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Perspective

A Novel Diagnostic and Therapeutic Strategy for Cancer Patients by Integrating Chinese Medicine Syndrome Differentiation and Precision Medicine*

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ABSTRACT Applying Chinese medicine (CM) is an important strategy for malignant tumor treatment in China. One of the significant characteristics of CM is to treat diseases based on syndrome differentiation. For Western medicine, it is of important clinical significance to formulate guidelines for the diagnosis and treatment of cancer patients based on the characteristics of disease differentiation. In Chinese clinical practice, the combination of disease differentiation and syndrome differentiation is an important feature for cancer treatment in the past. Currently, molecular profiling and genomic analysis-based precision medicine optimizes the anticancer drug design and holds the greatest success in treating cancer patients. Therefore, we want to know which populations of cancer patients can benefit more from CM treatment if the theory of precision medicine is applied to CM clinical practice. So, we developed a novel diagnostic and therapeutic strategy "disease-syndrome differentiation-genomic profiling-prescriptions" for cancer patients by CM syndrome differentiation and precision medicine. As a result, this strategy has greatly enhanced the anti-tumor efficacy of CM and improved clinical outcomes for cancer patients with some gene mutations. Our idea will hopefully establish a novel approach for the inheritance and innovation of CM.

KEYWORDS Chinese medicine, Western medicine, syndrome differentiation, precision medicine, cancer treatment

Frontier

With the change of medical model, the content and application scope of multidisciplinary integrative cancer treatment are constantly expanding. The diagnosis and treatment model of Chinese medicine (CM) and Western medicine (WM) gains a success in the multidisciplinary integrative cancer treatment, such as increasing efficacy, decreasing toxicity, alleviating symptoms, improving quality of life, and reducing recurrence and metastasis. However, there are still problems such as multi-drug resistance, prominent adverse reactions, and limited survival time. Therefore, it is an urgent need to develop a new medical model to improve clinical efficacy for cancer patients and promote innovation of CM.

Precision medicine is a new medical concept and medical model that carries out precise diagnosis and fine classification of diseases through omics technologies such as genomics and proteomics and cutting-edge medical technologies, so as to provide personalized and precise treatment for diseases and specific patients. Modern studies have found that CM can carry out precise treatment by regulating several targets or signal pathways.[1-3] If precision medicine is applied to the integrative clinical practice of CM and WM, the clinical treatment of diseases is not only based on dialectical disease differentiation, but also according to the corresponding target molecular therapy. This strategy will hopefully not only expand scope of cancer diagnosis, but also significantly

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improve clinical outcomes for cancer patients.

Cancer Diagnosis and Treatment Model of CM and WM

The combination of disease and syndrome is one of the best models of integrated CM and WM. The syndrome of CM changes dynamically, while the disease of WM is relatively constant. The syndrome differentiation of CM is macro, individual and whole, while that of WM is micro, group and local. CM treatment of cancer is based on holistic view and syndrome differentiation, focusing on the symptoms and signs of the patients, and the impact of the disease on the whole body, while the treatment emphasizes on strengthening the root, regulating yin and yang, eliminating evil and detoxifying.[4] WM treatment of cancer is based on the disease itself, focusing on the stage, pathology and treatment of the disease, as well as the painful symptoms brought by the disease. The treatment with surgery, radiotherapy and chemotherapy aims to eliminate the tumor as the goal, while biological therapy, rehabilitation and palliative treatment aim to inhibit growth of tumor, and improve the quality of life.

The application of CM diagnosis and treatment model combined with disease and syndrome in the treatment of tumor is helpful to better interpret the core idea of multi-disciplinary comprehensive cancer treatment to control tumor in a planned and reasonable way. Meanwhile, CM can improve the patient's constitution, improve the patient's resistance to chemotherapy drugs, and has a certain inhibitory and killing effect on tumors. After surgery, radiotherapy and chemotherapy, the diagnosis and treatment model of the combined disease differentiation and syndrome differentiation is conducive to recovery as soon as possible, consolidating the curative effect, reducing recurrence and metastasis. Figure 1 summarizes the diagnosis and treatment model of CM and WM based on disease and syndrome.

Although the current diagnosis and treatment model of combining disease and syndrome has gained some success in treating cancer patients. However, there are many clinical problems such as poor curative effect and inaccurate treatment for cancer patients. As a result, we do not know which populations of cancer patients can benefit more from CM treatment. Therefore, how to explore the advantages of CM in cancer treatment has become an important issue of integrated CM and WM in the future.

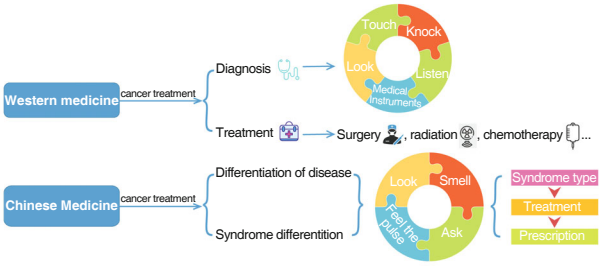

Figure 1. CM and WM Treatment Model Combining Disease and Syndrome

Precision Medicine Has Become Mainstream of Cancer Treatment

With the development of molecular biology, high-throughput multiomics and bioinformatics, precision therapy is playing an increasingly important role in oncology. Precision medicine is a new medical concept and medical model that carries out precise classification and diagnosis of diseases through omics technologies, such as genomics and proteomics and cutting-edge medical technologies, so as to provide personalized precision treatment for diseases and specific patients.[5] Currently, precision medicine has held the greatest success in cancer treatment by providing appropriate drugs to appropriate patients through molecular targeting combined with personalized medicine. Precision medicine model has become an urgent task and general trend in cancer treatment.

Due to the heterogeneity of tumors, gene mutations of different cancer cells in a patient with the same tumor are not necessarily the same, resulting in increased difficulty in cancer treatment. In addition, various new mutations, fusion genes and new bypasses are still accumulating on the way of cancer treatment. These new mutations and fusion genes may destroy the target of molecular drugs and their downstream signals, thus rendering the ineffective of these drugs.[6] In addition, a few drugs are involved in precision therapy, moreover, most of them are prone to develop the drug resistance after the repeated use. Moreover, many literature has reported that CM can regulate key pathogenic genes and mutation targets of tumors,[7-9] therefore, CM can also be used for precision therapy.

New Model of Tumor Diagnosis and Treatment by Combining CM and WM with Precision Medicine

Influence of CM Property on Cancer Targets

According to CM records, all CMs have their

own properties, including cold, heat, warm, cool and soothing properties. According to the research, the different properties of CM can improve the multi-drug resistance in the clinic.[1-3] Typical heat-clearing compounds Qingkailing Injection (清开灵注射液) and Tanreqing Injection (痰热清注射液) can increase the sensitivity of gefitinib by inhibiting the phosphorylation of AKT or ERK in H1975 and PC-9-PIK3CA-M cells, so it can be combined with gefitinib in the treatment of non-small cell lung cancer (NSCLC), while Shenfu Injection (参附注射液) with the function of warming-yang should avoid combination use with EGFR-TKIs.[1] This study shows that the different properties of CM can affect the resistance of other drugs. In addition, another study has found that the positive rates of HSP70 and p53 and the expression level of HSP70 in malignant tumor patients with CM heat syndrome are higher than those in non-heat-syndrome patients.[5] According to this conclusion, some heat-clearing herbs can be added to CM prescriptions and formulae for cancer patients with heat syndrome to down-regulate HSP70 and p53. Through network pharmacology, Gong, et al[3] found that the active ingredients of "Huanglian-Ganjiang" (*Coptis chinensis* Franch. and *Rhizome Zingiberis*) herb pair compatible with coldness and heat of Middle-Jiao can regulate multiple key targets and related pathways of colorectal cancer. Different medicinal properties of CM or herb pairs can target certain molecular targets to treat tumors.

Regulatory Effects of Natural Compounds of CM on Tumor-Related Targets

CM can also play a therapeutic role in tumor by regulating tumor-related targets. *Paris Polyphylla var. yunnanensis* could inhibit bladder cancer cell growth by activating DNA damage response pathway, degrading mutant p53 and stimulating CDKN1A expression.[7] Luteolin and its derivative apigenin significantly inhibited proliferation of lung cancer with KRAS mutation and down-regulated interferon-γ-induced programmed cell death 1 ligand 1 expression. Combined treatment with programmed cell death 1 blocker and apigenin/luteolin had synergistic effects and may be a prospective treatment strategy for KRAS-mutant NSCLC.[8]

Regulatory Effect of CM on Signal Pathway

CM can affect tumor growth and proliferation by regulating signaling pathways. Epiberberine from *Coptis chinensis* Franch. could target p53-dependent mitochondrial related pathways against MKN-45-related gastric cancer.[9] Berberine induced inhibitory autophagy by suppressing MAPK/mTOR/p70S6K and Akt signaling pathways, resulting in the growth inhibition of human gastric cancer cells *in vitro* and *in vivo*.[10] Cinobufacini is a famous CM extracted from *Toad venom*. Cinobufacini inhibited invasion and metastasis of colon cancer by suppressing Wnt/β-catenin signaling pathway and EMT.[11] Fuzheng Kang'ai Decoction (扶正抗癌汤) could inhibit metastasis of lung cancer by regulating STAT3/MMP9 signaling pathway and EMT,[12] suggesting that CM may be a promising new therapeutic strategy for cancer patients.

Relationship between CM and Its Possible Molecular Targets Was Predicted by Bioinformatics Technologies

Some existing databases can directly predict the relationship between CM and its possible molecular targets. For example, network pharmacology revealed the network relationship of drug-gene-target-disease interaction,[13] which has made a great breakthrough in clarifying the pharmacodynamic substance basis and mechanism of action, property theory of CM, and toxic mechanism of CM. This provides a certain basis for the modernization of CM and the international promotion. In addition, molecular docking technology can place small molecules (ligands) in the binding region of large molecular targets (receptors) through computer simulation, and then predict the binding force (binding affinity) and binding mode (conformation) between the active ingredients of CM and the target by calculating physical and chemical parameters.[14,15] Using molecular dynamics to study the dynamic process of biomolecular interaction to reveal the ligand-receptor interaction relationship has gradually become an important means widely used. Some databases, such as NPCDR (https://idrblab.org/npcdr/), can provide valuable data to CM, including clinical experiments/target and way of molecular regulation, and disease indications to improve the treatment effect, etc.[16]

The precision treatment of CM is reflected in many aspects. Experimental studies[17,18] have found that the precision treatment of CM has certain advantages in inhibiting the proliferation of tumor cells and reducing tumor size (Figure 2). Modern studies have found that CM can regulate targets and signal pathways and reverse multidrug resistance by targeting some molecules.[19,20] These results show that CM can not only be used as the traditional

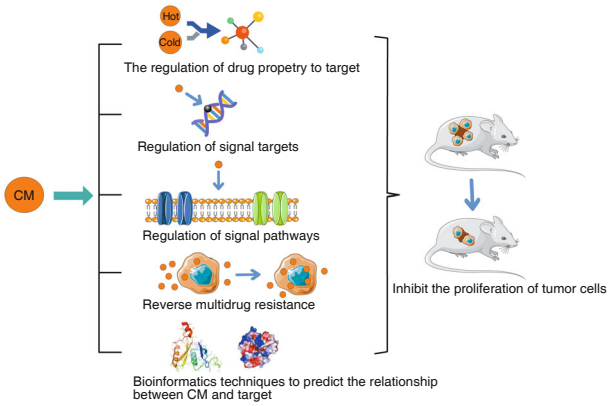

Figure 2. Schematic Diagram of CM Precision Treatment of Tumors

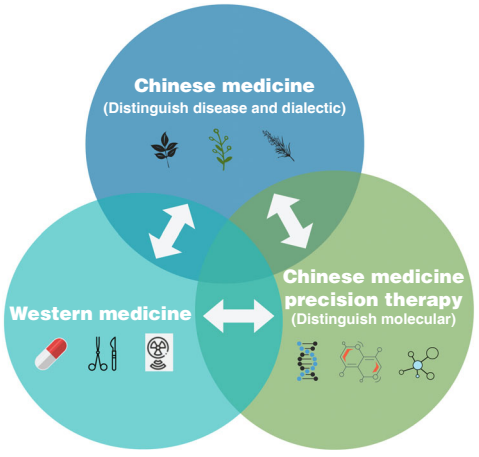

Figure 3. Treatment Mode of CM and WM Combining Disease Differentiation, Dialectical Differentiation and Molecular Differentiation

way for cancer patients by disease and syndrome differentiation, but also treat cancer patients by targeting molecules.

In CM syndrome differentiation, dialectical treatment and prescriptions is made at the same time. When the patient's abnormality related to some targets or pathways or drug resistance to some chemotherapy drugs is detected through precision medicine technologies, the corresponding CM can be regulated if it happens to be available. These CM herbs can be added to the original prescription to achieve the goal of regulating molecules to treat tumors. This combination model combines the holistic concept of CM in treating diseases with the precise targeting of key pathogenic factors of WM. This model improves CM's systemic and precise regulation to treat diseases, so that CM can also quickly regulate some disease-related targets. In addition, some CM herbs have the effect of reversing multidrug resistance. Adding these drugs into traditional prescriptions and combining with chemotherapy drugs can prevent drug resistance of chemotherapy drugs.

This new diagnosis and treatment mode of integrated CM and WM, which combines disease differentiation, dialectical differentiation and molecular differentiation, has greatly improved the anticancer potential of CM and augmented the curative effect of CM. This new diagnosis and treatment model can take the advantages of CM and precision medicine in cancer treatment, and is a good strategy for cancer patients (Figure 3).

Discussion

Guided by the concept of precision medicine, molecular typing or molecular diagnosis of tumors is well determined based on accurate diagnosis. The new diagnosis and treatment model of integrated CM and precision medicine combined with disease, syndrome and molecular differentiations can be used to monitor the tumorigenesis and cancer development in all aspects. This diagnosis and treatment model is an individualized medical method for cancer patients, aiming to make each patient not only treated according with the traditional disease and syndrome, but also treated according with the molecular targets.

Different from traditional cancer prevention and treatment strategies that combine disease and syndrome, a novel diagnostic and therapeutic strategy "disease-syndrome differentiation-genomic profiling-prescriptions" has been developed for cancer patients by CM syndrome differentiation and precision medicine. It is a new medical concept and and this method has greatly enhanced the anti-tumor efficacy of CM and improved clinical outcomes for cancer patients with some gene mutations. Also, this novel model can help us understand which populations of cancer patients can benefit more from CM treatment. We believe this strategy will hopefully not only expand the scope of cancer diagnosis, but also significantly improve clinical outcomes of CM for cancer patients.

Author Contributions

Yu SX was responsible for writing the manuscript; Liang ZM designed the thesis framework. Yu SX and Liang ZM made equal contributions to this work. Wu QB, Shou L, Huang XX, Zhu QR, Xie H, Mei RY, Zhang RN and Zhai XY collected materials; Xie T and Sui XB guided the manuscript.

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