International Research Journal of Pharmacy and Pharmacology Vol. 11(2) pp. 1-3, April, 2023
Available online https://www.interesjournals.org/pharmacy-pharmacology.html

Review Article

A Review on the Effectiveness of Combination Therapy of Drugs

Maria Koziolek*

Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Greece

*Corresponding Author's E-mail: mariakozi@gmail.com

Received: 01-Apr-2023, Manuscript No. IRJPP-23-96317; **Editor assigned:** 03-Apr-2023, PreQC No. IRJPP-23-96317 (PQ); **Reviewed:** 17-Apr-2023, QC No. IRJPP 23-96317; **Revised:** 21-Apr-2023, Manuscript No IRJPP-23-96317 (R); **Published:** 29-Apr-2023, DOI: 10.14303/2251-0176.2023.71

Abstract

Multidrug resistance (MDR) has long been a major obstacle in the treatment of malignant tumors. Combination therapy provides a viable and promising strategy to overcome MDR. This article discusses the advantages of nano-based combination therapy and proposes a 3R delivery principle (right place, right time, and right dose) as a reference for development of cancer nanomedicine containing drug combinations. The article also reviews the strategies of nano-based codelivery, with emphasis on the techniques designed to overcome chemoresistance, enhance drug targeting delivery, and reduce immunosuppression.

Keywords: Drug resistance, Combination therapy, Codelivery

INTRODUCTION

Malignant tumors are severe life-threatening diseases causing more than two millions of deaths in China each year. The cancer treatment methods available today include chemotherapy, hormone therapy, radiotherapy, surgery, immunotherapy, and targeted therapy. Drug-based treatments, such as chemotherapy, are commonly used to kill tumor cells. However, certain types of cancer cells are insensitive to drugs and resistant to treatment, which eventually leads to tumor recurrence and metastasis **(Maron BJ et al., 2002)**. In fact, effective treatment is primarily hindered by the rapid development of drug resistance **(Ommen SR et al., 2020)**. For example, 90% of chemotherapy failures in patients with metastatic cancer are attributed to multidrug resistance (MDR).

Drug resistance is manifested in many forms, including insufficient drug accumulation in the tumor, prevention of drug entry into the cells, increase in drug efflux, and enhanced DNA repair. Based on the particular modes of resistance, two mechanisms are well recognized, namely intrinsic and acquired resistance **(Maron BJ et al., 2015)**. These mechanisms are influenced by the tumor cells, as well as the tumor microenvironment (TME), which may serve as a biological and physical barrier against intratumoral drug penetration and diffusion, thereby diminishing the anti-tumor efficacy. This shows that in order to improve the efficiency of tumor treatment, it is necessary to cultivate a profound understanding of MDR causes **(Desai MY et al., 2013)**. It is also essential to develop new technologies and treatment strategies that circumvent MDR. For example, one of the useful strategies is the clinical use of a combination of two or more anticancer drugs to treat many types of tumors **(Ommen SR et al., 2005) (Plumier JC et al., 1996)**.

The term "MDR" refers to the various mechanisms by which tumor cells resist various drugs. As a rule, MDR is related with chemotherapy disappointment and expanded malignant growth related mortality. The active interaction of tumor cells with the extracellular environment results in the formation of the complex TME, which may encourage MDR and tumor metastasis. Due to the TME's complexity and heterogeneity, tumor cells frequently exhibit a variety of drug resistance mechanisms. Depending on whether they are governed by the cancer cell's internal or external environment, these mechanisms are classified as either cellular or non-cellular **(Nelson DP et al., 2002)**. They may likewise be separated into pharmacokinetic and pharmacodynamics opposition pathways. As shown in Figure, decreased drug inflow, increased drug efflux (related to drug efflux transporters), enhanced DNA repair, altered

drug-specific targets, and altered apoptosis pathways are the most common mechanisms of drug resistance in tumor cells **(Suzuki K et al., 2000)**. For instance, the up-guideline of efflux carriers after chemotherapy can effectively eliminate their substrates from growth cells, prompting neglected intracellular medication fixations and unfortunate remedial adequacy.

Blend treatment have been displayed to improve therapy proficiency in malignant growth patients, contrasted with monotherapy. The therapeutic effect of a reasonable combination of multiple drugs can be significantly enhanced at the best synergistic ratio. Through synergistic and complementary molecular mechanisms, combination therapy reduces the therapeutic dose required for treatment, minimizes adverse reactions, and prevents the development of drug resistance. A deeper comprehension of tumor biology, molecular pathways, and the interactions between tumors and their microenvironments is required for the development of combination cancer therapies, such as combined chemo drugs, chemo and immunotherapies, chemo and targeted therapies, chemo and gene therapies, and targeted therapies and immunotherapies. The activity examples of joined medications might be either synergistic or successive. The first is the focus of this article.

Due to differences in drug properties like solubility, permeation, stability, half-life, distribution in tumors, and metabolism, traditional combinations of free drugs rarely work well together. Additionally, the translation of cellular screening results is subpar due to the difference between in vitro and in vivo bio-fates, which makes it difficult to predict the outcomes of drug combinations. As a result, developing drug combination therapy necessitates synchronized drug action to link in vitro and in vivo studies. Important as well is the rational design of combined drug administration that adheres to the well-established principles of combination chemotherapy **(Nidorf SM et al., 1993)**. These principles include the absence of cross-resistance, the absence of overlapping side effects, synergistic antitumor effects, and different pharmacological mechanisms of the combined drugs (such as targeting different cell cycles). Typically, in vitro drug combination screening tests are carried out by simultaneously introducing the drugs to the cultured cells to provide nearly identical drug exposure. Nanotechnology-based co-encapsulation is a useful tool for drug delivery that ensures the same spatial and temporal drug distribution in the target tumor cells. Because it generates higher concentrations of drugs in tumor cells, increases drug stability, and reduces side effects, this strategy is also an important means of overcoming tumor resistance.

The majority of cancer drugs work by stopping the growth and reproduction of tumor cells. Drugs should ideally be concentrated in tumor cells with little exposure to healthy tissues and cells. For a considerable amount of time, the enhanced permeability and retention (EPR) effect has been regarded as the primary mode of nanocarrier delivery for tumor-targeting purposes. Despite this, there has recently been a lot of debate about this mechanism, given that the results of the preclinical research that is currently available are not in line with one another **(Yanagisawa Miwa A 1992)**. For instance, large animals rarely exhibit significant EPR effect, whereas murine models, which are the most frequently used experimental animals in cancer research, typically do. Additionally, a cancer study on dogs with spontaneous tumors found that soft tissue sarcomas did not contain accumulated liposomes, whereas most carcinomas did. As a result, it is believed that the EPR effect is largely dependent on the histology of the tumor, and that vascular tumors with leaky blood vessels, such as carcinomas, are more likely to experience it than non-vascular tumors with slow growth, such as sarcomas.

CONCLUSION

Drug resistance is inevitable when treating tumors, despite the significant clinical advancements made in cancer treatment. As a result, developing strategies for overcoming MDR has become crucial. The treatment of drug-resistant cancer has so far shown great promise for nano-based drug combinations. Optimizing the 3R delivery parameters and evaluating the combined drugs' biological fates and molecular mechanisms are crucial to the development of such nanomedicines. To effectively combat drug resistance, enhance patient survival, and reduce adverse reactions, additional nanomedicine research is required. Safety, biocompatibility, availability, and toxicity should be addressed in subsequent nanomedicine research. Additionally, the molecular regulatory mechanism in tumors and TME should be the primary focus of research efforts. This information is necessary for the development of novel drug delivery systems that have the potential to be very effective in the treatment of cancer.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

ACKNOWLEDGMENT

None

REFERENCES

1. Maron B J, Desai MY, Nishimura RA (2022).Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol. 79: 390–414.
2. Ommen S R, Mital S, Burke MA (2020). Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. AHA/ACC.142: 558–631.
3. Maron BJ, Rowin EJ, Casey SA (2015). Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. J Am Coll Cardiol. 65: 1915–1928.

4. Desai MY, Bhonsale A (2013). Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. Circulation. 128: 209–216.

5. Ommen SR, Maron BJ (2005). Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll. Cardiol. 46: 470–476.

6. Plumier JC, Robertson HA, Currie RW(1996). Differential accumulation of mRNA for immediate early genes and heat shock genes in heart after ischaemic injury. J Mol Cell Cardiol. 28: 1251-1260.

7. Nelson DP, Wechsler SB (2002). Myocardial immediate early gene activation after cardiopulmonary bypass with cardiac ischemia-reperfusion. Ann Thorac Surg. 73: 156-162.

8. Suzuki K, Sawa Y, Kagisaki K (2000). Reduction in myocardial apoptosis associated with overexpression of heat shock protein 70. Basic Res Cardiol. 95: 397-403.

9. Nidorf SM, Siu SC (1993). Benefit of late coronary reperfusion on ventricular morphology and function after myocardial infarction. J Am Coll Cardiol. 21: 683-691.

10. Yanagisawa Miwa A (1992). Salvage of infarcted myocardiumby angiogenic action of basic fibroblast growth factor. Science. 257: 1401-1403.