosis of cancer cells, activate immunity, inhibit gene expression, and block signal molecules. Through these effects, tumors can remain dormant.

Complementary use of Oriental herbal medicine with conventional chemotherapy enhances the anticancer mechanisms of conventional chemotherapy. With this, the most effective treatment course seems to be an initial combination low-dose chemotherapy, with long term chemotherapy with Oriental herbal medicine. For this combination therapy, further evaluation is needed to find possible interactions and side effects, the proper dosage, and other clinical applications.

4. Conclusion

The goal of tumor dormancy therapy is not to remove the tumor, but to stabilize tumor growth and maintain it in a dormant state. The therapy seeks to suppress cancer symptoms and prevent progression so that it can be cared for as a chronic disease. This patient-centered, rather than disease-centered, approach may prolong survival similarly to chemotherapy but incur less physiological damage to the patient. Tumor dormancy therapy consists of tumor anti-angiogenesis, induced cell death, hormone therapy, low-dose chemotherapy, immunotherapy, gene therapy, and signal-blocking agents. In particular, Oriental herbal medicine's potential to inhibit angiogenesis, promote apoptosis, and activate the immune system makes it a promising component of tumor dormancy therapy. Experimental evidence suggests that Oriental herbal medicine has excellent antitumor effects, reduced side effects when taken in combination with conventional chemotherapy, and improved patient-reported long-term quality of life. A tumor malignancy cannot be considered simply a tumor, but rather a dense, organized collection of blood vessels, fibroblasts, inflammatory cells, and extracellular matrices, with interactions that have significant implications for cancer treatment. Therefore, the future of cancer therapy should be aimed at the micro-environments surrounding the tumor and at other molecular structures and their interactions. More research on the specific mechanisms and at treatment applications of Oriental cancer medicine is necessary to utilize these novel therapeutic approaches to prevent the recurrence of dormant cancer cells.

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