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Review Article

Anticancer drug combinations: The next medical challenge

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Abstract

Since most cancers have multiple genetic alterations and molecular abnormalities, it is seldom very useful by using therapeutics of only one anticancer drug owing to refractory and drug resistance of cancer tissues. It has a long time consensus that anticancer drug cocktail instead single drugs might dramatically promote the control of cancer progresses and metastasis in most clinical cancer trials. Despite great popularity and as modern cliché for anticancer drug combination utilizations, the hidden rules behind anticancer drug cocktails is an emerging scientific problem and pivotal topic in new era of anticancer therapy studies. Most importantly, anticancer drug cocktails need to transform from empirical to science-guided enterprises. This review offers the scenarios of background knowledge of cancer therapy achievements for drug combinations until now, possible future landscape and direction for overcoming limitations, pitfalls and drawbacks of past cancer therapy and proposes more matured ones.

Keywords: cancer, anticancer drug, oncogene, cytotoxic

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1. Introduction

Since most refractory and late-staged cancers have multiple genetic alterations and molecular abnormalities [1-2], it is seldom very effective by using only one anticancer drug owing to relapse, aggressive property and drug resistance of cancer tissue exhibitions. Long before, it was proposed that anticancer drug cocktail instead single drugs usually improved the therapeutic efficacies to control the cancer progressions, invasions and metastasis in cancer patients [3-6]. There is a large-scale consensus among most doctors that anticancer drug cocktail is a good therapeutic option for improving anticancer chemotherapy in clinics. Despite its great popularity and as a modern cliché, how to provide the recipe of anticancer drug cocktails is an emerging problem and an area of

futuristic frontier. Since only a few anticancer drug combination models are subjected for mechanism investigations and highlighted into scientific rules, anticancer drug cocktail designs need transformation from empirical to science-guided modern systems. Only by this strategy, cancer therapy can make a difference. This review focuses on introduction of all challenges and discovery of the hidden rules for drug combinations in clinical cancer trials. The scenarios and landscapes of our understandings of anticancer drug combinations are provided and highlighted.

Limitations and drawbacks of single anticancer drug therapies

Weaknesses and limitations of single anticancer drug therapies are multi-factorials including higher mortality of cancer progressions and metastasis,

less satisfactory therapeutic outcomes and high occurrence of cancer metastasis. Many pathological or therapeutic factors play pivotal roles for cancer deaths. These multiple pathogenesis processes factors are weaknesses and big difficulty for present single anticancer drug therapies;

One of the reasons for unsatisfactory of cancer therapeutic outcomes is the toxicity of antineoplastic drugs to human bodies. The human tolerate dosage of anticancer drugs limits the high dosage for single anticancer drug therapies, which results incompletely killing of all tumor cells and promotions of multidrug resistance (MDR) tumor cells after several cycles of tumor proliferations and survivals. Anticancer drugs can be divided into two categories—cytotoxic anticancer drugs and cytostatic (targeted) anticancer drugs [7]. Since the cytotoxic antineoplastic drugs are commonly high toxic and wide-spectra, they also damage normal human cells at the same times of killing cancer cells. Thus the dosages of single antineoplastic drug in human therapy cannot be too high to be tolerated by humans. At the end, small proportions of cancer cells survive after one or two regimes of cytotoxic anticancer drug chemotherapy. These tumor cells will regrow to large tumor volumes and multidrug resistance (MDR) to cytotoxic anticancer drugs often occurs in these cancer cells. Yet unexpected clinical evidence is accumulated that cytotoxic anticancer drugs are good partner with most types of anticancer or assistant agents. More recently, some cancer therapeutic paradigms are noticed and practiced. Some good clinical paradigms are given for introducing modern ideas and drug combination strategies.

Despite high specificity of anticancer biotherapeutic agents and options, it has exhibited low inhibitory rates to tumor growth and survival benefits in clinical cancer trials. Owing to these characteristics of most biotherapies, the treatment outcomes by using biotherapy alone are rarely very successful. Few doctors use biotherapy as single agent to treat cancer patients. Combination utilizations of cytotoxic anticancer chemicals with biotherapy are optimal strategies for cancer treatments [8-10]. Important references are given later.

90% of cancer patients' deaths are caused by cancer metastases. It is neoplasm metastasis that

will finally cost the life of cancer patients. The best option for late-staged cancer therapy may optimize and improve therapeutic norms and strategies by changing therapeutic details and routines. The best example and arguments may be combinations of cytotoxic anticancer chemicals with cytostatic anticancer drugs, antimetastatic drugs or biotherapies. Many other anticancer drug combination options are also proposed. More recently, some cancer therapy paradigms are noticed and practiced that combine cytotoxic anticancer drugs with other therapeutic agents.

Different types of anticancer drugs and varied combination strategies

Most effective cancer therapeutic practices are combinations of different types of anticancer drugs. Anticancer drugs are categorized with cytotoxic anticancer drugs, molecular-targeted cytostatic anticancer drugs, biotherapy agents, antimetastatic drugs and etc. Several types of anticancer drug combination systems are temporarily categorized as followings;

1. Combine anticancer drugs of different targeting and mechanisms of action;
2. Reduce the toxicities of cytotoxic anticancer drugs by other drugs;
3. Combinations of chemical cytotoxic anticancer drugs or radiotherapy with different types of biotherapeutic agents;
4. Combine cytotoxic anticancer drugs with cytostatic (targeted) anticancer drugs;
5. Combine cytotoxic anticancer drugs with less toxic assistant or adjuvant agents;
6. Combine anticancer drugs with drugs with improvement of drug resistances;
7. Combine anticancer drugs targeting primary tumors with antimetastatic drugs;
8. Combine anticancer drugs with cancer stem cell modulators or inhibitors;
9. Combine anticancer drugs by individualized or personalized evaluation and predictions of drug toxicity and responses etc

The panorama of these drug combination strategies are separately outlined and discussed in following sectors.

Combine anticancer drugs of different targeting and mechanisms of action;

Since no golden rule of anticancer drug combinations can be followed and suitable for all cancer patients, some propositions should be made first. Now cancer can be categorized into six distinct hallmarks (Table 1) [2]. It is proposed herein whether it is optimal for utilizations of different categories of inhibitors as drug combination strategies for cancer patient therapeutics. Furthermore, a great number of cellular genotypic or phenotypic characteristics can be altered in single different hallmark of human tumors by varied categories of anticancer drugs [10]. As a result, anticancer drugs targeting different cancer molecules, phenotypes and pathways might cooperate with each other to kill or inhibit cancer growths more effectively.

shortcoming of cardiotoxicity. Owing to the strong cardiotoxicity, doxorubicin cannot be given with high dosages in clinical cancer treatments, which results in incompletely killing all tumor cells in cancer patients after doxorubicin therapy. Soon after finding this clinical evidence, some other anticancer compounds or even drugs have been found to counteract this unique toxicity in animals and humans [11-14]. More satisfactory discovery was to find that doxorubicin and Biz compounds including razoxane and probimane could cooperate one and another in combating with tumor growths and metastasis in experiments and clinical trials [11-12, 15-16]. More recently, razoxane has been licensed for ameliorating the harmful effects of doxorubicin leakage from blood vessels in cancer

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

Reduce the toxicities of cytotoxic anticancer drugs by other types of drugs;

Reducing the toxicities of cytotoxic anticancer drugs by other drugs is a common model of drug combinations. Since most cytotoxic anticancer drugs are very toxic, some types of toxicities of cytotoxic anticancer drugs cannot be tolerated in normal humans. Monitor or even counteract by other types of drugs, including other anticancer drugs may enjoy great successes in future. Best example is the combinations of anthracyclines such as doxorubicin with bisdioxopiperazine compounds (Biz) such as razoxane [11-14] and probimane [15-18]. Doxorubicin, the most effective and wide-spectra cytotoxic anticancer drug has an obvious

patients in US [19]. Similar examples of reducing drug toxicities of anticancer drugs can be enumerated greatly across the wide-volume of references [20].

Cytotoxic drugs and biotherapy combinations

The best feature of anticancer therapies is to cooperatively utilize advantages of each anticancer drug category. Thence integrate and promote present therapeutic norm into a new paradigm. One of these attempts and paradigms is to combinatory use of cytotoxic chemicals with biotherapies [8-10]. Cytotoxic anticancer drugs are wide-spectra cancer inhibitors that are active against almost all cancer categories. However, cytotoxic anticancer drugs are toxic to normal

human tissues in the same times. Thus, no 100% cancer inhibitory rate dosages can be applied to cancer patients. If cytotoxic anticancer chemical drugs can kill 70% to 95% of tumor cells, some highly specific biotherapies are proposed to kill the rest of tumor cells with no marked toxicities [8-10]. This is a promising design and might be one of the smartest tactics innovated ever before. This strategy can be regarded as a paradigm of future cancer chemotherapy. Anticancer drugs rarely kill all tumor cells by using one type of drugs. If several cancer cells remain, they will quickly regrow to large-volume of cancer. So patients' immune surveillance systems or other high specific biotherapies might play pivotal role for the long-term effectiveness and survival benefits of cancer patient therapy. The development of biotherapies is currently insufficient and will be the great task of future therapeutic seeking and applications. The best example and paradigm nowadays is to combine cytotoxic anticancer chemicals with monoclonal or polyclonal antibodies [21-29]. The obvious combinative efficacies are frequently reported among international journals. On the other hand, other biological means, such as vaccines or cytokines etc can also combine with cytotoxic chemotherapy. Different anticancer biotherapies are outlined in Table 2. (Table 2)

Table 2. Different anticancer biotherapies

Biotherapy	Targets
Monoclonal or polyclonal antibodies	Tumor biomarkers
Vaccines	Tumor antigens
Gene therapy	Escalated tumor genes or antigens
Cytokine therapy	Human tumor environment
Immune-therapy	Tumor antigens
iRNA	Tumor genes

The advantages of combination strategy of cytotoxic anticancer drugs with biotherapy are easy to be seen. The biotherapies for cancer are often relatively mild but high specificity. Although they are difficult to kill large tumor volume, they are

high specific and only kill small amount of tumor cells with completeness and no obvious toxicity except some cytokine therapies. The cytotoxic chemotherapy as we guess should always be given before the biotherapy. It is the cytotoxic chemical drugs to reduce tumor tissues to a minimum volume, then high specific biotherapy to kill the rest of tumor cells no matter these tumor cells are MDR or not. This might be an ingenious paradigm and hopeful we can achieve better therapeutic outcomes according to this principle and workable new systems. In future, more effective biotherapies might be innovated to be used with cytotoxic anticancer drugs and improve cancer treatment significantly.

Challenge and drawbacks for this strategy are still remained at present stages. Firstly, currently biotherapy is not perfect for their low cytotoxicity against large tumor volumes. It is seldom to completely destroy all cancer cells if the tumor volume is more than 0.5 cm. There are still several steps to go in drug combinative applications. In the future, we need to innovate and produce more effective biotherapy for cancer therapy, especially against formed metastatic foci because this is the main cause of cancer patients' deaths.

Secondly, we do not know which specific biological or pathological pathways go aberrant in tumors in clinics. As a result, we must firstly know the pathological profiles (tumor biomarkers or bioinformatics) of tumors to treat them by most clinical relevant biotherapeutic agents such as antibodies or small RNA [29-31]. By pursuing this paradigm, well drug combinations of anticancer drugs can be organized and properly targeted.

The third reason is the high cost of biotherapy, especially antibody and microRNA (the highest cost of effective immune-therapy can be as high as 200,000 USD for a single therapeutic cycle in one patient) [29]. So patients' financial criteria is an important factor to decide whether we can undergo antibody therapy or not. On the other hand, therapeutic antibodies inhibit cancer growth or metastasis only for several months. After therapeutic antibody administrations for several months, human bodies will produce immune response against therapeutic antibodies [32]. Then, therapeutic efficacies of antibodies will be compromised.

There is a long way to go for this kind of therapeutic strategy and more efforts in this matter ought to be made. It is the time to verify all our assumption in this special therapeutic rule in clinical cancer trials.

Combine cytotoxic anticancer drugs with assistant agents

The causes for the death of cancer patients can be multi-factorial in clinics. Apart from direct causes from tumor progressions and metastases by all genetic possibilities, other clinical complications or psychiatry factors will more or less speed up the death of cancer patients. So many assistant therapies will give the cancer patients who have some clinical complications or psychiatry ill-conditions [33-49].

Next to cancer metastasis, the second deadly pathological feature of cancer patients is the venous thromboembolism [33]. For example, cancer patients with venous thromboembolism symptoms have the higher possibilities and rates of cancer patient deaths and been hypothesized to be counteracted with assistant therapy of anticoagulants (AC) and/or fibrinolytic agents (FA) such as warfarin, heparin or oxalysine. The other important problem is which categories of solid cancer are suitable for prophylaxis anti-thrombosis therapy. There is no significance improvement of patients' survival in most cancer categories by anti-thrombosis therapy. Only 1/3 of cancer patients shows survival benefits by AC, while the other 1/3 cancer patients might be improved by FA [36-37]. More recently, lung cancer patients' survival has been found to improve a great deal in patients, especially non small cell lung cancer patients by giving anti-thrombosis therapy [41, 44]. On the other hand, survival benefits can be reached by anti-thrombosis therapy in patients having breast cancers [33]. Overall, patients with solid tumor categories might be more likely improved by anticoagulant or fibrinolytic agent therapies [36-37]. Nevertheless, one thing has to be noticed that anti-thrombosis therapy must be combined with anticancer drugs because no therapeutic improvement was reported in the group treated with heparin alone [45].

A lot of people believe that cancer is an incurable disease. Some of them frighten to death after hearing they contract cancer. Their mental strength

of cancer patients collapses afterward of telling truth. Generally the fear of death in cancer patients will speed up the patients' death. It has been hypothesized whether antidepressants can be used as an assistant therapy for patients with psychiatry ill-conditioned [48-49]. This is a rarely noticed therapeutic option and subject to less systemized investigations. But it may be a unique therapeutic target if we can revisit this approach.

Treatment of cancer by traditional Chinese medicine (TCM) is a hot topic in modern China. There are many favorable reports for TCM in treatment of cancer patients [50-54]. According to rules of TCM, human bodies are formed and balanced by fighting between inner upright strength and outside damaging air. Individualized therapy of TCM should be mainly based on either strengthening inner upright air and preventing or expelling the outsider damaging air. In most cancer cases of TCM treatments, patients need to seek strengthening upright air therapy rather than preventing or expelling outside damaging air therapies. Most TCM doctors in China hold such a view now.

Cancer is a deteriorating and wasting disease. Cancer patients, especially late stage cancer patients, need more nutrients to keep the body in normal form. This type of assistant therapy also has their western backgrounds. This type of assistant therapy, such as antioxidants or selenium additives was used in clinics and was found from the references published in international journals [55-57].

As assistant treatment for cancer patients, mounting assistant anticancer therapy paradigms have been proposed and proved to prolong patients' survivals in wide ranges of cancer patients. For assistant therapies, in most times, it needs to combine use with anticancer or antimetastatic drugs. Or the therapeutic benefits of many assistant therapies should be greatly undermined.

Combine use of drugs both antiproliferative drugs (primary tumor) and antimetastatic drugs

A lot of cancer patients die of cancer metastasis (90% of cancer deaths). It means current antimetastasis therapies are unsatisfactory and imperfect owing to pathogenesis of neoplasm

metastasis processes is complicated [58-66]. Despite some achievements in metastatic therapy study, most effective therapies are unknown to us and the treatments for cancer patients with neoplasm metastasis often fail. [65-66] In order to improve patients' survival, it needs to promote some ground breaking strategies to overcome this problem at large. Apart from manufacturing more effective and higher specific anticancer or antimetastatic drugs [61-66], combinative utilizations of drugs both antiproliferative drugs (primary tumor) and antimetastatic drugs is supposed to be one of good paradigms to elongations of survival for late-staged cancer patients. Different stages of cancer patients need to be targeted by different types of drug therapy. No fixed antimetastatic agent can be prescribed to all cancer patients with neoplasm metastasis. Individualized antimetastatic therapy must be followed. [65] Theoretically, good antimetastatic therapy should not be uniformed and must be tailored for different pathogenic stages. There is great potential for this type of drug combination studies.

Combine cytotoxic drugs and cytostatic drugs

Combinations of cytostatic (targeted) anticancer drugs by detections of cancer biomarkers with cytotoxicity anticancer drugs based on drug sensitivity testing (DST) are promising avenues to improve cancer patients' therapeutic outcomes in clinics. Anticancer drugs (chemical agents) are divided into two distinct categories; cytotoxic drugs or cytostatic drugs [7]. Cytotoxic drugs indiscriminately kill both cancer and normal tissues. Generally speaking, cytotoxic anticancer drugs are effective to almost all types of cancer cells. But this kind of anticancer drugs is also toxic to normal tissues and easily acquires the characteristics of multi-drug resistance (MDR) in treated cancer cells. Furthermore, cytotoxic anticancer drugs cannot be used in extremely high doses that can kill all cancer cells and exhibit long-term therapeutic efficacies for most cancer patients by using single cytotoxic anticancer drug. Cytostatic anticancer drugs, on the other hand, aim at targeting specific oncogenic genes, biological molecules or receptors and so on. Though overall antiproliferative effects of cytostatic anticancer drugs alone are relatively lower than cytotoxic anticancer drugs, cytostatic anticancer drugs have much less toxicity to normal

tissue and their therapeutic responses to tumor are relatively long and persistent. The therapeutic index of cytostatic anticancer drugs is usually higher than cytotoxic anticancer drugs

The licensing of cytostatic anticancer drugs is developed very fast. It brings about a question of how to utilize these different cytostatic anticancer drugs. Selections and optimizing therapeutic recipes of cytostatic anticancer drugs by identifying the abnormal tumor biomarkers in individual patients is an effective avenue of anticancer drug predictions. Each important abnormality of cancer biomarkers will be antagonized by relevant cytostatic drugs that are designed to target different molecules or pathways [67-72]. By combination of cytotoxic anticancer drugs with cytostatic anticancer drugs, the therapeutic responses to tumors can be improved or even eradicating of tumor cells from patients. This type of drug combinations might be optimized based on detecting the quality and quantity of tumor biological markers from tumor samples or patient's blood.

Combination of anticancer drugs and cancer stem cell (CSC) modulators or inhibitors

CSC are the main components of cancer therapeutic resistance, neoplasm metastasis and treatment relapse [73-77]. Many CSC modulators or inhibitors have been discovered and developed within the past decades. Their combinations with standard anticancer drugs have been widely reported. (Table 3) In spite of this popularity, less successful clinical evidence has been found in clinics. Many factors behind scenes need to be uncovered.

The CSC modulators or inhibitors in this stage are imperfect owing to its moderate toxicities and marginal therapeutic benefits in clinics. Before becoming a major therapeutic paradigm, basic understanding the pathogenesis and therapeutics of CSC is indispensable.

Present customs of drug discovery, development, and/or licensing for different drugs and therapeutic regimes

Discover and develop more effective anticancer drugs are indispensable and ultimate goal of drug manufactures. Since cancer is different diseases

Table 3. Examples of combination therapy with stemness modulator drugs and standard anticancer drugs

Stemness modulator drugs	Standard anticancer drugs	Cancer types
Salinomycin	Gemcitabine	Pancreatic
	Octreotide modified paclitaxel	Breast
	Etoposide	Hepatic
	Doxorubicin	Uterine, sarcoma, breast
SANT-1	SAHA	Pancreatic
GSI-XII	Bortezomib	Multiple myeloma
	ABT-737	Multiple myeloma
Curcumin	Dasatinib	Colon
	Gemcitabine	Pancreatic
	Gemcitabine	Bladder
	Paclitaxel	
	Tumor necrosis factor (TNF)	
	TNF-related apoptosis inducing ligand	
	5-FU plus oxaliplatin	Colon
ER-400583-00	Radiation	Gliomas
VEGFR2 targeting antibody	Cyclophosphamide	Gliomas

with pathogenesis characteristics of unlimited growth, different categories of anticancer drugs might be sensitive to different tumor types and pathologic stages.

Reorganized from reference 73

Modern anticancer drug screening systems need diversified tumor models and molecular targets. No anticancer drug, except cytotoxic drug, might be sensitive to most of tumor models in vitro and in vivo. Possible false-positive or false-negative drug efficacy against tumor growth in vitro and in vivo models might happen if the insensitive tumor models or higher anticancer drug concentrations/dosages are applied. Since too much factors can determine whether a new compound can be entered into next round of drug response identifications and assessments by both animal models and clinical trials, any inappropriate

tumor models may lead to complete failure of drug tests. Owing to the diversity of tumor models, drug responses and toxicities is affected at least 50% for its quality standard. High expenditures of anticancer drug development are often encountered. Averagely, 1.0-1.8 billion UDS must be covered for licensing a single anticancer drug in US [78-79]. From this scenario, only big pharmaceutical companies from wealthy countries such as Swiss, UK, Germany and US can offer successful licensing worldwide. Skyrocketing therapeutic fee will be paid for single cycle of clinical therapies using new or patent-protected anticancer drugs. Rethink of anticancer screen and development systems has been reiterated frequently. The new movements of anticancer drug developments may impact the therapeutic routines of cancer patients' treatments and provide fertile soils for the growth of personalized cancer therapy

[80-82]. Further information will be given in following.

Developments of new antimetastatic drugs

Since 90% of cancer deaths are caused by cancer metastasis in clinics [58-66], it means current antimetastatic drug developments and therapeutic knowledge are unsatisfactory. Except neoplasm metastasis biology and pathology mechanisms of action, neoplasm metastasis treatments both in animals and in humans have been achieved very little [65-66]. Boosted efforts for antimetastatic treatment and drug development study have licensed a number of antimetastatic drugs worldwide. Nevertheless, they do not play decisive roles in clinical cancer trials. A lot of reasons can be counted for the shortage of effective antimetastatic therapies and drugs [62-66].

Rules of drug combination by personalized cancer therapy (PCT)

Like HIV cocktails, the best drug combination strategy is to combine drugs of different mechanisms of action. The diversified targets and drug types may exhibit optimal integrated benefits of antiviral agents and obtain low possibility of drug-induced resistance for therapy. For individualized cancer therapy, properly pathological or pharmacology information, such as the drug sensitivity testing (DST) of cytotoxic anticancer drugs and drug response predictions of cytostatic anticancer drugs on specific tumor biomarkers, may achieve positive therapeutic outcomes by different PCT options and avenues? [80-84] The unresolved question is what the scientific rules behind the doctors' medical experience, past reference and randomized selections are based upon. In future, transformation of drug combination systems from empirical to science-guided well formed individualized cancer therapy is indispensable.

Cost-effective considerations

Generally speaking, drug combination has better therapeutic outcomes than single anticancer drug treatment in clinical cancer trials. But concomitantly, it often costs much more than single drug. Skyrocketing budget of anticancer drug development, patent protection, and market propaganda and advertisement for drug license makes high costs of drug for cancer patients (1-1.8

billion for licensing single anticancer drug). [78-79] From this reason, cost-effective consideration for drug combinations is part of basic and clinical cancer chemotherapy work and studies, especially when some high priced drugs are intended to be used in clinical practices [85-86].

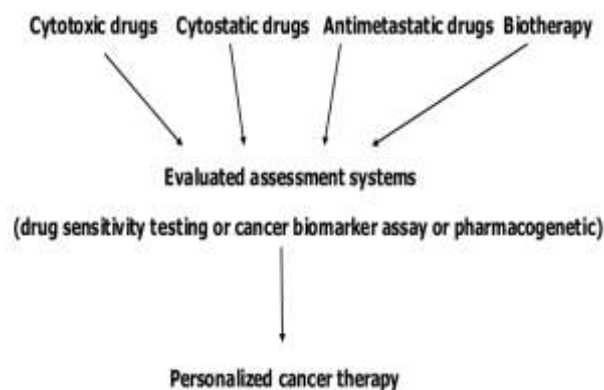


Figure1. The outlook of different drug combination selections

Discussion

Since huge possibilities of drug combination protocols can be assembled in clinics, it needs great deals of efforts and moneys to complement and optimal selections. Mounting experimental data and clinical evidence suggest it is a good way to use drug combination in controlling tumor growth and metastasis. However, the toxicities of drug combination in some clinical cases are also increased by the increase of drug numbers. Drug sensitivity tests, cancer biomarker detecting and pharmacogenetics are designed to select effective and optimal numbers of anticancer drugs and discard ineffective drugs for economic or therapeutic reasons [85-86] and pharmaceutical considerations, such as nano-drugs [87-89]. They can make a good balance between drug activity and toxicity. However, new technologies do not always mean good things. New balance between drug efficacies and toxicities might happen [88-89].

Conclusion

In future, we must pay more attentions on the breakthrough of drug combinational rule discovery and systemized. Only by these discoveries and systemizations, therapeutic efficacies for cancer treatments can be improved. There is no central dogma available for clinical utilizations of

anticancer drug combinations by repeatable protocols to follow. But we hope this article can serve as a gateway between past and future cancer chemotherapy norm.

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Competing interesting

Authors have declared that no competing interests exist

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