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Drug Combinations in Cancer Treatments

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Abstract

Most cancers have multiple genetic alterations or abnormalities. It is seldom very useful by only using one anticancer drug. Human cancer is a refractory and resistant disease, and like HIV virus, it might need anticancer drug cocktail instead single drugs to dramatically control the progresses of the disease. Anticancer drug cocktail might be one of the good solutions for anticancer chemotherapy. How to combine use of anticancer drugs is a new problem and area of anticancer drug therapy. This editorial addresses this problem in depth.

Introduction

Most cancers have multiple genetic alterations or abnormalities. It is seldom very useful by only using one anticancer drug [1-2]. Human cancer is a refractory and resistant disease, and like HIV virus, it might need anticancer drug cocktail instead single drugs to dramatically control the progresses and metastasis of the disease [3-5]. Anticancer drug cocktail might be one of the good solutions for anticancer chemotherapy. How to combine use of anticancer drugs is a new problem and area of anticancer drug therapy.

Cytotoxic Drugs Combine with High Selective Biotherapy

Cancer is a high mortality disease and the therapeutics for cancer, especially for cancer metastasis is still imperfect. Many cancer patients die of cancer metastases—almost 90% cancer deaths are caused by tumor metastasis [6-9]. One of the reasons for unsatisfactory of cancer therapy is the toxicity of antineoplastic drugs to human bodies. Anticancer drugs can be divided into two categories—cytotoxic anticancer drugs and cytostatic anticancer drugs [10]. Since the cytotoxic antineoplastic drugs are very toxic and they will kill normal human cells at the same times of killing cancer cells. So the dosages of antineoplastic drugs in human therapy cannot be too high, or the patients cannot tolerate them. In the end, small proportions of cancer cells survive after cytotoxic anticancer drug chemotherapy. These tumor cells will regrow to large tumor and Multidrug Resistance (MDR) often occurs in these cancer cells. It is these cancer cells to kill patients. The best example nowadays and in future is to combine cytotoxic anticancer chemicals with cytostatic anticancer drugs, antimetastatic drugs or biotherapies.

The best strategy of anticancer therapy is to better utilize and update present therapeutic norm. One of these attempts is to combinatory use of cytotoxic chemicals and biotherapies. If cytotoxic anticancer chemical drugs can kill 70% to 95% of tumor cells, some highly specific biotherapies will kill the rest of tumor cells [4-5]. This is our ultimate goal. This strategy is a paradigm of future cancer chemotherapy. We all know anticancer drugs rarely kill all tumor cells. If several cancer cells remain, they will quickly regrow to large-volume of cancer. So patients' immuno-surveilence systems or the effects of high specific biotherapies [5] will decide the long-term effectiveness of patients. The developments of biotherapies currently insufficient will be the great task of future therapeutic studies. The best example and paradigm nowadays is to combine cytotoxic anticancer chemicals with monoclonal or polyclonal antibodies [11-18]. On the other hand, other biological means, such as vaccines can also combine with cytotoxic chemotherapy (Table 1).

The biotherapies for cancer are often relatively mild and high cost and are difficult to kill large tumor volume. Yet they are high specific and only kill small amount of tumor cells with completeness and no toxicity. The cytotoxic chemotherapy as we guess should always be given before the biotherapy. It is the cytotoxic chemical drugs to reduce tumor 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 is a perfect strategy and hopeful we can achieve better outcome according to this paradigm and principle.

This is a perfect strategy and anticancer drug combination. But some problems and challenge still remain.

First, currently biotherapy is not perfect. The cytotoxicity of most current biotherapy is weak. It is seldom to completely destroy all cancer cells if the tumor volume is more than 0.5 cm. They are still several steps to go. 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.

Second, we do not know which biological pathways go aberrant in specific tumors in clinics. We must first know the characteristics of tumor to treat by detecting tumor biomarkers or bioinformatics [21]. Then we can design the suitable biotherapy regimes.

The third reason is the high cost of biotherapy, especially antibody and micro RNA. So patients' financial status is an important factor to decide whether we can use biotherapy to not.

There is long way to go and we must make more effort in this matter.

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 antigen
iRNA	Tumor genes

Table 1: Different anticancer biotherapies.

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The more we pay our attentions on this matter, the more satisfactory results we can get in.

Combine use of Drugs both Antiproliferative Drugs (Primary Tumor) and Antimetastatic Drugs

A lot of cancers die of cancer metastasis—almost 90% cancer deaths are caused by tumor metastasis. In order to improve patients' survival, it needs to brainstorm and streamline new strategy to overcome this problem. Apart from manufacturing more effective and specific anticancer or antimetastatic drugs [6-9], combine use of drugs both antiproliferative drugs (primary tumor) and antimetastatic drugs is supposed to be another good strategy to patients' survival. How to use antimetastatic drugs have been discussed in references [8-9].

Tumor metastases involve a fixed course of pathophysiological processes. Human cancer metastasis encompasses several different substages (1) invade locally through surrounding Extracellular Matrix (ECM) and stromal cell layers; (2) intravasate into the lumina of blood vessels; (3) tumor cells survive the rigors of transport through the vasculature; (4) arrest at distant organ sites; (5) tumor cells extravagate into the parenchyma of distant tissues; (6) initially survive in these foreign microenvironments in order to form micro metastases, and (7) reinitiate their proliferative programs at distant sites, thereby generating macroscopic, clinically detectable neoplastic growths [6-9]. From this pathologic point of view, since a metastasis must travel more than one body-organ, the obvious different anatomic organs may possibly trigger different molecules and pathways linking neoplasm metastases. This reasonably results in being affected or inhibited with different types of drugs in different stages of metastatic processes. In return, different anticancer drugs will certainly not act in the same way in all metastatic organs.

In future, drug combination will consider these pathological information and use drugs wisely [4,22].

Combine Cytotoxic Drugs with Cytostatic Drugs

Combine use of cytostatic and cytotoxicity anticancer drugs based on detection of cancer biomarkers [6-9,21]. Anticancer drugs are divided into two categories; cytotoxic drugs or cytostatic drugs. Cytotoxic drugs indiscriminately kill cancer or normal tissue. Cytotoxic anticancer drugs are effective to almost all types of cancer cells. But this kind of anticancer drugs is often toxic to normal tissue and easily exhibit of Multidrug Resistance (MDR). So cytotoxic anticancer drugs cannot be used very high doses or very long term to kill all cancer cells.

Targeted cytostatic anticancer drugs aim to target to specific mutated genes, molecules or receptors. Though overall antiprolifetrative effects of cytostatic anticancer drugs are relatively lower than cytotoxic anticancer drugs, they are much less toxicity to normal tissue and their responses to tumor are relatively long.

Combine use of cytostatic anticancer drugs from knowing the abnormality of tumor markers in individual patients. Each important abnormal of cancer markers will be targeted by relevant cytostatic drugs [4,21,22]. By using the combination of cytotoxic anticancer drugs with cytostatic anticancer drugs, the drug response to tumors can be very high or even eradicating of tumors. This type of drug combinations might be chosen based on detecting tumor markers.

Rules of drug Combination

With respect with HIV cocktail, the best drug combination is to combine drugs of different mechanisms. The more diversified the drug types have, the more integrated benefits the therapy might gain and achieve. However, if we can know the drug sensitivity testing of cytotoxic anticancer drugs and drug response of cytostatic anticancer drugs on a specific tumor species by detecting cancer biomarkers, may we have better therapeutic outcome?

Conclusion

Generally speaking, drug combination has better therapeutic outcomes than single anticancer drug. But concomitantly, it often costs much more than single drug. Cost-effective consideration for drug combinations [23] is one part work of a clinician and basic cancer chemotherapy studies, especially when some high priced drugs are intended to be used.

Mounting experimental data and clinical evidence suggest it might be a good way to use drug combination in controlling tumor growth and metastasis. However, the toxicities of drug combination to human are also increased with the increase of drug numbers. Drug sensitivity tests, cancer biomarker detecting and pharmacokinetics are designed to select effective drugs and to discard ineffective drugs. They can make a good balance between drug activity and toxicity.

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