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Personalized Cancer Therapy: A Perspective

Da-Yong Lu[1*], **Ting-Ren Lu**[2] and **Hong-Ying Wu**[2]

[1]*Shanghai University, Shanghai 200444, PR China*

[2]*College of Science, Shanghai University, Shanghai 200444, PR China*

[*]**Corresponding author:** Da-Yong Lu, Shanghai University, Shanghai 200444, PR China, Tel: +86-21-66137032; E-mail: ludayong@sh163.net

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Abstract

Cancer is different diseases with a common pathological feature of unlimited growth. Aim of this perspective is to update current and future individualized cancer therapy methods and results, and give new directs to improve. Present understanding and predictions of drug responses to tumor growth or metastases and anticancer drug toxicities to patients are not well-formed, but there are two ways of receiving these types of information from tumors; (i) drug sensitivity testing; (ii) the detection tumor genetic, transcription and molecular information—bioinformatics of cancer cells or patients. Individualized Cancer Therapy (ICT) has been designed to meet the requirement of selecting anticancer drugs in clinics and attracting increasing attentions in medical circle and will be irreversible trend in the future. The survival of cancer patients can be improved by many existing specific strategies of ICT, including drug sensitivity testing, cancer molecular biomarker detections, cancer biomarker-oriented therapy, anticancer drug pharmacogenetics, cancer metastasis therapy, drug combinations and cost-effective of ICT.

Keywords: Individualized cancer therapy; Personalized medicine; Cancer treatment; Drug sensitivity testing; Pharmacogenomics; Cancer biomarkers; Cancer bioinformatics; Omics techniques; Antimetastatic therapy; Biotherapy; Drug combinations; Cost-effectiveness

Introduction

Cancer is different diseases with a pathological feature of unlimited growth. The hallmarks of cancer can be multiple genes and multiple stages [1,2]. Since tumors originate from a wide variety background of genotypically or phenotypically abnormal tissues that create the unlimited growth of cells, different genotypically or phenotypically abnormal tissues ought to be sensitive to different anticancer drugs. Thus, most cancer patients are unsuited to the use of "uniform" or "standardized" chemotherapy [3,4]. As no single drug or combination has so far been found to be optimal for cancers of all origins, developing good and clinically sensitive anticancer drug selection system is no less important than the discovery of new anticancer drugs. "Individualized Cancer Therapy" (ICT) are designed and tailored to meet this requirement of improving therapeutic quality by selecting and prescribing well-matched anticancer drugs and avoiding ineffective anticancer drugs by a series of systematic ways in clinics.

The first experiments relating to this issue can be dated back to the early 1950s [5,6]. Those reports hypothesized that drug sensitivity to tumor biopsy *in vitro* was the same as drug responses in patients. Systematic investigations and utilizations of drug sensitivity tests in clinics began in the late 1970s [7-9]. Since then, drug sensitivity tests have been the mainstream of ICT strategy and continue to be one of the best ways of selecting therapeutic agents.

Cancer is a disease of genetic alteration and abnormalities. Thus the best therapeutic approaches should target these genetic alterations and abnormalities. However, different cancers are caused by different genetic alterations and abnormalities. Thus before an appropriate therapy can be initiated, it needs first to know the exact genetic alterations and abnormalities of a specific cancer in clinics. Only DNA, RNA or protein detections of these genetic alteration or abnormalities in tumor cells can offer useful prediction of drug responses. DNA, RNA or protein detections of cancer cells offer information of the exact sites of oncogenic or metastatic processes and is the underpin of modern individualized cancer therapy and can be divided into four general categories;

Drug sensitivity testing *in vivo* and *in vitro*.

Detection of RNA, protein or glycoprotein tumor biomarker at sub- or quantitative level to predict use of anticancer drugs targeting on detected oncogenic and metastatic molecules. We can categorize it into "detection of cancer biomarkers of omics techniques".

Detection of polymorphism of human or tumor genes to predict the activity of anticancer drugs against tumor tissues and human or active anticancer concentrations in human blood and toxicity of drugs to human bodies. It has been categorized into pharmacogenomics of anticancer drugs.

Individualized antimetastatic therapy.

90% of cancer deaths die of cancer metastasis. However, currently cancer therapies are mainly focusing on anticancer drugs targeting primary tumor instead of metastatic foci. So although the primary tumors have been inhibited by sensitive antiproliferative drugs, patient's survival has been increased very little [4]. If we can change our focus on development of effective antimetastatic drugs and design individualized antimetastatic therapy strategies and thereby enhancing patients' survival in late staged cancer patients [10-13].

Methodology

Drug sensitivity testing

History of drug sensitivity testing

Individualized Cancer Therapy (ICT) was pioneered by drug sensitivity tests more than half a century ago—6 decades [5,6]. It gained more notice and was boosted during the 1970s [7-9]. Drug sensitivity testing compares the anticancer activities of candidate drugs on surgically removed tumor samples, and those anticancer drugs showing the best responses are selected for use in succeeding treatments. Before 2000, individualized cancer therapy is generally thought as drug sensitivity testing.

Methodology of drug sensitivity testing

Drug sensitivity tests can be conducted *in vivo* and *in vitro*. The Subrenal Capsule (SRC) assay [9] is the earliest and best known *in vivo* method. It involves transplanting surgically removed tumors into the renal capsules of mice and evaluating the candidate anticancer drugs within 4-11 days intervals. *In vitro* drug sensitivity testing methods involve cytological or cyto-chemical evaluations of drug response including the Micro-culture Tetrazolium (MTT) method [14,15], the ChemoFx method [16], the ATP luminescence assay [17-19] and the collagen gel droplet-embedded culture method [20] and so on. Usually, the effects of drugs on tumor enzyme activity, energy consumption or cell numbers are assessed. For example, Kondo and colleagues described a test involving drug effects on succinate dehydrogenase activity in tumors [21]; this was the prototype of the currently used MTT method.

Relationship of drug response between drug chemosensitivity and clinical tumor treatment

In approximately 80% clinical reports shown there is solid relationship between the results of drug sensitivity testing and clinical drug response data (Partial Remission—PR or Complete Remission—CR). Most clinical data show that drug response through drug sensitivity testing is parallel with drug responses in cancer patients clinically. In most cases, drug response (PR or CR) in cancer patients are improved by reference with the results of drug sensitivity testing. However, only less than 25-35% clinical reports stated that there is improvement in patients' survival by using drug sensitivity tests. In most cases, patients' survival is almost the same in spite of using drug sensitivity testing [3,4].

Possible reasons of unsatisfactory in increasing patients' survival in spite of using *in vivo* or *in vitro* drug sensitivity testing can be postulated in the following three reasons; (i) inappropriate use of methodology and techniques of drug sensitivity testing; (ii) tumor tissues are easy to acquire Multidrug Resistance (MDR), the tumor tissue then regrow after short term of inhibitions of tumor tissues by selected anticancer drugs and patients die at same rates and intervals; (iii) therapy does not target on neoplasm metastases.

Many factors and technical details determine the success or failure of a drug sensitivity testing. Any neglect of experimental details will lead to complete failure of drug sensitivity test. Drug sensitivity test aims at selection of anticancer drugs. Previously, many reports compared drug sensitivity of 2 to 5 anticancer drugs and only one dosage (concentration). However the best suited drug may not be in these 2-5 anticancer drugs or not in the correct dose ranges of a drug sensitivity tests. It might be possible we cannot select best suited anticancer drugs from a panel of less sensitive anticancer drugs [3,4]. Similarly, any tested anticancer drugs must have a least two dosages in drug sensitivity testing. Otherwise, the false-positive or false-negative data may be obtained. Like these experimental details, if we notice, analyze and adhere to all experimental details of a drug sensitivity tests, the real drug response to a tumor might be well obtained and a success of a test can be expected.

Induction of MDR in tumor cells often makes it failure in conventional chemotherapy. The longer a chemotherapy regime takes, the more likely tumor cells might induce MDR. After induction of MDR in tumor cells, there is no difference between conventional chemotherapy and drug selections by drug sensitivity testing. Only some drug export channel inhibitors can be added to offset the outflow of anticancer drugs in MDR induced cancer tissues.

90% cancer deaths are caused by cancer metastasis [10-13]. However, drug sensitivity testing is commonly to test drug response to primary tumor. Not specific targeting to metastatic tumor makes therapy less benefits to patients' survival. In future, ICT specifically targeting on neoplasm metastasis is in high demand, especially to late stage of cancer patients.

Cancer biomarkers and cancer bioinformatics for ICC

Theory

Cancer is a disease of genetic alterations or abnormalities. The best therapeutic approaches should target these genetic alterations and abnormalities. However, different cancers are caused by different genetic abnormalities, such as mutation, translocation, deletion, insertion or replication etc. Thus before an appropriate therapy can be initiated, it needs to know the exact genetic alterations and abnormalities of a specific cancer in clinics [3,4,22-26]. Various molecules have been widely reported to have diagnostic and/or prognostic value in cancer patients. Such molecules range from immunoregulatory [27] and inflammatory factors (interleukins and cytokines) and signal transduction regulators (tyrosine kinase, cycloxygenase-2, MAPK, etc.) to factors related to tumor pathology (metastases, angiogenesis and apoptosis) such as Vascular Epithelial Growth Factor and its receptor (VEGF and VEGFR), Epidermal Growth Factor Receptor (EGFR) and fibrinogen [3,4]. These biological molecules can be altered or abnormal for promotion of pathogenesis of tumor growth or metastases. These pathogenic biomarkers in tumors are specific targets for drug antagonism or disruption.

Seeing is predicting

In early stage, cancer biomarker detections are focused on detecting one or several pathogenic molecules (commonly protein or glycol-protein). Targeted monoclonal antibodies or other targeted anticancer drugs are prescribed to high cancer biomarkers patients. Recently, high throughput cancer bioinformatics methods are used to identify a spectrum of cancer biomarkers including tumorigenic initiators and promoters, and further deciding which targeted anticancer drugs are most likely to target these neoplasm tissues [3,4,22-26]. Since tumors are progressive pathogenesis processes with more than a hundred genetic changes accumulating in a single cell [4], high-throughput methods are needed to identify or pinpoint these underlying abnormalities. The multidisciplinary nature of bioinformatics makes it relatively higher cost and as assistant tools to decipher of cancer

bioinformatics data. Individualized treatment based on detecting and understanding genetic and molecular variations by cancer bioinformatics means is a relatively modern strategy.

Cancers have been from different etiological bases but share the same pathological characteristic of unlimited growth. They result from genetic malfunction and molecular disturbances. Using the cancer genome to help understand the cause of cancer and variable response to drugs will be its most important application to cancer biology and medicine. More than a thousand types of genetic abnormality can cause about more than one hundred different tumor types. More than one hundred different anticancer drugs are available for treatment of different cancer categories and types.

Bioinformatics is a genomics-based approach and provides a variety of techniques for analyzing abnormalities of DNA, RNA, proteins and glycoligands as a whole in tumors. In the earliest era of biomarkers of bioinformatics evaluations, clinical cancer practice was to predict patients' prognoses [28] or classify tumor origins [29]. Presently, the best example of utilizing biomarkers or bioinformatics for predicting anticancer drug responses is to decide on antibody therapy (treatment of cancer patients with monoclonal antibodies) or other biotherapeutic means such as therapeutic vaccines. In the early stage of cancer patients, if a tumorigenic biomarker in a tumor tissue has been detected at an abnormally high level, it is reasonable to assume that the monoclonal antibodies specifically targeting this biomarker will be ideally effective against this tumor. Numerous reports have addressed this issue and some successful results have been obtained [30-35]. On the other hand, the monoclonal antibodies are very expensive and several thousand US dollars drug expenditure can be used only in a single therapeutic cycle. Usually, only a few months of survival benefit is all that can be expected in late stage of cancer patients. The short term survival benefits of therapeutic antibodies might be caused by production of human immune responses to these antibodies [36].

Strategies

Extrapolating exact alleles of genetic alteration or abnormalities in cancer cells is no easy task. It contains detection of DNA, RNA, Protein and glycoprotein. In the detection of proteins or glycoproteins, the results are straightforward. However in detection of oncogenomic information, the extrapolation is relatively complicated. A genome is more than a bundle of genes. Apart from protein-encoding regions, non-protein-encoding regions and repetitive DNA are also present in human genome [37]. Human or oncogenome contain non-coding RNA genes, regulatory sequences, structural motifs; it maintains short-range and long-range spatial organization of sequences; and it contains evolutionary information. Thus extrapolation of genetic abnormalities from a tumor tissue needs high technology and revolutionary knowledge and calculating systems. The more we understand the human genome, the more correct genetic information and accurate therapeutic targets we can choose from and optimal clinical outcome can be achieved.

Pharmacogenetics

Introduction

By entering this millennium, a systematic study of pharmacogenetics has been intensified. People began to know that most drugs undergo structural modification by hepatic or other organ metabolism enzymes in human bodies to activate or inactivate of drug activities [38-40]. Some drug modifications can produce anticancer metabolites or detoxifications of active metabolites to non-active metabolites. What percentage and balance of these active or inactive drug metabolites are decided or determined by human inherent genetic conditions in patients. It is known that the plasma concentrations and toxicities of anticancer drugs can vary more than ten-fold among different cancer patients who are given the same dosages of anticancer drugs in clinics because of genetic variations or genetic polymorphisms in drug metabolism enzymes or cancer biomarkers. The purpose of pharmacogenetics is to predict the fraction of active or inactive metabolites and required dosage of a drug and the possible drug sensitivity to tumors [41-47]. Overall, pharmacogenetics or pharmacogenomics is an effort to maximize efficacy and minimize toxicities of drugs in patients.

Methodology

Pharmacogenetics or pharmacogenomics detects genetic information such as Single Nucleotide Polymorphisms (SNP), haplotypes, microsatellites or simple sequence repeats, insertion and/or deletion, copy number variations and aneupoidy of human metabolism enzymes and tumor tissues.

There are two basic models of anticancer drug pharmacogenomics:

control and optimizing the concentrations of active anticancer drugs;

pharmacogenetic study of anticancer drug targeting genes (tumor tissues).

There are a number of different metabolites of anticancer drugs in human blood or plasma. They are determined by human metabolizing enzymes. Many different human metabolizing enzymes determine metabolism of different anticancer drugs. If one human metabolizing enzyme is affected by genetic polymorphism, some anticancer prodrugs cannot produce enough active anticancer drug metabolites. Then the tumor inhibition of anticancer drugs will be reduced. On the other hand, active anticancer drugs will be more quickly detoxicated or excreted by human metabolizing enzymes. If these human metabolizing enzymes are inactivated by genetic polymorphism of enzyme genes, the active anticancer drugs will greatly be accumulated in blood and plasma of human bodies. These patients will show the strong toxicity of anticancer drugs, some of them even life threatening. This is the major part of anticancer drug pharmacogenetics [48,49].

Parmacogenetic study of drug targeting genes is another part of anticancer drug individualized therapy. Anticancer drug exhibit anticancer activity by inhibiting targeted molecules or genes. If these targeted genes or molecules are influenced by human genetic polymorphism, such as SNP, and drug's response to these genes will change greatly. These targeted molecules or genes can be all oncogenic or metastatic related genes or molecules.

The overall theme of pharmacogenetics is the right drug for the right patient. It includes detection of polymorphism of following genes [42,43] (Figure 1);

Upstream mechanisms

Drug transporters; (drug resistance)

Drug-metabolizing phase I enzymes (CYP subfamily enzymes); (prodrug to active metabolites or inactivation of drugs)

Drug-metabolizing phase II enzyme (other than CYP enzymes); (inactivation of drugs)

Drug target interactions

DNA biosynthesis and metabolism; (alkalating agents and platinium drugs)

DNA repair mechanisms; (toxicity or resistance of drugs)

Cell signal receptor

Mitotic spindle (possible of drug resistance)

Hormoral-regulated enzyme

HIF-related pathways

Nuclear factors related pathway

Downstream mechanisms (apoptosis genes and chemokines)

Tumor suppressors p53 (drug response or resistance)

Bcl

FAS/CD95/APO-1

PTEN

Tumor Necrosis Factors (TNF) and interleukin-10

Interleukin-6

Tumor metastasis-related pathways (drug targets against neoplasm metastasis)

MMPs

CAM (Cell Adhere Molecular); integrin, cadherin, selectin, etc

Angiogenesis genes

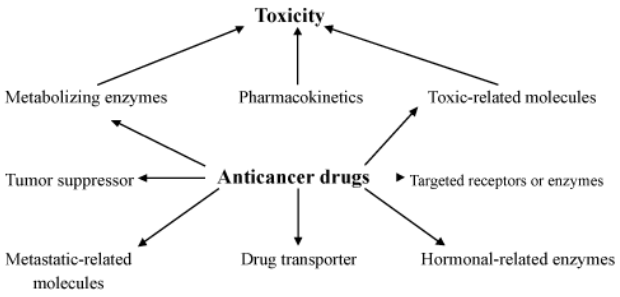

Figure 1: The field of pharmacogenetics in individualized cancer therapy.

Explanations of polymorphism of key enzymes or molecules for understanding response, resistance or toxicity of drugs, or finally understand drug response to tumor metastasis.

Examples

Platinum agent-induced gastrointestinal toxicity is associated with polymorphism of ERCC gene and irinotecan-induced hematologic toxicity is associated with the polymorphism of metabolizing enzyme UGT1A1*28 [48]. The toxicities of a drug can be different reasons and multiple organs. It increases the difficulty of pharmacogenomics studies of drug toxicities. So many of side effects if not very severe or not easily defined are commonly neglected in pharmacogenetics or pharmacogenomics study. There is no clear-cut definition among the degree of toxicities. It depends on the experience of a doctor and facilities of a hospital.

Thiopurine S-methyltransferase (TPMT) is a metabolizing enzyme to inactivate some active metabolites of anticancer drugs, such as 6-mercaptopurine, azathiopurine and 6-thioguarine. Normally, 90% of individuals have high enzymatic activity of TPMT. 10% individuals have intermediate TPMT activity. 0.3% of individuals have low or even no detectable TPMT activity. Among these persons, variations of TPMT*2, TPMT*3A and TPMT*3C consist of 95% TPMT enzyme activity deficiency. Unable to inactivate active metabolite of drugs will cause severe toxicity to patients, even life-threatening [49].

Individualized antimetastatic chemotherapy

Problems arise

Cancer metastasis is the key of cancer patients' deaths. Since more than 90% cancer deaths are caused by cancer metastasis, it is logical to believe that more attentions should be paid to them. Previously and present, treatment and therapy of cancer patients are mainly focused on primary tumors and antimetastatic drugs are often used as assistant therapy and only several types of antimetastatic drugs have been licensed. Also, many individualized cancer therapy methods, such as drug sensitivity tests or pharmacogenomics are designed to primary tumors. So cancer patients' survival has been improved to a small extent in clinics. Now there seems basically no better option other than drugs for antimetastatic treatments, yet cancer metastasis treatment commonly does not work in most cases in clinics. Any small breakthrough for antimetastatic therapy will lead to great clinical achievements in cancer therapies [50]. Thus herein it is reiterated that more attentions should be paid to development of more effective antimetastatic drugs and treatment of neoplasm metastases according to clinical circumstance of patients and find effective therapies to formed metastatic foci [11-13].

Shall antimetastatic therapy be different from antiproliferative therapy?

Shall antimetastatic therapy be different from antiproliferative therapy [51]? It has been found that the hallmarks of cancer [2] are somewhat different from the hallmarks of metastasis [2,52]. The hallmarks of cancer are those genes that decide the unlimited growths of cancer cells. However, the hallmarks of metastasis are those genes that decide the interactions between tumor cells and environments (human bodies). They are different types of genes and drugs. However, current clinical therapy mainly provides antiproliferative agents to cancer patients and most of cancer deaths (90%) are caused by neoplasm metastasis.

Therapeutic mechanisms of current antimetastatic drugs

Primary tumors are embedded in surrounding matrix. Tumor cells and their surrounding matrix can secrete a spectrum of proteinases that will break up these surrounding matrixes and make tumor cells penetrate through these matrixes and finally invasion and metastasis. These proteinases are mainly composed of Matrix Metalloproteinase (MMPs). So, MMPs inhibitors are agents proposed to inhibit tumor metastases. These agents have been licensing since 1990s in USA and they are one type of antimetastatic drugs [53,54].

Metastatic cells, after extravasation to remote organs, need new blood vessels to offer nutrients to transform the micrometastatic tumor to macrometastatic nodule. The formations of these blood vessels are controlled by vasculature growth factors, such as EGF, VEGF. Drugs that control the secretion and functions of these vasculature growth factors are known as potential antivascular antimetastatic drugs [55,56].

These two types of antimetastatic drugs are the main source of current antimetastatic therapy in clinics [57].

Shortcomings of present antimetastatic therapy

Paradoxically to our efforts and expectations, tumor angiogenesis or MMP inhibitors are sensitive to several types of cancer and no obvious improvements and therapeutic benefits by conventional antimetastatic drugs (usually antivascular agents or MMPs inhibitors) have been achieved to rest of metastatic tumors types, especially late stage of cancer patients [58,59]. More importantly, some unfavorable side-effects of these inhibitors in humans have been reported [60-63]. Clinical antimetastatic drug therapies should change our focus to new targets [50]. Both finding important drugs and targeting new antimetastatic pathways are essential and indispensable. However, these attempts have not developed into many useful new licensed antimetastatic drugs.

Should human tumor metastasis be treated according to clinical situations —individualized antimetastatic therapy?

Present antimetastatic therapy treats patients equally. No specific prescribing attentions are paid according to clinical situations of patients.

Tumor metastases involve a fixed course of pathophysiological processes. Human cancer metastasis encompasses several different substages (1) invade locally through surrounding Extracellular Matrix (ECM) and stromal cell layers, (2) intravasate into the lumina of blood vessels; (3) tumor cells survive the rigors of transport through the vasculature; (4) arrest at distant organ sites; (5) tumor cells extravasate into the parenchyma of distant tissues; (6) initially survive in these foreign microenvironments in order to form micrometastases, and (7) reinitiate their proliferative programs at distant sites, thereby generating macroscopic, clinically detectable neoplastic growths [10-13]. From this pathologic point of view, since a metastasis must travel more than one body-organ, the obvious different anatomic organs may possibly trigger different molecules and pathways linking neoplasm metastases. This reasonably results in being affected or inhibited with different types of drugs in different stages of metastatic processes. In return, different anticancer drugs will certainly not act in the same way in all metastatic organs [10-13,63,64].

In general, it was proposed that the MMPs inhibitors might be more active in preventing tumor cells from detaching primary locations [63]. It has been shown that only 1/1,000,000,000 to 1/5,000,000,000 tumor cells can survive in vascular or lymphatic circulations and finally produce remote forms of metastatic tumor cells [65]. Immuno-modulators might promote the activity of macrophages in killing tumor cells during the vascular and lymphatic circulations [66,67]. Thus, immune promoters can inhibit tumor metastasis in the way of tumor cell blood transportations. On the other hand, tumor cell congregations are less easily targeted by human immune cells. Thus, blood coagulating molecules, such as fibrinogen or thrombin, their biological states can also decide the rate of tumor metastasis [68-75]. Angiogenesis inhibitors might be used as the substage of attaching of tumor cells to remote organs and micrometastasis formation. However, highly cytotoxicity agents might be more effective in the treatment of formed metastatic foci and preference-organs [10-13, 64] (Figure 2).

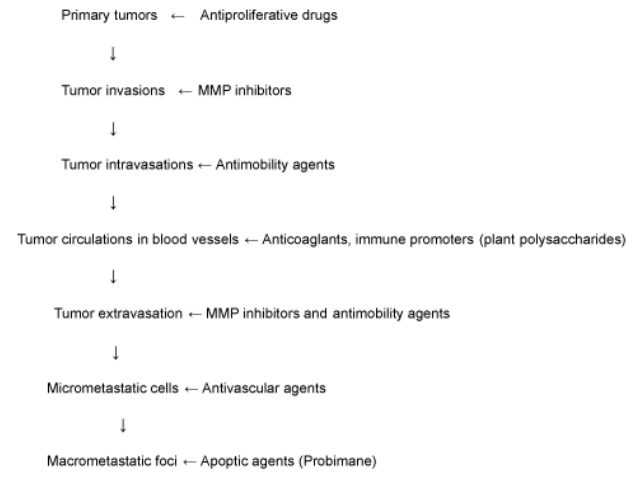

Figure 2: Antimetastatic therapy according to metastatic cascade [12,13].

Targeting the formed metastatic foci in clinics

Most cancer patients die of cancer with formed metastatic cancer. In these patients, MMPs inhibitors or antivascular agents do not work all the time. Thus, high active drugs targeting to these metastatic tumors need to be developed. Recently, it is known that transmission of primary tumor to metastatic tumors in body is the transmission from epithelial to mesenchymal and transmission of metastatic tumors is from mesenchymal to epithelial [76,77]. Thus it might be mechanistically different between drugs targeting primary tumors and formed metastatic tumor [78] (Figure 3).

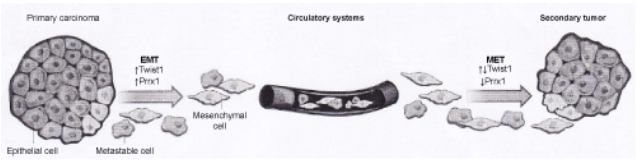

Figure 3: Overall picture of primary tumor and metastatic tumors [78].

There is an opposite biological pathways and mechanisms between primary tumor and metastatic tumors. So we propose here that anticancer agents inhibiting primary tumors might be a promoter to metastatic tissues. Future strategies to formed metastatic foci ought to be boosted.

Drug combinations

Most cancers have multiple genetic alterations or abnormalities. It is seldom very useful by only using one anticancer drug [79,80]. Human cancer is a refractory and resistant disease, and like HIV virus,

it might need anticancer drug cocktail instead single drugs to dramatically control the progresses of the disease [4,81,82]. Anticancer drug cocktail might be one of the good solutions for anticancer therapy. How to combine use of anticancer drugs is a new problem and area of anticancer drug therapy study.

Results and Discussions

A recent genomic study of >3,000 tumors across 26 cancer types has been underway. Only 1/4 of these tumors contain known cancer genes [83]. It means that most tumors are caused by undefined cancer genes. Thus there is a great potential for further investigations of cancer biomarkers.

The success or failure of a chemotherapy regime is determined by a number of clonal or stem cells in a tumor tissue [20,84-88]. The effectiveness of conventional therapy is affected by the rate of cancer stem cells in tumor tissues. The acquisition of stem cells in cancer tissues can renew themselves that can hardly cured by present anticancer drug treatments. These self-renewals of cancer cells help to increase tumor malignancy (dedifferentiation, dormancy, invasion, metastasis, relapse, chemotherapy-refractory, immune-escape and stimulating angiogenesis of tumors) [84-88]. Thus drug sensitivity tests aiming at determining drug response against clonal or stem cancer cells might be more useful and suitable for hospital routine in future. New stage of *in vitro* drug sensitivity testing should be innovated and emphasized on these tumor types for predicting drug response to a tumor tissue.

Mounting experimental data and clinical evidence suggest it might be a good way to use drug combination in controlling tumor growth and metastasis. However, the toxicities of drug combination to human are also increased with the increase of drug numbers. Drug sensitivity tests, cancer biomarker detecting and pharmacogenetics are designed to select effective drugs from anticancer drug arsenals and to discard ineffective drugs. They can make a good balance between drug activity and toxicity.

Many strategies of individualized cancer chemotherapies are complementary with each other. Clinically, we can apply two or three types of ICT strategies in one cancer patient. It needs to treat cancer patients according to cancer patients' clinical situation and financial condition. If we are more familiar with all parts of individualized cancer therapy strategies, the more we can help cancer patients. However, these therapies must be based on cost-effective evaluations. Cost-effective study of drug combination and biotherapy is a main part of individualized cancer therapy. In future, we ought to use low costs, high effective anticancer drugs in individualized cancer chemotherapy. Considering more than $10,000 expenditure of common cycles of drug combination, the biomarker detection fee ($100-5,000) is relatively cost-effectiveness. After detecting cancer biomarkers, it will increase the Quality Adjusted Life Year (QALY) of cancer patients, especially in some early stage of cancer [25,89,90]. Almost each of presently used ICC strategies is cost-effective along with times.

Conclusion

Drug sensitivity testing and pharmacogenomics are the mainstream of current Individualized Cancer Therapy (ICT). Detection of human or cancer genetic, transcript, protein or glycoprotein molecular and bioinformatics need less and less moneys and large bio-information in future. For instance, the speed of drafting genome increase 15,000-50,000 times compared with first success drafting human genome 10 years ago [83,91,92]. The cancer biomarker or bioinformatics detection-based ICC strategy will also upgrade with times and lower cost with technical innovations and might create more potential ICC strategies in the future.

In order to in depth understand all strategy of ICC, we urgently need well-designed, prospective, double-blind studies to systematically evaluate all possibility and forward this strategy racing with times (Figure 4).

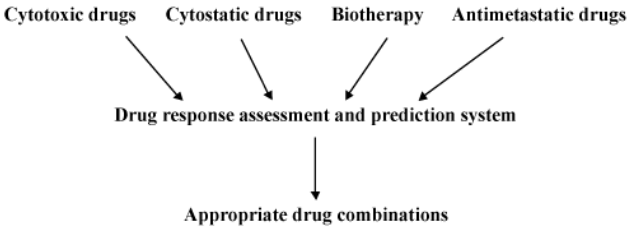

Figure 4: General Scheme of individualized cancer therapy.

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Competing Interesting

Authors have declared that no competing interests exist.

Authors Contribution

This article is mainly written by Dr. Da-Yong Lu, Prof. Ting-Ren Lu and Miss Cao discussed many details of the article.

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