

## Anticancer Drug Combinations, A Big Momentum is Needed

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### Abstract

Most cancer therapies are seldom effective by using one anticancer drug owing to refractory and resistance property of cancer tissues caused by multiple genetic alterations and molecular abnormalities. Despite great popularity of anticancer drug combination utilizations, the hidden rules behind scenarios emerge in new era of anticancer therapy. Most importantly, anticancer drug cocktails need to transform from empirical to science-guided enterprises. This editorial offers the background knowledge of drug combination therapy across the history. Possible future landscapes and drawbacks of current cancer drug combinative therapy are addressed and speculated.

**Keywords:** Drug combination; Drug resistance; Neoplasm metastasis; Biotherapy; Cytotoxic anticancer drugs; Cancer stem cell; Personalized cancer therapy

### Introduction

Cancer is a common disease that claims life about 7-10 million people annually in the world. As a result, cancer remains to be a great medical challenge worldwide [1-3]. Many efforts can impact the overall therapeutic efficacies and outcomes of cancer treatments. One of these efforts is anticancer drug combinations. Long before, it was widely accepted that anticancer drug cocktail instead single drugs usually improved the therapeutic efficacies greatly [4-10]. Despite its great popularity and as a modern cliché, how to prescribe the recipe of anticancer drug cocktails are emerging problems. Since few anticancer drug combinations modular have been subjected for mechanism investigations and highlighted into scientific principle discoveries, anticancer drug cocktail designs need to transform from empirical decision into science-guided modern predictive systems. Only by science-guided strategy, cancer drug combinative therapy might make great difference. The scenarios of our understandings of anticancer drug combinations are addressed and highlighted in this perspective.

### Limitations of single anticancer drug therapies

Weaknesses and limitations of single anticancer drug therapies are higher diversity of tumor malignancies and incomplete killing all cancer cells owing to the toxicities of anticancer drugs. Many diversity phases of pathogenesis play pivotal roles for resistance of drugs and cancer patient's deaths. Owing to the toxicity of a lot of antineoplastic drugs to human bodies, the human tolerate dosage of anticancer drugs must not be ranged at the high dosage for single anticancer drug therapies, which results in incompletely killing of all tumor cells and inductions of multidrug resistance (MDR) tumor cells after several cycles of tumor proliferations and survivals at normal drug administration doses. Anticancer drugs can be divided into two categories-cytotoxic anticancer drugs and cytostatic (targeted) anticancer drugs [11]. Since the cytotoxic antineoplastic drugs targeting at inhibiting tumor proliferations are commonly high toxicity and wide-spectra effectiveness, 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 again and multidrug resistance (MDR)

to cytotoxic anticancer drugs often occurs in regrowed cancer cells. Yet cytotoxic anticancer drugs are good partner with most other types of anticancer (targeted agents), biotherapy or assistant therapies.

### Introductions of general ideas and different drug combination modular

Previously, combination utilizations of cytotoxic anticancer chemicals with biotherapy or other therapeutic means are good strategies for cancer treatments [8-10]. Many similar examples are given later and will be discussed one by one. Several modular 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 for drug resistance improvements;
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.

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### **Different modular of anticancer drug combination strategies**

Since no central dogma of anticancer drug combinations suitable for all cancer patients has been found, some propositions should be made first. It is proposed herein whether it is optimal for utilizations of different categories of inhibitors as drug combination principles for cancer therapeutics. Furthermore, a great number of cellular genotypic or phenotypic changes of human tumor hallmarks can be individually targeted by relevant anticancer drugs [8]. 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.

### **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 modular of drug combinations. Since most cytotoxic anticancer drugs are very toxic, some types of toxicities for cytotoxic anticancer drugs are difficult to be tolerated at high doses in normal humans. More structural revisions by medicinal chemistry comparisons or even counteract by other types of drugs may enjoy great successes. Best example is the combinations of anthracyclines such as doxorubicin with bisdioxopiperazine compounds (Biz) such as razoxane [12-15] and probimane [16-19]. More interestingly, doxorubicin and Biz compounds could cooperate one and another in combating with drug-resistance and neoplasm metastasis [12,13,16,17].

### **Cytotoxic drugs and biotherapy combinations**

One of these modular and paradigms is possibly the combination of cytotoxic chemicals with biotherapies [8-10]. Cytotoxic anticancer drugs are wide-spectra cancer inhibitors that are active against almost all cancer categories. But commonly, no dosage of 100% cancer inhibition can be applied to cancer patients. If cytotoxic anticancer chemical drugs only 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]. The best example supporting this paradigm is to combine cytotoxic anticancer chemicals with mono-clonal or polyclonal antibodies [20-28]. The obvious combinative therapeutic efficacies are frequently reported among international journals.

### **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 of tumor progressions and metastases by all genetic possibilities, other clinical complications or psychiatry factors will more or less speed up the deaths of cancer patients. So many assistant therapies will give the cancer patients who show some clinical complications or psychiatry abnormal conditions [29-42]. Next to cancer metastasis, the second deadly pathological feature of cancer patients is the venous thromboembolism [29]. 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. Only half of patients are statistically significant to improve survivals by anti-thrombosis therapy. Approximately 1/3 of cancer patients show survival benefits by AC, while the other 1/3 cancer patients can be improved by FA [30-32]. More recently, lung cancer patients' survival has been reported to improve a great deal by giving anti-thrombosis therapy [32,35]. A lot of people believe that cancer is an incurable disease. Some of

them frighten to death after hearing they contract advanced cancers. Their mental strengths of these cancer patients collapse afterward of hearing truth. Generally, the fear among cancer patients will speed up the patient's deaths. It has been hypothesized whether antidepressants can be assistant therapies for patients with psychiatry problems [8,41,42]. This is a rarely noticed therapeutic option and subjected to less systemized investigations. But it may be a unique therapeutic target if we can revisit this approach afterwards. As assistant treatment paradigms for cancer patients have been proposed to mainly prolong patient's survivals in wide ranges of cancer patients and promote the quality of patient's life. Assistant therapies, however, need to combine use with anticancer or antimetastatic drugs. Or the therapeutic efficacies of many assistant therapies should be greatly undermined, or even useless in clinical trials.

### **Combine use of drugs both antiproliferative drugs (primary tumor) and antimetastatic drugs (remote disseminations)**

A lot of cancer patients die of cancer metastasis (90% of cancer deaths). It means current antimetastasis therapies are unsatisfactory and imperfect due to the complicate processes of neoplasm metastasis [43-51]. Despite some achievements in metastatic therapeutics, cancer metastasis treatments often fail in clinical trials [50,51]. Apart from manufacturing high effective and specificity anticancer or antimetastatic drugs [46-51], combinative utilizations of both antiproliferative drugs (primary tumor) and antimetastatic drugs is supposed to be a useful paradigm for survival elongations of many advanced (late-staged) cancer patients. Theoretically, good antimetastatic therapy should not be uniformed and must be tailored for different pathogenic stages [50,51].

### **Combine cytotoxic drugs with cytotoxic drugs**

Anticancer drugs (chemical agents) are generally divided into two distinct categories; cytotoxic drugs or cytostatic drugs [11]. As anticancer drugs are great in number (84 anticancer drugs licensed in US and 178 drugs licensed in the world in 2013) [52,53], most of anticancer drugs are cytotoxic and cytostatic drugs. Thus combining cytotoxic drugs with cytotoxic drugs and cytotoxic drugs with cytostatic drugs is the major types of drug combinations in clinical trials. Since there are diversity in therapeutic efficacies, toxicities, mechanisms of action and therapeutic pathways by different anticancer drugs in individual cancer patients, may some other predictive or selective systems (such as drug sensitivity testing etc) be borrowed? [54-56].

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

CSCs are the main components of cancer therapeutic resistance, neoplasm metastasis and treatment relapse [57-61]. Many CSC modulators or inhibitors have been discovered and developed within the past several decades. CSC modulator or inhibitor combinations with standard anticancer drugs have been widely reported (Table 1). In spite of this popularity, less successful 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. Moreover, CSC only consists of less than 10% of tumor volumes [45], can this small proportion of CSCs play pivotal role for neoplasm metastasis and therapeutic relapse? Before becoming a major therapeutic paradigm, basic understanding the pathogenesis and therapeutics of CSC is indispensable.

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

**Table 1:** Examples of combination therapy with stemness modulator drugs and standard anticancer drugs.

### Present customs of anticancer drug discovery, development, and/or licensing

Discovery and developments of more effective anticancer drugs are indispensable parts of drug manufactures and advancements of cancer therapies. Since cancer is different diseases with pathogenesis characteristics of unlimited growth and metastasis, different categories of anticancer drugs might be sensitive to different tumor types and pathologic stages. Tendency of modern anticancer drug developments is to screen for diversified tumor models, drug molecular targets and pathways. [52,53,62,63] The quality of drug responses and toxicities evaluations is almost affected by 50% owing to the diversity of tumor models. High expenditures of anticancer drug development are often encountered. Averagely, 1.0-1.8 billion USD must be covered for licensing a single anticancer drug in US [52,62]. From this scenario, only a few of big pharmaceutical companies from wealthy countries such as Swiss, UK, Germany and US etc can offer anticancer drug licensing worldwide. Soaring cancer therapeutic fee will be paid for clinical chemo- or biotherapies using patent-protected anticancer drugs. Rethink of anticancer evaluation and development systems has been discussed frequently [63]. Any new movements of anticancer drug developments may impact the cancer therapeutic routines and provide fertile soils for the growth of personalized cancer therapy and drug combination modular [54-56]. Further information and future perspective will be given in the followings.

### Discussion

Since huge possibilities of drug combination protocols can be assembled in clinics owing to large numbers of anticancer drugs being licensed worldwide (178 anticancer drugs worldwide in 2013) [53], it needs great deals of efforts and moneys to complement and optimally designing. Mounting experimental data and clinical evidence suggest that it is a good way for using drug combination in combating tumor growth and metastasis simultaneously. However, the toxicities of drug combination are parallel 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 [54-56] and pharmaceutical considerations, such as liposome-entrapped drugs or nano-drugs [64-66]. They can make a new balance between drug activity and toxicity. However, new technologies do not always

mean good things. These new options (modern techniques) are too early to be superstitious. For example, nano-anticancer drugs are not always affinity to tumor tissues and less toxicities to humans. The toxicities to human immune cells and systems are increased by nano-anticancer drug treatments. New balance between drug efficacies and toxicities might happen [64-66].

### Conclusion

In future, we must pay more attentions on the breakthrough of drug combinational rule discoveries and systemized. Only by these discoveries and systemizations, therapeutic efficacies for cancer treatments can be well improved and developed for a long run. Since there is no central dogma available for clinical anticancer drug combinations of repeatable experimental protocols and hospital routines, we hope this article can serve as a gateway between past and future cancer chemotherapy norm and help to build a bridge to embrace better therapeutic options.

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