

Anticancer Drug Combinations, Studies from Different Pathways

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Abstract

Most cancer therapies are seldom effective by single anticancer drug based on multiple genetic alterations and molecular abnormalities. Anticancer drug combination utilities need to transform from empirical to science-guided enterprises. This editorial offers the background knowledge of drug combination therapies by mathematical enquiry. Possible future landscapes and drawbacks of current cancer drug combinative therapy are addressed and speculated.

Keywords: Drug combination; Mathematics; 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 [1,2]. 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 [3-10]. 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, 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.

Method

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.

Previously, combination utilizations of cytotoxic anticancer chemicals with biotherapy or other therapeutic means are good strategies for cancer treatments [8-11]. 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 [10];

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.

Mathematics of anticancer drug combinations

Since 178 anticancer drugs have been licensed worldwide [12], mathematically, huge numbers of drug combinations can be used.

According to mathematic equation (calculation for 3 drug combinations);

$$C = (178 \times 177 \times 176) / (1 \times 2 \times 3) = 924176$$

It means there are 924176 options in clinical situations. At present, we cannot compare these combinations in lab and in clinics. Yet we can imagine that these therapeutic efficacy data comparisons will be finished according to the rapid progresses of automatic or computerized experimental investigations within 10 years. These types of efforts should be encouraged.

Two strategies can be speculated to solve this problem.

1. Assessments of drug combinational possibilities with equal attentions. This strategy needs labor-intensity and long period of times for large-scale experimenting and complex data analysis/statistics.
2. Discover good anticancer drug combinations and relationship step by step. For example, we may identify and verify good drug combinational possibilities by one drug categories first. Then, gradually enlarge anticancer drug numbers and mechanisms of action on this field of anticancer drug combinational studies. Like anthrocycline, camptothecine and other series

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Received October 15, 2015; **Accepted** December 24, 2015; **Published** December 31, 2015

Citation: Lu DY, Chen EH, Lu TR, Ding J (2015) Anticancer Drug Combinations, Studies from Different Pathways. Cell Dev Biol 4: 166. doi:10.4172/2168-9296.1000166

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of anticancer drugs can be screened by one anticancer drug in each drug categories.

Since these researches are labor-intensive and money-driven, it is impossible to assess all different levels of anticancer drug developments (*in vivo* experiments or clinical investigations) at early stages. We suggest that these anticancer drug combinational studies must be focused on *in vitro* anti-proliferative studies for limiting on 1-3 tumor cell lines. Higher levels of anticancer drug combinational paradigms can be assessed based on *in vitro* study outcomes. If this is the case, we can achieve more and cost less.

Discussion

Technical concerns

To perfect anticancer drug combination study, many new ideas and techniques must be invented. For example, excellent automation techniques are the top priority. However, these techniques are mastered by only several leading pharmaceutical companies in developed countries. These technical advancements of developed countries will support their leadership position in world arena. This is unfair to other developing countries even when they have good pharmaceutical talents. In order to avoid these unfair competitions, international treaties ought to be better signed among most countries. Growing joint-venture activities and projects might finally help to overcome cancer mortalities in future.

Mathematician and physical-majored talents

Owing to the huge numbers of drug sensitive testing data, mathematic or statistics for these large data analysis ought to be participated by mathematicians or physics-majored students or scholars [13]. These types of research personnel may play unique roles on this field.

Pharmaceutical considerations

Since huge possibilities of drug combination protocols can be assembled in clinics owing to large numbers of anticancer drugs being licensed worldwide [12], 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 combating tumor growth, invasions and metastasis. 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 [8-10] and pharmaceutical considerations, such as liposome-entrapped drugs or nano-drugs [14-17]. However, new technologies do not always mean good things. 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.

Future directions

In future, we must pay more attentions on the breakthrough of drug combinational rule discoveries and systemized and/or study each possibility of drug combinations. Only by these discoveries and systemizations, therapeutic efficacies for cancer treatments can be well developed. 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 bridge to embrace better therapeutic options.

Conclusion

Only after completions of all possible assessments of anticancer drug combinations, we can satisfy and enjoy the fruits and improvements of scientific developments and clinical therapeutic outcomes. This is a economic burden yet enormous benefit task. If we can implement it, many beneficial achievements may be expected. Let us kick off these studies.

Acknowledgement

This work was funded by Shanghai Science and Technology Foundation of High Educations 97A49.

Competing Interests

Authors have declared that no competing interests exist.

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