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Anticancer Drug Combination, From Possibility to Principles

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Abstract

Advanced stage of cancer patient therapies is unsatisfactory and high-mortality of the disease now. A growing consensus for late-stage cancer patient treatment calls for excellent drug combination in clinical trials. Some progress in this respect has been made worldwide.

Despite growing popularity in clinical applications, the anticancer drug combinational rules remain to be discovered and massively applied according to clinical situations and personalized status of cancer patients.

In the past decade, we have focused on this matter with watchful eyes and scientific imaginations. This article reiterates these types of cancer managements by providing more matured standards and personalized systems. Future landscapes and insights into cancer drug combinational studies and applications are addressed.

In order to update this promising clinical paradigm, some key avenues of therapeutic promotion for anticancer drug combination are highlighted in this article. Experimental or clinical pathways and techniques to update cancer treatment will be carried out in the clinic. A variety of clinical drug selection systems in the future are challenged.

Keywords: Drug combination; Drug selection; Neoplasm metastasis; Biotherapy; Chemotherapy; Personalized cancer therapy

Introduction

Backgrounds for cancer treatment

Cancer is a common and aggressive disease that claims for annually 7 to 10 million deaths (12% of all human mortalities) in the world [1,2]. As a result, cancer remains to be one of the greatest medical challenges globally. Efforts and ideas can help us to navigate the long course of promoting therapeutic responses and outcomes in the clinic. One of these medical efforts is to optimize anticancer drug combinations and translate them into useful clinical paradigms for cancer patients.

Clinical dilemma

Single anticancer drug treatments against invasive and remote cancer metastasis rarely work due to multiple genetic alterations and molecular aberrations in patients with advanced-stage of cancer [3]. More than 80% cancer death is caused by neoplasm metastasis (advantage-stage). Targeting metastasis is an indispensable part of cancer treatment promotions and life-saver for a great number of patients [4-6].

Scientific study

Owing to the high mortalities of advanced cancer, it was gradually agreed that anticancer drug combination instead single drugs might improve this dreadful situation of cancer treatments [7-9]. Anticancer drug combination designs and optimizing as we previously suggested needed to transform from empirical decision into science-guided modern approaches for predicting drug combination responses and outcomes in different therapeutic systems or biomedical techniques [9-11]. Only by science-guided strategies, cancer drug combination might see great improvement. Yet, long way can go through in this avenue [10]. Approaches and hidden rules must be explored for drug combination promotion in clinical cancer trials.

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Therapeutic Challenge

Advanced-stage of cancer patients

Cancer patients are generally different in genomic alteration (heterogeneity) and pathological stages (1-4 stage). However, great part of human mortality is associated with advanced-stages of cancer patients. Correspondingly, treatment of aggressive malignancy plays key role for long benefits in patient survivals and even achieving cancer curability for patients with metastasis. To achieve this goal, anti-cancer drug combination is the top priority for advanced-stage of cancer patient treatment.

Comparison treatments between HIV infection and advanced-stage of cancer

Similar condition as Human Immunodeficiency Virus (HIV) infection treatment, the rate of patient survivals increases dramatically by drug combination (High Active Antiretroviral Therapy (HAART) [12,13]. The survival rate of HIV/AIDS (Acquired Immune Deficiency Syndrome) patients rose from 0% to >50% in two year's treatment observations.

Similarity with HIV/AIDS treatments, metastatic treatment (10-13% mortality rates for 5 years) is also suitable for drug combination treatment. From this mindset and discovery, systematic study for establishing good clinical paradigms for drug combination is required [10,11]. The therapeutic similarity and diversity between two diseases should be investigated in the future.

New principles discoveries

Drug combination needs systematic approach to support-including principles of chemistry, pharmacology and medicine. The vast number of possibilities of drug selection in every patient will be greatly narrowed and scientific-guided by clinical treatment study. After optimized drug selection, therapeutic response and outcomes to tumor growth and metastasis will be improved. Drug combination strategies will be updated in patients one by one and step by step. This article addresses these paradigms of clinical drug selection and technique edge for overcoming current therapeutic dilemma of metastatic treatments.

Modality Analysis and Supports

Combinational models

Basic anticancer drug combinational models lack scientific guidance. However, it is easier said than done because little scientific pathway has been given now [9]. Let alone scientific approaches for drug combination guidance.

International drug combination guidelines for cancer treatment provided for different modalities are based on singular or narrow-range studies. The majority of part references are based on sporadic ways or single experimental or clinical studies. Moreover, clinical drug combination selections are generally from past reports by comparing relatively small sized patient's regimes or doctor's experience. These types of anticancer drug combinational practice are far from perfections. New generations of anticancer drug combinational systems and clinical application modalities should be updated.

Complexity of clinical trials

A vast range of different agents (>2000 different chemicals) have been reported to affect tumor growth, survival and metastasis. Thus, combination therapeutic options are thus complex and large number for great diversity in structure and therapeutic potency. The discovery and developments of more effective anticancer drugs mean to select growing numbers for potential therapeutics.

Since cancer is different diseases (>200 subtypes) with pathogenesis characteristics of unlimited growth, survival, migration and remote metastasis (>13 cancer hallmarks) [3]. Different hallmarks need different anticancer drugs (different tumor subtypes and pathologic stages in each patient), especially in genomics [14]. Analyzing and selection of existing pharmacological data is complex and useful strategies for cancer metastatic treatment [15].

Modality Deduction

Pharmacological types of drug combination selection

Currently pharmacological anticancer drug combinational modular is based on past reference selection and deduction [10,11]. These types of drugs combinational modular are divided into Table 1.

Anticancer drugs can be divided into two categories-cytotoxic anticancer drugs (wide-spectra) and cytostatic anticancer drugs (narrow-spectra but target) [21]. The best deduction of drug combination is to combine drugs of two categories.

Tumor biomarker profiling

Above-mentioned anticancer drug combinational modular is only the smallest options in real clinical therapeutic settings. More effective anticancer drug combinational strategies might be still hidden to us. According to the present speed of drug combination discoveries (random and empirical), there must be a long way to go (at least 2 decades to make significant and full assessment).

Apart from structure variation of drugs, information of oncogenic onset or progress of tumors in individual patients might also be useful for drug combination selection [32,33]. To collect information of biomarker profiling or hallmarks in tumor tissues, targeted drugs specifically against tumors should be included in drug combination options in the clinic. By these medical diagnostics, the number of drug combination selection could be narrowed down.

Mathematical modality

A layout of drug combination study by all possibilities can be evaluated in equal attentions [11,12]. Herein, we discuss this strategy in scientific and technical manner.

To achieve the goal of full combination comparisons, mathematical calculation and algebra should be utilized beforehand. By all drug efficacy comparison and calculation, large scale of pharmacological evaluation (mainly drug sensitivity testing) will be undergone first [34].

Table 1: Most used drug combinational models or paradigms.

Most used drug combinational models		Reference
Anticancer drugs	Drugs to reduce the toxicity of anticancer drugs	[16]
Cytotoxic drugs or radiotherapies	High selective biotherapies	[17-20]
Cytotoxic drugs	Targeted agents	[21]
Cytotoxic drugs or radiotherapies	Less toxic assistant or adjuvant agents	[22-24]
Cytotoxic drugs	Drug-resistant approve agents	[25]
Western medicine	Traditional Chinese medicine	[26-28]
Drugs targeting primary tumor	Antimetastatic agents	[29-30]
Anticancer drugs	Cancer or virus vaccines	[31]

Let us introduce calculation formula. If the number of selective drugs is X and combination number of drugs in each patient is A, approximate all possibility number will be

All selection ≈ X^a (Equation 1)

About 180 to 200 anti-cancer drugs have been licensed worldwide [35,36], its numbers of all selection of drug combinations can be calculated in more precision ways.

According to mathematic equation (calculation for 3 anticancer drug combinations

$$C = \frac{180 \times 179 \times 178}{1 \times 2 \times 3} = 955860 \text{ and } C = \frac{200 \times 199 \times 198}{1 \times 2 \times 3} = 1313400$$

(Equation 2)

It means there are 955,869 to 1313,400 selections must be covered in all clinical drug combination response comparisons. At present, we cannot compare all these combinational possibilities easily in lab and in the clinic. Yet the complexity of vast different types of therapeutic response comparison will be finished according to the rapid progresses of high-throughput or computerized technical supports within five years. These types of experimental drug combination evaluations should be aimed and promoted at early as possible.

Strategy comparisons

Several strategies can be speculated to solve this complexity of drug combination selection

1. Assessments of drug combinational responses by high-throughput techniques [37-40]

2. Discover pharmacologic relationships between drug targets and synergistic efficacy to assist drug response comparisons

3. Cutting-edge biologic technique advances, like single cell multi-omics data for complete understanding cancer pathophysiology and phenotype

4. Establishing personalized medicine platforms to help drug combination optimization

5. Learn from knowledge of clinical medicine, especially traditional medicine

6. Balance between mathematics solution and pharmacological categorization (maximizing benefit effects in every patient).

The details of these avenues have much to describe. We delineate them as below (Figure 1).

Technical Advances

Miniature technology

Today, our pharmacological knowledge for cancer treatment is elementary. Drug selection optimizations have much to improve. Technical promotion (most likely high-throughput techniques, miniature and automatic assay may improve this condition.

Technical advances are the main research drivers for drug combination selection. Early techniques such as Drug Sensitivity Testing (DST) before 2,000 are labor-intensive and money-driven [41]. It is impossible to assess different levels of anticancer drug combination selection and comparison at early stages.

Anticancer drug combinational efficacy evaluation must be focused on *in vitro* technology. High-throughput anticancer drug evaluative systems, especially tunable microfluidics can partly solve problem of large number drug combine selection in the clinic. By upholding this strategy, we can achieve gradually cost reduction and efficacy promotion.

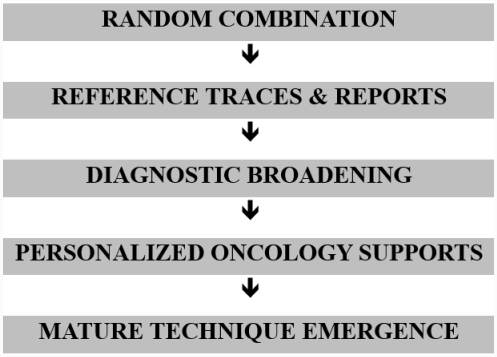

Figure 1: Early progress of anticancer drug combination study.

Cancer biomarker profiling analysis

Cancer biomarker profiling analysis can also be used to predict drug responses. Perfecting anticancer drug combination by cancer pathogens (genome and biomarkers) is the top priority. Technical advancements of single-cell multi-omics selection [42,43] will help anticancer drug response prediction for advanced-stage of cancer patients.

However, these researches need great clinic data and pathogenic knowledge distribution. In order to avoid unfair competition, international treaties ought to be better signed among most countries. Growing joint-venture activities and projects might finally help to overcome cancer treatment deficiency in patients with metastatic spread at secondary sites.

Computational network and personnel safe-guide

Owing to the huge numbers of drug sensitive or anti-proliferative activity testing data, mathematic or statistics data comparison and analysis for large clinical data ought to be equally participated by mathematicians or physics-majored students or scholars [44,45]. These types of research personnel may play unique roles on this field of anticancer drug combinational evaluation studies.

Pharmacologic Insights

Major theory

Anticancer drugs are chemically and pharmacologically classified for different categories. They are categorized as different mechanisms and targets; generating as

- Cytotoxic drugs (DNA chelating, damage or breaking)
- Gene expression changes (DNA mutation, deletion, copy number and translocation)
- Oncogene expression or producing
- Enzyme inhibitors (tumor microenvironment or others)
- Signal transduction (phosphorylation and receptors)
- Phytochemical components (reactive oxygen stress effectors)

Table 2: Association between drug selection and personalized platforms.

Personalized platforms	Main advantages in technology	Reference
Drug sensitivity testing	Testing tumor responses to drugs	[34]
Cancer biomarkers	Prediction of targeted drugs	[78]
Pharmacogenomics	Helping drug doses or selection	[76]
Precision oncology	Prediction pathogenesis pathways & network	[70]

- Immuno-modulation (PD-L1 inhibitors, antibody or others)
- Glyco-biology (glycan, ligands and glycolipids)
- Tumor plasticity (epithelial-mesochymal transition)
- Stem-like behavior
- Tumor metastasis (cell migration, metastatic cascade or others)
- Angiogenesis (vascular growth factors)
- Apoptosis (specific molecules and deposition enzymes)
- Suppressive gene regulation
- Gut or vaginal microbiota
- Sexual hormone receptors or inhibitors
- Metastatic cascade (invasion, migration and remote spread)
- Others

Combination of different targets and mechanisms may be an optimized pathway [9]. With vast ranges of oncogenic and metastatic factors, drug combination selection should be specified. Further combination activity comparisons and study based on this theoretic ideology may help us predict and improve therapeutic responses in the clinic. This is indispensable for the treatment of advanced-stage of cancer.

New modality establishment

Since no principle of anticancer drug combinations is available for clinical cancer trials, some new suggestions should be raised to update drug combination optimization. Now cancer can be categorized into thirteen distinct cancer hallmarks [3]. Whether combining inhibitors of different cancer hallmarks can be a future trend of therapeutic paradigms. Each cellular genotypic or phenotypic change of human tumor hallmarks can be individually combined by relevant anticancer drugs [46-49]. As a result, anticancer drugs targeting specific cancer molecules, phenotypes and malignant pathways might integrally inhibit cancer growths, invasions and remote metastasis more effectively. This is a general rule. Its perfections need time, money, ideas and human resources. Gradual progresses in the framework of drug combination study will be referred in Figure 2. From these experimental and clinical studies, drug combination selection and patient's survivals can be improved.

Drug Development

Efficacy to different cancer phenotypes

Anticancer drug combinational studies and applications, though overwhelming, are far from complete. As we can see, huge amount further work needs to be done. To begin with, the discover of effective and targeted anticancer drugs is the key. In this stage of drug development, drug activity and responses to different cancer phenotypes or hallmarks should be evaluated first.

Different drug properties

Apart from systems of anticancer drug combination selection, diversity of anticancer drugs should be noticed. Anticancer drug, except cytotoxic drug, is rarely sensitive to almost all tumor models *in vitro* and *in vivo*. Possible false-positive or false-negative drug therapeutic response prediction is very common before drug licensing and clinical application [49]. If the insensitive tumor models or lower anticancer drug dosages in animals and patients are applied, research and clinical outcomes will be wrong.

Since too many internal and external risk factors can change compound response data against different cancer categories. Noting every research details, tumor model utilities and selections may be helpful for drug tests and evaluations. After careful experimental and clinical study, different features of anticancer drugs can be understood. Certainly, drug delivery systems (nano- or others) are also useful information for drug combination selection and optimization.

Antimetastatic drug

Approximately 90% cancer deaths are caused by cancer metastasis in the clinic [4-6]. Current antimetastatic drug developments and therapeutic knowledge are lag behind [50-52]. If we can develop more effective antimetastatic drugs, drug combinations are proposed to be more efficacy and life-saving. It should be specified for different antimetastatic drugs.

Except neoplasm metastasis biology and pathology mechanisms, metastasis treatments between animals and humans should be emphasized. It is the current hotspot for metastatic studies. Combination of anti-proliferative drugs with antimetastatic agents will be a futuristic trend.

In the past decades, even though antimetastatic treatments and drug development show some positive sign, they nonetheless do not play decisive roles in clinical cancer treatments. Facing the shortage of effective animal models [53,54] and potential targets waiting for breakthroughs [55-59], the complex courses of metastasis cascades are the main reason to elucidate and clarify. With the quick development of antimetastatic drugs, drug combination efficacy can be greatly promoted.

Drug delivery systems

Up-to-date pharmaceutical delivery systems, such as liposome-entrapped drugs or nano-drugs can make a new balance between drug activity and toxicity. New options (modern delivery techniques) begin to show some advantageous characteristics of high tumor affinity and barrier penetration. New balance between drug efficacies and toxicities must be translated into new horizon and clinical paradigms [60-66]. Considering drug delivery in combined drug selection should be noted in the future.

Drug doses and toxicity

Treatment of a disease by combined drugs is like a battle in face of enemy. We need Air-Force, Marine and Infantry. In traditional Chinese medicine, the combined recipes must have king, courts, assists and soldiers (Jun-Chen-Zuo-Shi). Each one has his own responsibilities. Someone is the headquarter, others are soldiers. Every drug in combination recipes is not equal. According to Chinese tradition, different roles of treatment agents must have different dose-

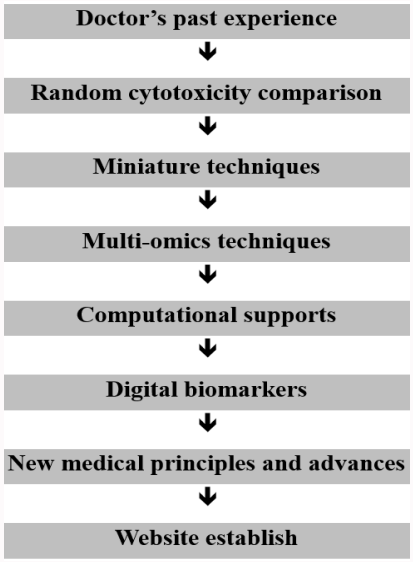

Figure 2: Roadmap for drug combination study.

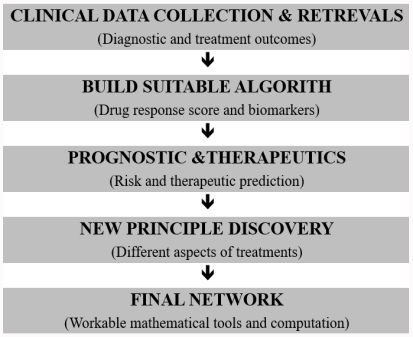

Figure 3: Mathematics in diagnostic and therapeutic study and progress.

ranges. These kinds of medical principles should be introduced to anticancer drug combination treatment in the clinic.

In addition, drug toxicity should also be considered in drug treatment study. If more than two anticancer drugs are very toxic in a recipe, their treatment dose-ranges should be carefully adjusted. The choice of dose-ranges is correlated with therapeutic benefits and outcomes. Certainly, extensive study should be focused in the future.

Personalized Medicine

Clinical significant

As cancer is different types of disease (>200 subtypes) and diversity properties of effective anticancer drugs, personalized medicine or precision oncology (individualized cancer therapies, PM or PO) are those technologies available for overcoming cancer therapeutic shortages [33,67-78]. This is one of the fastest growth disciples in the fields of clinical cancer applications. Though personalized strategies are currently waiting for breakthroughs [77], it strongly linked to anticancer drug combination applications in the clinic. Details are discussed below.

Strategy insights

Unlike HIV cocktails, cancer treatment is much more complicated than HIV/AIDS infection, which needs different types of disease diagnosis and drug selection. The best drug combination selections

Table 3: Association between clinical dataset and artificial intelligence.

Clinical application	Artificial intelligence techniques
Raw data output & process	Natural Language Processing (NLP) Convolutional Neural Network (CNN)
Data memory	Recurrent Neural Network (RNN)
Data translation	Artificial Neural Network (ANN)
Machine learning	Supervised/Unsupervised Learning (SL or UL)
Theory formation	Regression algorithms & Classification algorithms
Decision-making	Markov Decision Process (MDP) Reinforcement Learning Algorithms (RLA)

are those strategies for different mechanisms of action. The diversity of personalized oncology may affect anticancer drug combination selection and optimization against drug-induced resistance and relapses. As multi-disciplinary approaches, their clinical applications need modern medical and pharmacological knowledge and long-term investigations [10,11].

Different disciplines and platforms

Several types of personalized strategies for anticancer drug selection have been popularized in the clinic, such as the Drug Sensitivity Testing (DST), tumor biomarkers for the predictions of drug response, patient's genetic data (pharmacogenetics or precision oncology) for the predictions of drug doses and selection among a varies types of drugs [79-81] (Table 2).

The shortcomings of present drug combination regimes in the clinic are based on doctor's medical experience, recommended guidelines, past references and randomized selections. Different types of PO try to avoid such randomized medical decisions-doctor's experience alone. Different drug selection pathways are suitable for various personalized strategies.

In the future, transformation of drug combination selection systems from empirical to science-guided, well informed personalized cancer therapy is indispensable and will become clinical routines and patient's first choice. These biological techniques are suitable for different clinical occasion and drug combination optimization can improve the outcomes of drug treatment for advanced-stage of cancer patients.

Mathematics and personalized strategies relation

Different drugs in combination are not effective in equal bases (same efficacy). Like herbal medicine in China, different plants in prescription are divided as king, court, assist and soldier. Similar as battlefields, armies are coordinated and act in individual components. The different doses of each plant may treat different patients according to personal condition. This norm of Chinese medicine can be borrowed to modern cancer chemotherapy. This system of drug combination study should be progressed and theorized.

From this medical knowledge, we can determine which drug is most important to cancer treatment. We thence can increase the proportion and doses of this drug in combination comparisons and maximize therapeutic responses in the clinic. All these therapeutic modalities will be promoted in the future.

At present, drug dose selection of different drugs is no less complex than drug selection in the clinic. In this stage of clinical knowledge, it is difficult to achieve breakthroughs in several years. Mathematic support for clinical trials is an indispensable pathway for all disease treatments. Computational network or artificial intelligence is mostly utilized techniques or systems for analyzing

clinical data and decision-making in drug combination comparison and application [82-86]. Association between clinical dataset and artificial intelligence is represented in following (Table 3 and Figure 3).

Conclusion

Currently, the knowledge and difficulty for drug combination is beyond expectation. Our understanding towards anticancer drug combination is somewhat like a tip of huge iceberg. A great amount of work is ahead. In the future, we must pay more attentions on breakthroughs of drug combinational rule and principles that can systemize into a brand-new discipline. Only by these discoveries and systemizations, therapeutic efficacies for cancer treatments can be well improved and developed into a clinical paradigm.

Since no central dogma that can be repeatable in experiments and hospital routines for anticancer drug combination, this article can serve as a gateway between past and future (temporary roadmap). Let's focus on this matter quickly and strongly and kick off these researches as soon as possible. A great difference can be expected in cancer drug combination in five to ten years.

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