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DRUG RESISTANCE IN CANCER CHEMOTHERAPY- AN OVERVIEW

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ABSTRACT

Drug resistance is one of the primary obstacles in cancer chemotherapy. The causes of drug resistances are varied. The primary resistance attributed to genomic instability while alteration in membrane permeability of drug and inability to reach the target sites, drug inactivation by enzymes, mutation and altered expression of target proteins there by affecting drug target interactions are some of the mechanism of acquired drug resistance. In addition to genetic changes there are epigenetic changes or non mutational mechanisms which occur quickly in response to environmental changes. Normal tissues never develop resistance to chemotherapy, because they possess intact genetic machinery. Drug resistance in addition to reducing clinical effectiveness, result in early termination of treatment, reduced relapse free interval and survival. There are various methods for overcoming these major disadvantages of cancer chemotherapy. Combination chemotherapy with clear understanding of the biochemical, molecular and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination is one method. Optimal cancer drug scheduling is also a strategy for controlling resistance to therapy. Control avenues of drug administration and dose intensification provide better outcome. Despite various measures to overcome drug resistance, the problem especially multidrug resistance is still casting its shadow in successful chemotherapy. A better understanding of mechanism of drug resistance, its genetic and epigenetic links will open up new avenues in circumventing this fundamental problem and prolong the life expectancy of the patient. This article gives an overview of drug resistance encountered in cancer chemotherapy.

Keywords: Cancer, Chemotherapy, Cell cycle, Drug resistance

INTRODUCTION

The term chemotherapy coined by Paul Ehrlich ('magic bullet') referred to the use of chemical compounds in the treatment of diseases, without injuring the host cells¹. Nowadays this term broadly refers to anti-neoplastic drugs in the management of neoplastic diseases. Advances in chemotherapy have provided important proof of the principle that anti cancer drugs can cure cancer, and subsequently have been integrated into treatment programmes with surgery and radiation therapy².

Chemotherapy currently has various roles like in induction treatment for advanced diseases, as an adjunct to local forms of treatment, and as neoadjuvant therapy for localised disease³. The term induction therapy implies the use of chemotherapy as the primary treatment for patients who present with advanced cancer for which no alternate treatment exists. Adjuvant chemotherapy denotes the use of systemic treatment after the primary treatment has been controlled by an alternative modality such as radiotherapy and surgery. Neo adjuvant chemotherapy refers to the use of chemotherapy

as the initial treatment for patients who present with localised cancer⁴. Chemotherapy targets proliferating cells but exerts little selectivity on the proliferating normal tissues⁵. The primary obstacles to the clinical efficacy of chemotherapy have been the toxicity to the normal tissues of the body and the development of cellular resistance to these chemotherapeutic agents. Drug resistances occur in most tumours treated with chemotherapy. Normal tissues never develop resistance to chemotherapy, because they possess intact genetic machinery⁶. Sensitive cancer cells later develop resistance because of drug-induced mutations in their DNA⁷. In the last decade, molecular techniques for analysis of the DNA of normal and neoplastic cells identified some of the critical mechanisms through which chemotherapy induces cell death⁸. A new level of understanding of the molecular pathways through which chemotherapy works has opened up avenues for novel therapeutic approaches. Such strategies not only enhance the chemo sensitivity of malignant cells to treatment, but also reduce toxicities and prevent the emergence of drug resistance.

MECHANISM OF DRUG RESISTANCE

One of the frequent problems encountered in cancer chemotherapy is drug resistance. Only tumour cells that are sensitive to the action of drugs are killed⁹. There are several types of drug resistances which are broadly divided into primary or inherent and acquired. Various mechanisms are attributed to drug resistance. Alteration in membranes permeability causing inability to enter the target cells, increased drug efflux, inactivation by enzymes affect the concentration of drug within the cancer cells¹⁰. Drug target interaction is prevented by mutation or altered expression of the target protein. Defects in apoptosis, senescence, repair mechanisms affect signalling pathways of drug target receptors¹¹. Alterations in complex

pathways associated with growth factors, ion and nutrient transports and utilization, hormone responsiveness, oncogene and protein kinase signalling pathways, chromosome structure and gene expressions are involved in drug resistance^{12, 13}. The efflux mechanisms especially by efflux pumps like P-glycoprotein and the multidrug-resistance protein which belongs to Adenosine Triphosphate – Binding Cassette family are particularly important in multidrug resistance¹³. There are various studies confirming the importance of genetic changes for acquired resistance during cancer chemotherapy¹³. Mutational changes can be single step or multistep. In addition to genetic changes there are epigenetic changes or non mutational mechanisms which occur quickly in response to environmental changes¹⁴.

Tumour growth rate along with phase and cell cycle specificity are other major factors that determine the sensitivity of cancer cells to chemotherapy¹⁵. The growth of a neoplasm depends on several interrelated factors like normal cell cycle time, growth fraction, total number of cells in the population and the intrinsic cell death rate¹⁶. Cells progress through a cell cycle comprising four phases: G_1 , S , and G_2 , M . At the end of the G_2M phase, cells divide and new cells begin their cycle in G_1 . Cells remain in the quiescent phase G_0 (quiescence) in the absence of external changes, otherwise they may return to the proliferative cycle (at the first step of S phase)¹⁷. There are certain check points in between cell cycle phase transition, the most important of which occur at the $G_1=S$ and $G_2=M$ transitions¹⁷. There are exchanges of cells between phases G_0 and G_1 all the time till restriction point occur at G_1 . Then the proliferation of cells continues until actual division. This can be prematurely interrupted by anticancer drugs¹⁷. Many anticancer drugs cause direct damage to DNA, which triggers cellular checkpoints¹⁸. The resistant cells survive and multiply and result in re growth of cancer

cells not sensitive to the administered drug^{19, 20}. Figure 1 depicts the cell cycle^{16, 19}.

The cytotoxic effects of cancer drugs follow log cell kill kinetics. According to the log-cell-kill hypothesis constant fraction of tumour cells are eliminated²¹. i.e Cell kill is proportional regardless of tumour burden. The viability and character of remaining tumour cells can be analysed by histological examination of residual tumour cells²². The experimental data in human solid cancers follows Gompertzian kinetics i.e, the growth fraction of tumour is not constant but decreases exponentially with time²². The location of tumour is in its particular growth curve determines the response to chemotherapy in drug sensitive tumour²³. Figure 2 depicts log cell kill hypothesis^{16, 21, 22}.

DISCUSSION

a. Clinical significance of drug resistance

The efficacy of a treatment regime is determined by the complete response rate²¹ and the relapse-free survival from the time treatment is discontinued. The relapse-free survival is the major end point in adjuvant programmes. If a patient is having good response to chemotherapy, further treatment need to be continued while a poor response points out the need to consider an alternative method of treatment²⁴. Drug resistance in addition to reducing clinical effectiveness, result in early termination of treatment and reduced relapse free interval and survival.

b. Measures for overcoming drug resistance

There are various methods for overcoming these major disadvantages of cancer chemotherapy. Combination chemotherapy using conventional cytotoxic agents attain several important objectives not achieved with single agents²⁵. It provides maximal cell killing with tolerable side effects and in addition can slow or prevent the development of resistance²⁶. Principle of selection of drugs in an effective drug combination follows the following principle;

like only drugs known to be partially effective against a given tumour when used alone should be selected; drug selection should be based on the spectrum of toxicities without any overlap in toxicities²¹. There should be a clear understanding of the biochemical, molecular and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination to allow for maximal effect^{16, 27}.

Drug discovery efforts are now directed toward restoring apoptosis in tumour cells, as this process or their absences have profound influence on tumour cell sensitivity to drugs²⁸. In high grade tumours although more aggressive, drugs are generally more effective in combination and may be synergistic through biochemical interactions²⁹. New regimens are designed based on useful interactions³⁰. When the drugs share common mechanism of resistance or have overlapping toxicities combinations are considered irrational³¹. Tumour cells in population in patients with visible disease exceed 1gm or 10⁹ cells and each cycle of therapy kills less than 99% of cells. So treatments are repeated with multiple cycles to effectively kill the entire tumour cells³². Optimal cancer drug scheduling is a way of controlling resistance to therapy. Control avenues of drug administration and dose intensification provide better outcome¹⁶.

CONCLUSION

Despite various strategies to overcome drug resistance, the problem especially multidrug resistance is still casting its shadow in successful treatment of cancer therapy. A better understanding of mechanism of drug resistance, its genetic and epigenetic links will open up new vistas in circumventing this problem and prolong the life expectancy of the patient.

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Cell Cycle & Percentage of time spent in each phase by a typical malignant cell

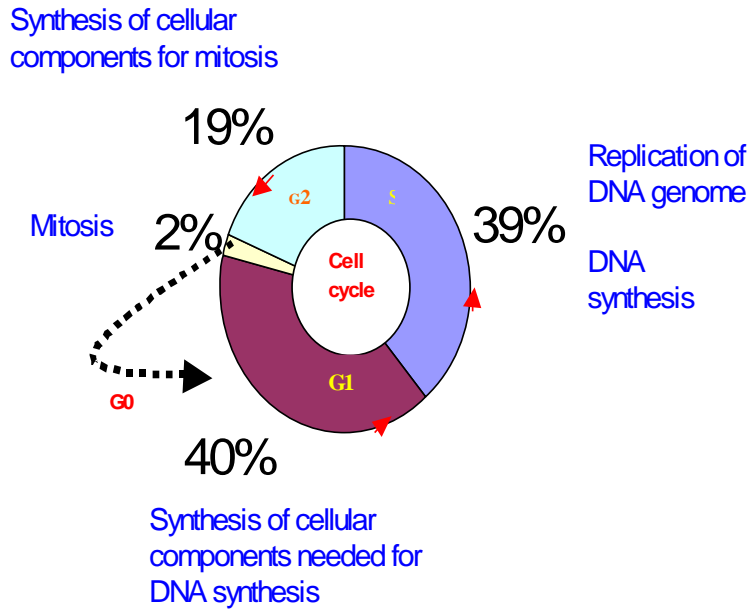


Figure1: Cell cycle

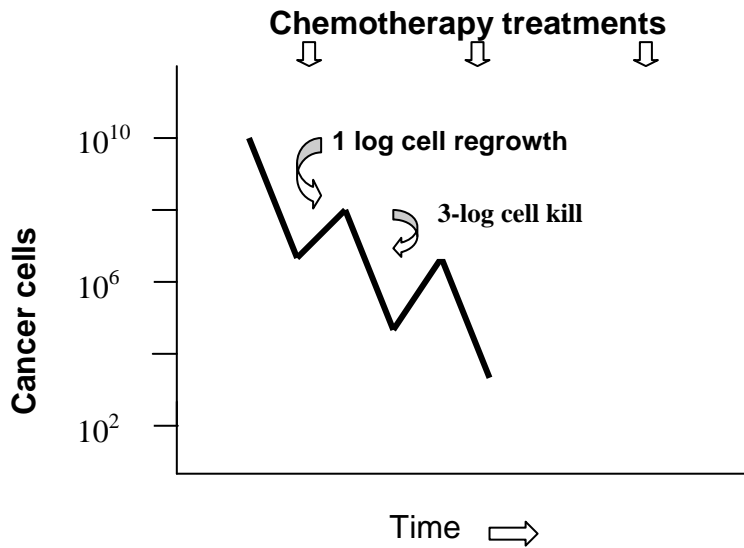


Figure 2: Log cell kill