

The highest realm of precision treatment of cancer – Extending from micro-level precision to holistic personalization

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REVIEW

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ABSTRACT

Background

Precision medicine opened the era of precision cancer treatment based on genetic variation, abnormal protein and other personalized factors. However, control of cancer cell proliferation and disease diffusion is not all we can do in cancer treatment. The strength of the human immune system, human basic physiological functions and normal metabolic activity, as well as the elimination of disease complications, these are the important aspects closely related to cancer lesions and therapeutic effect. Precision medicine is rapidly starting to build a micro-level personalized human pathological condition description system by the current results of genes, proteins, metabolites, and other genomics research. Chinese medicine (CM), which has a history of more than 2,000 years in China, is a mature medical system which describe and adjust-control the state of the human body from the overall level personally. The future precise treatment of cancer requires micro-level precision, and personalized holistic human status control. Thus, the introduction of the CM's system of syndrome differentiation and treatment, making micro-level precision treatment gradually extended to personalized holistic human status control of the patient, will be the highest attainment of precision medicine in the treatment of cancer.

Aims

From the perspectives of theoretical and clinical practice, in personalised cancer treatment, it's need target therapy for cancer lesions as well as proliferation control. It's also requiring symptomatic treatment for different dysfunctions and complications in organs and systems based on holistic status. By achieving an organic integration of the micro-level precision of treating local lesions and the holistic personalised recuperation, the highest realm of precision treatment of cancer can be achieved.

Key Words

Precision medicine, Chinese medicine, cancer, status medicine, personalized medicine, disease medicine

What this review adds:

1. What is known about this subject?

Precision treatment for cancer based on personal differences of genetic mutation, has given new hopes for cancer treatment. However, the current progress shows that, its prospect is not as optimistic as what scientists foresee. Cases of self-healing cancer, indirectly treated with the use of traditional Chinese medicine through holistic conditioning, are common occurrences.

2. What new information is offered in this review?

Viewing cancer patient as a whole, combining target therapy for cancer lesions, proliferation control, as well as treatment for various dysfunctions and complications based on a holistic level, would significantly enhance the proficiency of cancer treatment.

3. What are the implications for research, policy, or practice?

Under the concept of “integrity within the human body”, by organically combining the local and targeted treatment of modern medicine, and traditional Chinese treatment from a holistic status, it greatly improves the proficiency of cancer treatment. This concept has an important practical significance of the research of cancer treatment methods,

clinical practice, as well as policy proposals alike.

Introduction

Today, cancer has become the major cause of human death. The treatment of cancer based on stage of its development and the application of medicines in accordance with the types of cancer cells unavoidably encounter significant side effects. Even with the application of medicine according to cell classification, there is no indication of desirable universality.

The success of human genome project, especially, the progress in the gene mutation and cancer disease related research, broke up the old concept of treatment according to cancer type. It opens the era of precision treatment for cancer that based on personal differences of genetic mutation.

Will the medical process towards personalized medicine triggered by precision medicine (PM) just remain at the micro-level? In the process of fighting against cancer till today, medical scientists have clearly recognized that the control of cancer cells multiplication and proliferation are not all about cancer treatment. Some aspects related to disease progression and therapeutic effects cannot be ignored, for instance, the surrounding environment of cancer lesions, as well as the complications resulting from cancer and the holistic status of the cancer patient including digestion and absorption function, bone marrow function, immunity levels, etc. In other words, the personalized process of PM only at the micro-level is far from enough. For precision treatment of cancer, it also needs to control the personalized patient pathological status.

How do PM to achieve holistic personalization? What is the relationship between micro-level precision and holistic personalization? In the process of the future cancer therapy, can it achieve an organic integration and harmonious unity? This will be the problem that we have to face in the era of cancer treatment towards precision treatment.

PM opens the era of personalized cancer treatment

American scientists first proposed the PM plan. Its short-term goals focus on effectively raising therapeutic level for cancer through precise diagnosis and accurate selection of drug. The continued findings of abnormal target links on genetic mutation, protein synthesis and metabolic, as well as the advent of corresponding target drugs, all contribute to show good prospects in the treatment of cancers. In this regard, the whole world waits in great expectations.

For example, in clinical trials of cetuximab treatment for colorectal cancer or imatinib treatment for chronic myelogenous leukemia, after a thorough study, researchers found that some patients were unresponsive to the treatment.^{1,2} The problem of cetuximab treatment is KRAS mutation, and the problem of imatinib treatment is T315I mutation.³ In other words, the personalized differences resulting from genetic mutation directly affect the selectivity of drug effect. So, can we match gene in cancer therapy just like the matching of blood type in blood transfusion, to provide the right therapy for the right people at the right time?

Genomic medicine research reveals that cancer is driven by many molecular level diseases. It suggests that cancers probably will have their own gene imprinting, cancer markers and different types of mutations. This new understanding of the carcinogenic mechanisms has influenced drug and antibody design process for the assessment of cancer risk, diagnostic classification, and treatment strategies. Some of the targeted therapies that have been or are being developed were put into clinical application. They play an important role in the breakthrough of the main obstacle encountered by cancer treatment, such as unexplained drug resistance, cancer genomic heterogeneity, cancer response monitoring, and cancer recurrence, etc.

Under the banner of PM, new driver gene and new targeted therapies gradually emerged, such as, Dabrafenib for BRAF V600E mutation, anti-HER2 (human epidermal growth factor receptor 2) therapy for HER2 mutation, and crizotinib for c-MET amplification, and cabozantinib for rearranged during transfection (RET) fusion.⁴⁻⁶ PM treats some serious illness, such as, lung cancer, subdivided into a number of minor ailments or even rare diseases. For ROS proto-oncogene 1 (ROS1)-positive lung cancer, lung cancer accounts for only about 1%. Lung cancer is a serious illness, but ROS1 lung cancer is a minor ailments⁷. On the other hand, PM turns many different types of cancer into a series connected new disease class. For instance, the well-known ALKoma, i.e., anaplastic lymphoma kinase (ALK) gene fusion may be found in lung cancer, or malignant lymphoma, or certain rare childhood cancer. All can be treated by ALK inhibitor treatment.⁸ From that it seems PM has broken through the limitations of traditional disease classification system in practice. It calls for the birth of a cross associated new disease status description system. This described system is called the status description system; the medical system based on it is called status medicine. Today, the concept of PM is far from people conventional

understanding. It is the precision basis change in reference frame. It is to change from the precision of disease type that defined by traditional disease classification system, into the precision of status description system that can describe the personalized human body status.

Can we, as people will expect, fight cancer and win the wars against diseases merely based on precision treatment on the micro-level? The science researchers begin to query. In September 2016, two articles appeared in “Natural Science” and “The New England Journal of Medicine” magazines, summarized the clinical results of personalized treatment of cancers, both gave pessimistic critics.^{9,10}

In real life, we often hear some cancer self-healing cases through diet control, Qigong, and conservative CM treatment. It shows the overall functional status of the patient plays a crucial role during the occurrence, development, evolution and treatment of cancer.

Modern medical research on cancer shows that there is a close relationship between cancer disease and the human body overall dysfunction as well as pathological condition. These pathological conditions commonly referred to as precancerous lesions or cancer high incidence diseases. In other words, these diseases provide favourable environment for cell mutation and cancer development. The elimination of precancerous lesions and correction of pathological conditions will create an environment detrimental to the survival and development of cancer. Hence it may result in the reversal of cancer disease.

So, what PM can get to achieve the holistic level personalized human disease status description system, and thus achieving the holistic level of personalized treatment?

CM: Medical system of holistic human status description and control

Today, acupuncture originated in China, with its amazing clinical results, spread throughout the world. Acupuncture is just a branch of CM treatment technology. The more profound and broader clinical value of CM syndrome differentiation and treatment system is still not understood or accepted by mainstream medicine. It is still covered with a layer of mystery cloak in the eyes of Western scientists and medical experts. The reason is acupuncture can easily be grafted onto the technical level content of disease medical system, whereas CM syndrome differentiation and treatment system involved medical cognitive method and theory that is irrelevant to disease medical system.

Today, the mainstream scientific method of natural science changes from simplicity response to dealing with complexity. In medical, mainstream medical system changes from disease medicine to personalized status medicine. As everyone knows, the core of PM: the status medicine that reflecting personalized human body status, is the human cognition model and medical traditional that having a longer history comparing with modern science and medicine. In the West at hundreds of years ago, during the process of modern experimental medicine establishment, 'unscientific' ingredients of traditional medicine were abolished. Since the childish of science, the personalized status medicine was abolished as it was under the cover of some quaint terminology such as, yin and yang, the five elements, qi, water, fire, and wind, etc.

Today, the method for building complex system status model by metaphor and analogy has become the accepted method of complexity science to study the complex system. When we put metaphors and analogies as a scientific method, and adopt the new scientific ideas brought by complexity science, to re-examine CM that having thousands years of history in China. Then we will note that since the earliest Chinese medical theory masterpiece The Medical Classic of the Yellow Emperor (Huangdi Neijing), metaphors and analogies—CM practitioners called it analogy based on image similarity method, has been widely used in the course of CM theoretical system establishment. The CM theory model system was established through the holistic observation of the basic human physiological and pathological phenomena which based on the Analogy based on Image Similarity method of yin and yang, the five elements, and the eight trigrams.

In CM, the human body is divided into several functional subsystems that based on health-related functional behaviour such as, Xin (Heart), Gan (Liver), Pi, Fei (Lung), and Shen (Kidney), i.e., five Zang. A set of status variables are introduced to represent the functional status of each subsystem. For instance, a set of status variables are introduced for Xin, the leader of five Zang, such as, Xin qi, Xin blood, Xin yin, Xin yang, blood smoothness (presence or absence of stasis), Xin fire status (presence or absence of fire), etc. Thus, it constitutes the Xin subsystem status space. Each status variable usually may represent normal and several abnormal statuses, such as, normal Xin qi, Xin qi deficiency, Xi qi void, etc. The abnormal status, termed as syndromes in CM, is defined by a set of perceivable symptoms and signs. For instance, the corresponding symptom of Xin qi deficiency includes palpitations, shortness of breath and worse after move, as well as pallid

complexion, etc. The symptom of Xin qi void includes palpitations, sweating, shortness of breath and worse after move, lassitude, weak pulse or knotted pulse, etc.¹¹

The set of all human body subsystems formed the human body status description system. In clinical consultation, we can fully understand the health status of a patient by identifying the abnormal status variables from the patient's symptoms and signs. In a statistic analytical model with the condition of not more than 5 status abnormal variables, the algorithm of about 100 status abnormality may yield 10 billion of different conditions. Thus, it forms a human body status system that can describe more than 10 billion personalized statuses.

The status description system of CM is based on holistic level and derived from the basic functional division of basic human physiological and pathological activities at the holistic level. In it, 100 basic syndromes (status variables) combination can cover all human body's pathological process. Obviously, CM body status description has the top and highest level of abstraction. More importantly, for thousands years of clinical practice since ancient times, CM has established a complete and perfect human body status control system through all aspects in theory, treatment, prescription and drugs.¹²

Thus, there are two personalized body status description systems at micro-, and at macro-levels. On one hand, the body status description system that established based on molecular level elements such as, human genes, proteins, and metabolites. On the other hand, the relatively macroscopic body status description system that established based on human behavioural function and laid in holistic medicine over two thousand years of history: CM syndrome system.

Differences of two different levels personalized body status description systems

Generally speaking, the lower the level of status variables, the greater the magnitude of the total variable number that required to completely represent all human physiological and pathological activities. On the contrary, the higher the level of status variables, the better the level of abstraction, and the smaller the magnitude as well as the fewest total number of required status variables. From the perspective of precision pharmaceutical research, the drug developed from controlled macroscopic status variables has relatively macro and wide coverage in usage. It covers the sum of various micro-level variables' direct and indirect effects. From the perspective of identification and control, the more

macroscopic status variables are, the better the abstraction. Then the human body status description system will be simpler, and will be easier to be understood and controlled. The accuracy required to identify the human body status will be lower. For the drug dealing with macroscopic variables status, the requirement of drug effect understanding accuracy will be reduced as well. Like on the satellite, if we have to observe a soldier's beard on ground, we have to use a high-powered telescope. But if we want to observe a mountain or a river there, we do not need that precision at all. Similarly, if we launch a missile with ordinary energy and targeting a vehicle, we have to position and control the trajectory precisely. But if we are targeting a city with a bomb, the precision of position and control will be greatly reduced.

Obviously, the precision of micro-level variable does not mean that it is precise to the personalized human body status. Under the same precision, the higher the variable level, the higher the precision for describing holistic human body status. Just think, if we take a 100-variables status description system (such as, CM syndromes) as a reference, to get the patient's status, and we identified 80 variables precisely. Then we can say that we achieved 80% accuracy in studying the patient status. Whereas, if we take a 10,000-variables status description system (such as, modern medicine detection index) as a reference, to get the patient's status, even though we precisely identified 500 variables, we can only say that we achieved 5% accuracy in studying the patient status. That is why the precision of CM in symptoms and signs identification is far less than modern medicine, however, the latter cannot compare to CM in grasping the patient's holistic status. Clearly, for an accurate understanding of human body status, it is not only involved the technical issues of precision in measuring methods and instruments. But it is also vitally related to the level of the body status description system reference, as well as the total number of status variables involved. The lower the level of the human body description system, the more the total number of parameters is introduced, and the greater the difficulty to achieve the précised identification.

The required precision for human body status control is closely related to the level of variables we have to control. The higher the level, the lower the required precision, and the lesser the side effects of the drug developed, and vice versa. Compare with system of microscopic variables, the drug found from the system using macro status variables as reference usually can control the body's macroscopic properties and functions. Thus, it has a broader usage scope. In the past several decades, the study and research

on CM's viscera study, the analysis of syndrome, and the clinical study indicated that a single organ may always involve in the activity and functionality of multiple anatomical tissues and organs, and a syndrome (status variable) involves multiple abnormal elements and variables at micro level. Thus, taking a syndrome as controlled variable and develop a drug to deal with the syndrome. Its direct or indirect effects will undoubtedly play a therapeutic role for the abnormal elements and variables. If we start from the microscopic variables of the lower level to achieve the macro-level effect, it means to study drugs for multiple microscopic variables individually. Even if we found all micro-level variables related to the macro level and developed precision drugs targeting them, it does not mean that the abnormal macro-variable (syndrome) must be restored to normal by taking in the drugs. The reason, as complexity science research has already given a clear conclusion: for a complex system, the control of high-level element does not simply equal to the sum of its constituent lower-level elements control.

Modern herbal researches also prove the case from a practical standpoint. For example, according to CM, the most important function of ginseng and astragalus is replenishing qi. The study of modern pharmacological analysis showed that medicine for replenishing qi usually has certain functions at the micro-level. Such as, regulation of glucose metabolism and lipid metabolism; promote protein, DNA, RNA synthesis, and increased albumin and γ -globulin content; increased peripheral leukocytes, and increase phagocytosis of reticuloendothelial system; enhance cellular and humoral immune function; and so on¹². So if we take in a variety of Western medicines with various functions, such as regulating glucose metabolism and lipid metabolism; promoting protein, DNA and RNA biosynthesis; increasing phagocytosis of reticuloendothelial system; enhancing cellular and humoral immune function; etc. then can it be combined to form the functions like CM replenishing qi medicine? On this issue, no matter it is based on pharmacologist analysis research or physician clinical practice, the answer is very clear, no. Obviously, to lower the level of controlled variables will greatly increase the complexity in drug research. It will increase the uncertainty of drug functions observation from a macro perspective. Compared with the path of modern medicine, CM path is easier and more effective in search of precision medicine, and the developed drug has higher accuracy in response to holistic human body status.

In the near completion of the Human Genome Project, Scientists discovered that there were already more than 100

million types of gene mutations. However, biologists knew that proteomics and metabolomics abnormalities occur in human life process are much more than gene mutations, and they show a significant dynamic characteristics that is different from the relatively stable gene mutations. It is unthinkable astronomical for the combinations of single variable in the size of more than one hundred million. That is, to establish a human body status description system at this level means higher accuracy, and a large magnitude of data. Therefore, whether it is to achieve precision of diagnosis detection, drug research, or control of human body status, we have a long way to go.

Today, modern medicine returns to holism from reductionism in theory, and medical model changes from disease medicine to status medicine. The gap of concept and methodology between CM and Western medicine has been filled. The era like the blind bear breaking stick – breaking a stick must throw away another stick – has become the past. The cancer treatment not only need a precise understanding of cell mutation at the micro-level, but also need a grasp of personalized human body status at the holistic level.

Highest attainment of cancer treatment: organic combine of micro-level precision and holistic level personalization

In cancer treatment, the precise control of cancer and lesions is essential, and CM cancer treatment lack of it. Even if the target drug developed based on PM research, the side effects cannot be completely avoided. The holistic correction and repair of the target drug are necessary. Some aspects that related to the development and conversion of cancer cannot be ignored, such as, pleural effusion, ascites, cholestasis, inflammation and other complications eliminate; human digestion and absorption recovery; sustaining of liver detoxification and metabolic functions; and strengthen the immune system. Therefore, the holistic status control and the holistic recuperation for cancer patient are indispensable.

Today, people have become accustomed to a 'taking-in principle' for solving different problems with different theories in natural science. For instance, in physics, to deal with macro analysis and large-scale, high-speed universe problems with general relativity, and to solve microscopic atoms and elementary particles level problems with quantum mechanics; in architectural design, to put structural design based on building mechanics and ancient Chinese architectural style features into an organic integration; in computer software design, software architects take software languages of different features for

solving different problems into an organic integration. In those processes, people do not mind what theory it is, or which country the methods came from, or which system the problem derived from.

For cancer treatment, we can certainly to solve the problem of cancer lesions and cancer cell proliferation based on micro-level status description system. Then CM theoretical model as well as syndrome differentiation and treatment system can deal with holistic problems, such as, to deal with the side effects of target drug long-term usage, to eliminate the complications caused by cancer, to restore the digestion and absorption functions, to protect the detoxification and metabolic functions of liver and kidney, to enhance the immunity and physical fitness of human body, etc. Similarly, we do not mind whether the theory and method are come from CM, or modern medicine. It is the same as today's world popular evidence-based medicine concept.

At present, the US FDA divides the innovative clinical trials for PM into two categories. One of them is called Basket Trial.¹³ It puts different cancers of the same target gene into one basket for research study. Its essence is to deal with different tumours with one drug. Another clinical trial is called Umbrella Trial. It put lung cancers with different genes, such as KRAS, EGFR, and ALK roped together under an umbrella. That is, to complete the different target tests all at the same time. Then assign different precision drugs for different target genes. The biggest advantage of Umbrella Trial is to put very rare mutation events together and making rare events become 'common' events. It has special significance in accelerating clinical trials of rare diseases, or in providing precision treatment chances for a particular individual.⁸

The two types of clinical trials, Basket and Umbrella are revolutionary innovations for accelerating precision drug development and clinical oncology development. By launching the two clinical trials, cancer patients will be able to get effective drug treatment more quickly and do not need to wait for 7–10 years long as in the past. Thus, in not too long, PM will be aggregated into a huge target basis drug system. Dealing with macro-level targets, i.e., syndromes, CM current has the syndrome differentiation and treatment system that contains more than 100 syndromes and was long been clinically proven. In cancer required a comprehensive and integrated treatment, from micro-level precision to holistic personalization, it is not only within sight but also can be achieved.

PM for cancer: Call for program experts and precision treatment centre

The development of science leads people vision towards deep. The result of depth makes people move away from holistic understanding. With the total amount of medical knowledge was explosively growth, physicians are increasingly confined to narrowing field, and they know nothing or very little about adjacent fields. Human body is a whole of various closely related parts. The treatment for human disease never equals to the simple sum of disease treatments of all levels and various parts. For treatment to human diseases, the doctor is both required to grasp the disease parts and details, as well as the relationship between parts and the whole, in order to provide holistic personalized treatment for human body.

Decomposition and analysis are the characteristics of Western medicine. The clinical treatment limitations and unavoidable chemical drug side effects become a general consensus of physicians. The emerging precision medicine has put aside the fetters of traditional analysis medicine and disease medicine. It starts the attempt to establish a micro-level human body status description system. With the proposed concept of personalized medicine, modern medicine begin to rediscover the holistic medicine, and to embrace the holistic human body description and control system that supporting CM for thousands years.

Today, in natural science and social science applications, with the expansion of research target size and complexity, the separation between overall program design and specialty items design has achieved. In architectural design, it is divided into two stages, the overall design and working drawings, and carried out by different levels of designers. We cannot conceive of the eventually achievements of modern architecture without an overall construction plan design and specialty items design. In software system design, there is a division of work between structural designer and programmer. We cannot imagine how to coordinate all aspects of structures and functions in software without a structural design.

Our doctors face a complex giant system: the human body that is thousand times more complex than those artificial systems. In the era of disease medicine, doctors treat disease instead of patients. It is excusable to push patients moving around different disease departments. In the era of personalized medicine, in response to all aspects of patient discomfort and disease, there is no overall treatment program that based on the patient's personalized body status with comprehensive analysis and repeated scrutiny

development process. It is instead let the doctors of various branches go their own way and adopt the trade-off treatment. That is inconceivable. But it is the state of our clinical medicine today.

In personalized cancer treatment, we need target therapy for cancer lesions as well as proliferation control. We also need personalized syndrome differentiation and treatment system based on holistic status, as well as symptomatic treatment for different dysfunctions and complications in organs or systems. Moreover, we have to balance and correct the possible side effects of precision treatment for particular lesion. It needs a program expert, an experienced practitioner that has proficient in conventional cancer diagnosis and treatment as well as target treatment, and understands different clinical subjects of modern medicine, and familiar with CM.

The personalized treatment for cancer leads to complexity of treatment process and the requirement of holistic integration. It also looks forward to the birth of a professional "Centre of Precision Treatment for Cancer". There it will be equipped with conventional detection device of modern medicine, and the most advanced target detection equipment and methods. There will gather a team of professionals with proficient cancer diagnosis and targeted therapy, as well as the CM expert who is good at holistic recuperation. There will led by personalized precision medicine concept, and integrate the most cutting-edge treatment of modern biomedical technology with the long history of CM holistic recuperation methods, i.e., the syndrome differentiation and treatment system. Thus, it will achieve an organic integration of the cancer lesions micro-level precision and the holistic personalized recuperation.

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