

Review Article

Individualized cancer therapy

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Abstract

Cancer is the disease with a common pathological feature of unlimited growth and sometimes invasion and metastasis. Some parts of cancer patients are not given proper treatment by conventional cancer treatments. Individualized cancer therapies (ICT) are designed to improve cancer patients' treatment outcomes. This perspective is to update current and future ICT methods and therapeutic strategies, and give new directions for revising cancer treatment from empirical to technical-assistant therapy. Present understanding and predictions of drug toxicities and responses to tumor growth or metastases in cancer patients are not well-formed, mostly from doctors' past experience—empirical. There are fundamentally four types of ICT methodologies (i) drug sensitivity testing; (ii) detection of tumor genetic, transcription and molecular information (bioinformatics) from cancer cells in patients, (iii) pharmacogenetics, (iv) individualized antimetastatic therapy. Since different ICT strategies have their own advantages or disadvantages, optimizing utilizations of different ICT strategies need modern insights and are future trends. Persistent investigations and studies are not avoidable. The survival of cancer patients can be improved by many existing strategies of ICT, and clinical cancer therapy will be updated by finding the relationship between cancer biology, pathology and therapy. Deeper understanding these theories and technologies by ICT will surely benefit clinical cancer trials.

Keywords: Individualized cancer therapy; personalized medicine; cancer treatment; cancer hallmark; drug sensitivity testing; pharmacogenomics; cancer biomarkers; cancer bioinformatics; omics techniques; antimetastatic therapy; biotherapy; drug combinations; cost-effectiveness

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1. Introduction

Cancer is the disease with a pathological feature of unlimited growth and sometimes invasion and metastasis. The hallmarks of cancer could be multiple genes and multiple stages [1-2]. Since tumors are originated from a wide variety backgrounds of different pathogenesis causations. Different pathogenesis causations are sensitive to different anticancer drugs and therapeutic strategies. Thus, most cancer patients are unsuited to use “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 anticancer drug selection system in clinics is no less important than the discovery of new anticancer drugs. “Individualized cancer therapy” (ICT) are tailored to meet all requirements of improving

therapeutic quality by selecting and prescribing well-matched anticancer drugs and avoiding ineffective anticancer drugs through different scientific systems, such as drug sensitivity test, tumor bioinformatics detection, pharmacogenetics and individualized antimetastatic therapy in clinics.

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

Emerging problems relating to cancer therapy

Since cancer is the disease of genetic alteration and molecular abnormalities, the best therapeutic approaches should target these genetic alterations and molecular abnormalities. However, different cancers are caused by different genetic alterations and molecular abnormalities. Thus before an appropriate therapy is initiated, it needs first to pinpoint the exact genetic alterations and molecular abnormalities of a specific cancer in clinics by DNA, RNA or protein levels of detections in tumor cells and they can offer useful information for prediction of drug responses to human cancers and toxicities in humans. DNA, RNA or protein detections of cancer cells offer useful information of tumor oncogenic, invasive or metastatic processes and are the underpin of modern ICT and presently are categorized into generally four main systems [10];

- (i) Drug sensitivity testing *in vivo* and *in vitro*.
- (ii) 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. It is categorized into “detection of cancer biomarkers of omics techniques”;
- (iii) Detection of polymorphism of human or tumor genes to predict the activity of anticancer drugs against tumor tissues and toxicity of drugs to human bodies. It has been categorized as pharmacogenomics (PG) of anticancer drugs.
- (iv) Individualized antimetastatic therapy.

In the following sectors, all possible ICT systems are separately outlined.

2. Methodology

Drug sensitivity testing

History of drug sensitivity testing

ICT was pioneered by drug sensitivity tests [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, ICT was generally recognized as drug sensitivity testing.

Methodology of drug sensitivity testing

Different 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 drug

activities or responses of the candidate anticancer drugs within 4-11 days intervals. SRC method can be used for evaluations of many solid cancers, including gastric cancer, mammary tumors or lung cancer etc. The quick growth or large volumes of human solid tumors are suitable for SRC methodology. *In vitro* drug sensitivity testing methods involve cytological or cyto-chemical evaluations of drug response including the micro-culture tetrazolium (MTT) method [11-12], the ChemoFx method [13], the ATP luminescence assay [14-16] and the collagen gel droplet-embedded culture method [17] and so on. Usually, the effect of drugs on tumor enzyme activity, energy consumption or cell numbers is assessed. For example, Kondo and colleagues described a test involving drug effect on succinate dehydrogenase activity in tumors [18]; this was the prototype of the present frequently used MTT method—an *in vitro* system for evaluating antiproliferative activity of anticancer drugs.

Other *in vivo* models such as orthotropic human tumor models and clinical drug response testing in nude mice are also useful. However, these types of *in vivo* drug sensitivity testing models are expensive and labour intensity due to the cost of immune-deficient mice and hiring of experienced personnel.

Relationship of drug response between drug chemosensitivity testing and clinical cancer treatment outcomes

In approximately 80% clinical reports shown there is solid relationship between the results of drug sensitivity testing and clinical drug response data (partial response—PR or complete response—CR). In most cases, drug responses (PR or CR) in cancer patients are improved by referencing 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, 10-18].

Analyzing and reflecting different factors or details affecting clinical treatment outcomes by using drug sensitivity testing

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 [10].

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 in common 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 at least two dosages in drug sensitivity testing in future. Otherwise, the false-positive or false-negative data may be obtained [3-4]. Like these experimental details, if we notice, analyze and adhere to all experimental details of a drug sensitivity tests, the real difference of anticancer drug responses to a tumor might be well obtained and a success of a drug sensitivity test can be expected.

Induction of MDR in tumor cells often makes therapeutic failure [3]. After induction of MDR in tumor cells, the effectiveness of chemotherapies to tumors will be compromised. Some drug export channel inhibitors can be added to offset the outflow of anticancer drugs in MDR induced cancer tissues and increase therapeutic outcome.

New insights

Large part of cancer deaths are caused by cancer metastasis [19-23]. However, drug sensitivity testing is commonly to test drug response to primary tumor. Not specific targeting against metastatic tumor makes therapy less benefits to patients' survival. For example, *in vitro* drug sensitivity testing by using metastatic cancer tissues showed a therapeutic improvements and dramatic elongations of cancer patients' survivals for both early staged and late staged of patients [24]. In future, may some ICT specifically targeting on neoplasm metastasis be helpful for improvement of patient survivals, especially to late stage of cancer patients?

Similar to neoplasm metastasis, the success or failure of a chemotherapy regime is also determined by a number of clonal or cancer stem cells in a tumor tissue [10, 25-30]. The effectiveness of conventional cancer therapy is affected by the rate of cancer stem cells in tumor tissues. The cancer stem cells in cancer tissues can renew themselves that can be hardly controlled 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) [25-30]. 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, tailored and emphasized on cancer stem cells for predicting drug response to a tumor tissue, invasion and metastasis.

Presently, new types of genetic modified mice (GMM) have been engineered and breed. These kinds of mice have been engineered into more human genes and genome for supporting different tumorigenic environment, such as angiogenesis, invasion and metastasis by using these mice such as within mouse Avatars. The drug sensitivity testing in patients or anticancer drug development will be improved further by using GMM. Hopefully, we can benefit from these researches [31-33]. But most GMM are expensive owing to its intellectual property right protection.

Cancer Biomarkers and cancer bioinformatics for ICT Background and innovations

Cancer is a disease of genetic alterations or molecular abnormalities from widely differences of the biological or pathological causations. Normally cancer can be categorized from diversity pathogenesis causations into 6 different hallmarks of cancer (Table1) [2]. The best therapeutic approaches are proposed to target and inhibit every genetic alterations and molecular abnormalities in tumor tumors of individual cancer patients. However, different cancer hallmarks are caused by different genetic alterations, such as single nucleotide polymorphism (SNP), mutation, translocation, deletion, insertion or replication and molecular abnormalities, such as up-regulations of oncogene products or metastatic promoting factors etc. Thus before an appropriate therapy can be initiated, it needs first to know the exact extents of genetic alterations and molecular abnormalities specific cancer biomarkers or hallmarks in clinics [3-4, 34-39]. Various biological molecules have been widely reported to have diagnostic and/or prognostic value in cancer patients. Such molecules range from immunoregulatory factors [40], inflammatory factors (interleukins and cytokines), signal transduction regulators factors (tyrosine kinase, cyclooxygenase-2, MAPK, etc.) and factors relating to tumor pathology and therapy (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 the best targets for drug antagonisms or disruptions.

Table 1. Schematic outlook on biology and pathology mechanisms of cancer

Hallmarks of cancer	Possible molecular or pathological mechanisms
Sustaining proliferative signaling	Oncogene mutation, cell or proliferative signal over working, environmental alteration etc
Resisting cell death	Apoptosis (caspases, Bcl-2, Bax etc) and autophagy
Inducing angiogenesis	Vascular or inflammatory factors (VEGF, TNF) etc
Evading growth suppressors	Tumor growth suppressors (RB, TP53) etc
Enabling replicative immortality	Telomerase
Invasion and metastasis	Tumor stromal or matrix (MMP), Immunological factors and function, angiogenesis, glycoproteins, blood coagulation, epithelial to mesenchymal transition (EMT) and mesenchymal to epithelial transition (MET)

Modified from Reference 2

How to predict prognosis and drug uses in cancer patients by testing cancer biomarkers

In early stage of these researches, cancer biomarker detections are focused on detecting one or several pathogenic molecules (commonly protein or glycoprotein). Targeted monoclonal antibodies or other targeted anticancer drugs are prescribed against the up-regulated cancer biomarkers in cancer patients. Recently, some high throughput cancer bioinformatics methods (such as genechip or proteomic techniques) 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, 34-39]. Since tumors are progressive pathogenesis processes with more than a hundred genetic changes accumulating in a single cell [4], high-throughput methods are more likely to identify or pinpoint all underlying abnormalities in individual tumor tissues. The multidisciplinary nature of bioinformatics makes

it relatively higher cost and as stronger assistant tools to decipher cancer bioinformatics data. Individualized treatment based on detecting and understanding genetic and molecular variations by cancer bioinformatics applications mean relatively modern and advanced therapeutic strategies presently and in future.

Recent advancements

Cancers have been initiated from different etiological bases but share the same pathological characteristic of unlimited growth. Using the cancer genome to help understand the cause of cancer and variable response to drugs will be important avenue to understanding the cancer biology and medicine. More than a thousand types of genetic abnormality can cause about approximately one hundred different tumor types. More than 80 different mechanisms and types of anticancer drugs are available for treatment of different cancer categories and types in US [40].

Bioinformatics is a modern approach that provides a variety of techniques for analyzing abnormalities of DNA, RNA, proteins and glycoligands as a whole in tumors. In the earliest era of cancer biomarker detections by bioinformatics evaluations in clinical cancer practice was to predict patients' prognoses [41] or classify tumor origins and types [42-43]. Presently, the best example of utilizing cancer biomarkers or bioinformatics for predicting anticancer drug responses is to decide on antibody therapy (treatment of cancer patients with relevant monoclonal antibodies) [4] or other biotherapeutic means such as therapeutic vaccines or genetherapy [4,44-49]. 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 against this biomarker will inhibit and control the growth or metastasis of this tumor [4]. Numerous reports have addressed this issue and some successful results have been obtained [44-49]. On the other hand, the monoclonal antibodies are relatively more expensive than chemical drugs. Usually, only a few months of survival benefits can be generally expected in late stage of cancer patients. The short term survival benefits of therapeutic antibodies might be caused by triggering human immune responses to therapeutic antibodies [50].

Perspective of technical issues

Detecting or extrapolating exact alleles of genetic alteration or abnormalities in cancer cells by bioinformatics is no easy task. It is different from detection of DNA, RNA, single protein and other macromolecules. In the detection of single gene,

protein or glycoproteins, the results are straightforward. However in detection of oncogenomic information, the extrapolating information from DNA to RNA to proteins or other macrobiomolecules is relatively complicated. A human 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 [51]. Human or oncogenomes contain non-coding RNA genes, regulatory sequences, structural motifs, short-range and long-range spatial organization of sequences; and evolutionary information [51]. Extrapolating general genetic abnormality informatics from a tumor tissue needs high throughput technology and revolutionary knowledge and sophisticated calculating systems. For example, being tested- egfr, alk, HER-2, bcr-abl and etc, some previously poor prognostic tumours have been elongated considerably, such as some types of leukaemia or mammary tumours. The more we understand the human genome, the more correct genetic information and accurate therapeutic target prediction that can update our knowledge from empirical to modern technology assistant strategies.

Currently, many genetic or molecular cancer bioinformatics detection data needs mathematical or systems biological approaches to help our understanding of cancer carcinogenesis and oncogenic transformation. These types of researches are also very important and indispensable parts for individual cancer patients [4, 52-53].

Examples of clinical applications

In many clinical cases of human cancer, some of cancer patients are over-expressed with Her2 molecules. Cancer patients with over-expression of Her2 in tumor tissues are more refractory to conventional cytotoxic anticancer drug therapy and patient survivals are relatively poor. Trastuzumab, a targeted agent to Her2 can achieve more satisfactory survival benefits in cancer patients with cancer tissues of Her2 over-expressed. Likewise, Cetuximab, panitumumab or antroquinorol agents targeting against KRAS mutations or over-expressions are more sensitive to cancer patients with mutations and over-expression of KRAS. These agents can improve the outcomes of many cancer types, such as liver cancer, non-small cell lung cancer or other tumor types. Many similar examples can be obtained in clinical cancer trials.

Pharmacogenetics (PG) for cancer therapy

Basic information for PG

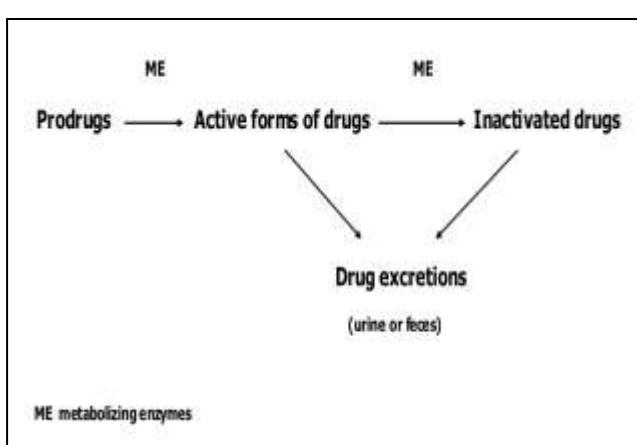
By entering this millennium, a systematic study of PG has been intensified worldwide. People began to notice that most drugs can undergo structural modifications by hepatic or other organ metabolism enzymes in human bodies to activate or inactivate of drug activities [54-56]. Some drug modifications 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 by inherent genetic status and makeup of patients. It is known that the plasma concentrations and toxicities of drugs including anticancer drugs can vary more than ten-fold among different cancer patients who are given the same dosages of drugs in clinics because of genetic variations or polymorphisms in drug metabolism enzymes. The purpose of PG anticancer study is to predict the fraction of active or inactive metabolites and required dosage of a drug and the possible drug sensitivity or responses to tumor growth and metastasis [57-64]. Overall, PG study is an effort to maximize efficacy and minimize toxicities of drugs in individual patients.

Methodology of PG study of cancer therapy

Anticancer therapy PG study detects genetic information such as single nucleotide polymorphisms (SNP), haplotypes, microsatellites or simple sequence repeats, insertion and/or deletion, copy number variations and aneuploidy of human metabolism enzymes in human and oncogenesis progresses of tumor tissues.

There are usually 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. Many anticancer drugs are prodrugs. They are ineffective in the original forms and activated by human metabolizing enzymes. If one human metabolizing enzyme is affected by genetic polymorphism, some anticancer prodrugs cannot produce enough active anticancer drug metabolites. Then the tumor inhibition by anticancer prodrugs 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 polymorphisms, the active anticancer drugs will greatly be accumulated in blood and plasma of human bodies thereby showing the strong toxicity of anticancer drugs, some of them are even life threatening. This is presently the major part of anticancer drug PG applications [64-65]. (Figure 1)

Figure 1. The diagram of relationship between drug concentration and polymorphism of metabolizing enzymes in cancer patients.



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

The overall theme of cancer therapy PG study also aims at the right drug for the right patient. It includes polymorphism detections of following drug targeted genes [10, 57-58];

Anticancer PG study and applications of key enzymes or molecules is useful for understanding response, resistance or toxicity of drugs, or finally predict drug response to tumor progression and metastasis

Applications

Many insightful PG clinical applications have been progressed and gradually perfected. Like PG study and applications of multitargeted anti-folate chemotherapy have been studied and applied in patients with non-small cell lung cancer or intestinal cancer [57-58].

Past decade, it has seen a tremendous progression in this field of personalized therapy. We must support cooperation between academic, drug manufacture and government funding worldwide in future and some unexpected fruitful outcomes may be hopeful later.

Table 2. The outlook or mechanisms of PG studies of anticancer drugs

Mechanism categories	Gene targets
Upstream mechanisms; (Drug metabolism and transporters)	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 platinum drugs) DNA repair mechanisms; (toxicity or resistance of cytotoxic anticancer drugs) Cell signal receptor Mitotic spindle (possible of drug resistance) Hormonal-regulated enzyme HIF-related pathways Nuclear factors related pathway etc
Downstream mechanisms;	apoptosis genes chemokines Tumor suppressors p53 (drug response or resistance) (Bcl, FAS/CD95/APO-1, PTEN, Tumor necrosis factors (TNF) and interleukin-10) Interleukin-6 etc
Tumor metastasis-related pathways	MMPs; CAM (cell adhere molecules)--integrin, cadherin, selectin; Angiogenesis genes Sialic acid related genes etc
Cancer stem cell-related genes or molecules	β-catenine, TGF-β, SDF1-CXCR4-CXCL12 MDR transporter etc

Modified from reference 10, 57-58

Individualized antimetastatic chemotherapy Pathological and therapeutic insights

Since cancer metastasis is the key factor for cancer patients' deaths, it becomes to realize that more attentions should be paid to it. Previously and present, treatment and therapy of cancer patients are mainly focused on primary tumors rather than neoplasm metastasis and antimetastatic drugs are not widely developed and used [19-23]. Moreover, many ICT methods, such as drug sensitivity tests or PG are mostly designed to primary tumors. So cancer patients' survival has been improved in a small

extent. Now there seems basically no important option other than drugs for antimetastatic treatments, yet many antimetastatic studies are not fruitful. Thus, any small breakthrough for antimetastatic therapy is proposed to make difference in cancer therapies [66]. It is highlighted to develop more effective antimetastatic drugs, especially against formed metastatic foci and treatment of neoplasm metastases according to clinical circumstance of patients [19-23]. Some possibilities can be avenues for inviting this breakthrough. They are outlined in following.

Is there difference between antiproliferative and antimetastatic therapy?

Shall antimetastatic therapy be different from antiproliferative therapy in some ways [67]? Or they are intertwined. It has been found that the hallmarks of cancer [2] are somewhat different from the hallmarks of metastasis [2, 68]. The hallmarks of cancer are those genes that decide unlimited growth of cancer cells. However, the hallmarks of cancer 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 yet caused by neoplasm metastasis.

Drawbacks and shortcomings of present antimetastatic therapy

Paradoxically to our efforts and expectations, tumor angiogenesis or MMP inhibitors (presently licensed antimetastatic drugs) are sensitive to several types of cancer. No obvious improvement and therapeutic benefit by these antimetastatic drugs to most highly metastatic tumors types, especially late staged cancer patients [69-70] is shown clinically. More importantly, some unfavorable side-effects of these inhibitors in humans have been reported [71-74]. It is better to change our focus to new metastatic-related targets [66], such as aberrant tumor sialic acids [75-82]. Finding both useful antimetastatic drugs and new antimetastatic targets are essential and indispensable. However, these attempts have not progressed into many useful new licensed antimetastatic drugs owing to lack government funding. Other clinical options are needed.

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

Present antimetastatic therapy treats patients equally. Generally no specific attention is paid according to

clinical situations of patients. Tumor metastases involve a fixed course of pathophysiological processes. Figure 2 depicts all possible metastatic cascades that can be controlled by different types of anticancer and antimetastatic drugs from past reported articles [22-23, 83-94].

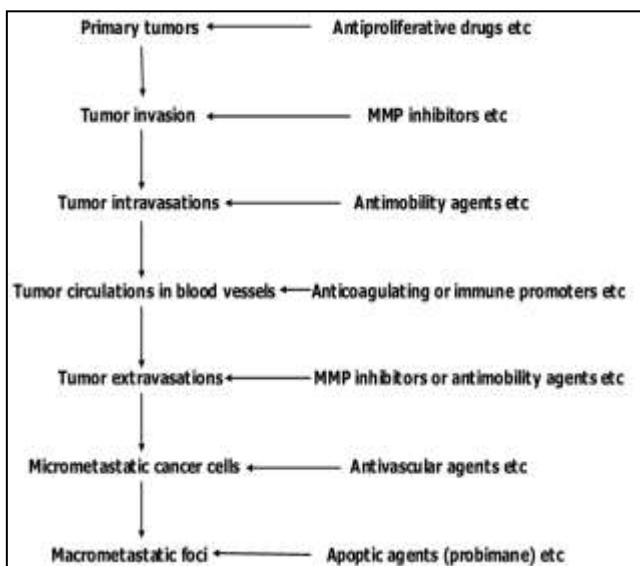


Figure 2. Antimetastatic therapy according to metastatic cascade [10, 22-23].

Targeting the formed metastatic foci in clinics

Most cancer deaths are caused by cancer with formed metastatic cancer. In these patients, MMPs inhibitors or antivascular agents do not work well. Thus, high active drugs specifically targeting formed metastatic tumors need to be developed, boosted and promoted. More recently, it is known that transmission of primary tumor to metastatic tumors in body is the transmission from epithelial to mesenchymal (EMT) and transmission of formed metastatic tumors is from mesenchymal to epithelial (MET) [95-100]. Thus it might be mechanistically opposite between drugs targeting primary tumors and formed metastatic tumor. There is an opposite biological pathways and mechanisms between primary tumor and metastatic tumors. So it is proposed here that anticancer agents inhibiting primary tumors might be a promoter to metastatic tissues. Future strategies to formed metastatic foci ought to be boosted and pay serious attentions.

Drug combinations

Most cancers have multiple genetic alterations and molecular abnormalities. It is seldom very useful by only using one anticancer drug [101-102].

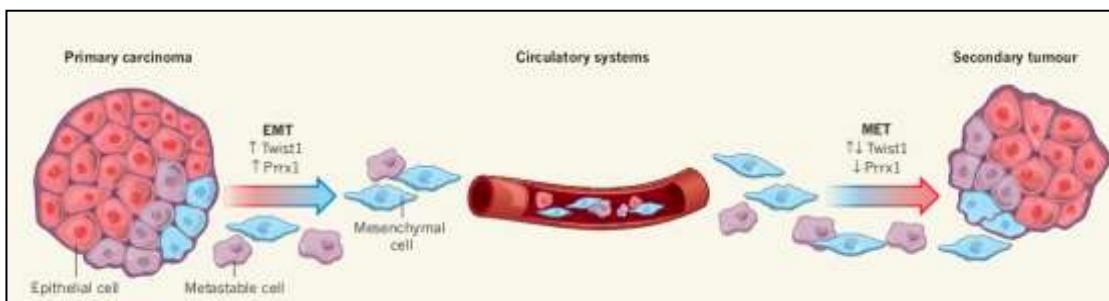


Figure 3. Overall picture of paradox pathological or therapeutic mechanisms between primary tumors and metastatic tumors [100].

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 and metastasis of the disease [4,103-104]. Anticancer drug cocktail might be one of the good solutions for anticancer therapy [101-102]. It is becoming a modern cliché of anticancer drug combinations that is more useful in clinical cancer treatment than single drugs [10]. Nevertheless, how to combine use of anticancer drugs is an emerging problem and area of anticancer drug therapy study [103-104]. Though drug combination is a common way to enhance patients' therapeutic outcomes and survivals, there is still much room for fulfillment and updating. In the past, clinical anticancer drug combinations is based on doctors judgment—by empirical rather than systematic and in-depth therapeutic mechanism researches and clinical investigations and detections. This leads to clinical therapies based on empirical, statistical data or past preferences than scientific-based drug combinations drawn from comparisons and investigations both in experiments and in clinics. Finding new laws regarding anticancer drug combination efficacy in anticancer and antimetastatic therapies must be an indispensable future trend and we cannot overlook it [103-104]. Anticancer assistant therapy is also useful for improving treatment outcomes of some very refractory cancer types [105]. In future, some new laws answering what types of anticancer or antimetastatic drugs are the best combination strategies are invited. These findings must be repeated again and again by using same drug category of different drugs.

Cost-effective of ICT Background

The pros and cons of personalized medicine are commonly met, e.g. pros: updating treatment schedule and benefits, reduced healthcare cost with more appropriate therapy; and cons: wide-scale

profiling is largely unrealistic due to cost of testing, lack of treatment alternatives, presently lack of reliable predictive biomarkers for many cancers.

Outlook of presently used systems

Though it is a good way to use drug combination in controlling tumor growth and metastasis, the toxicities and costs of drug combination to human are also increased with the increase of drug numbers. Drug sensitivity tests, cancer biomarker detecting and PG are designed to select effective drugs from anticancer drug arsenals and discard ineffective anticancer drugs. A good balance between drug activity, toxicities and cost is the state-of-the-art system and new law of anticancer drug combinations will promote clinical cancer therapy.

Many ICT strategies are complementary with each other. Clinically, two or three types of ICT strategies can be applied in one cancer patient. According to cancer patient' pathological situation and financial condition or more familiar with all parts of ICT strategies, the more we can help cancer patients. However, selections of ICT must be based on cost-effective evaluations. Cost-effective study of drug combination and biotherapies, such as gene therapy or antibody therapy is also main parts of ICT owing to their relative high costs. In future, low costs, high effective anticancer drugs in ICT will be prescribed to more cancer patients. Considering more than \$10,000 expenditure of common cycles of drug combination, the biomarker detection fee (\$30-5,000) 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 or young cancer patients [37, 106-107]. Almost each of presently used ICT strategies is cost-effective in many ways.

New perspectives of ICT

Present unsatisfactory cancer treatments, especially solid tumor treatment motivate new round of experimental and clinical campaign and ICT applications. Presently, anticancer drugs are more suitable for human leukemia treatment and less effective to solid human tumor, especially to late-staged cancer patients. In future, more effective ICT will be developed for the treatment of solid tumors in cancer patients.

Since we may not possibly use all of these strategies in one patient, amongst different types of ICT, which of ICT strategy is the best? Each of them has its own advantages and disadvantage. At present no one type of ICT strategies is obviously advantageous over the others. Also, no available ICT strategy has been well enough to significantly increase the patient's survival compared with conventional therapy. So we desperately need some dramatic moves to improve present ICT strategies or even create new systems by integrating the advantages of all ICT types. Although much effort has been made, many main obstacles still need to be hurdled. Reason is there is almost no survival improvement in patients with noticeable metastatic nodules in spite of applications of drug sensitivity testing [4, 10]. But it can be a future miracle if we can perfect them into a successful one. So are we ready for that yet? [108]

Conclusion

Presently, drug sensitivity testing, detection of human cancer biomarkers or bioinformatics, PG and individualized antimetastatic therapy are the mainstream of current ICT strategies. It will need less and less moneys and high-throughput bioinformatics in future. Speedy drafting human and cancer genomes by next generation sequence (NGS) [109-112] might change the landscape or blueprint of ICT study and application scenarios. NGS can be used in defining cancer pathology, staging and therapies. Some longstanding questions of cancer biology and pathology, such as relationship between heterogeneity of cancer and therapy or different treatment schedules between primary tumor and metastatic tumor might be solved by NGS. The cancer biomarker or bioinformatics detection-based ICT strategy will be updated with high-resolution and lower cost from technical innovations and advancements, and might create more potential ICT strategies in the future. The role of NGS for obtaining gene signatures and molecular targets will be boosted and promoted. The implications of advancements of NGS for the future ICT will be perfected because they provide more genetic, molecular or oncogenic information.

In order to in depth understand cancer pathology and therapy, well-designed, prospective, retrospective and double-blind ICT studies and applications are urgently needed and will forward this strategy from empirical to scientific-guided systems.

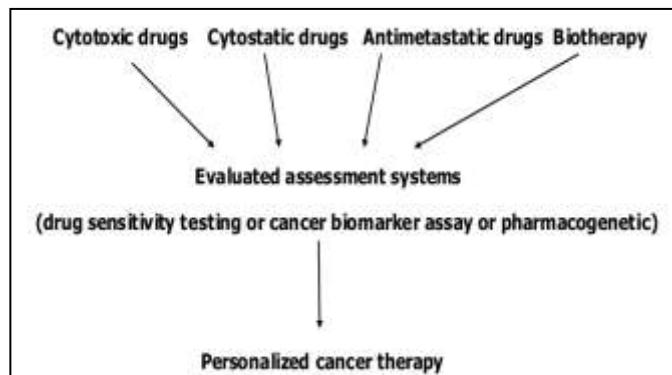


Figure 4. General Scheme of individualized cancer therapy and drug combinations [10]

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Competing interesting

Authors have declared that no competing interests exist

Author's contribution

This article is mainly written by Dr Da-Yong Lu, Prof Ting-Ren Lu, Jin-Yu Che and Hong-Ying Wu discussed many details of the article

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