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STRATEGIES TO OVERCOME CHEMOTHERAPEUTIC DRUG RESISTANCE – A MINI REVIEW

R. Vimalavathini*, Sindhuja A., Sreemathy K. and Jagadesan R.

Department of Pharmacology, College of Pharmacy, MTPG and RIHS, Puducherry.

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***Corresponding Author**
Dr. R. Vimalavathini
Department of Pharmacology, College of Pharmacy, MTPG and RIHS, Puducherry.

ABSTRACT

Chemotherapeutic drug resistance is a grave problem in cancer therapy. Novel ways of therapeutic targeting must be devised to understand and overcome drug resistance through the clinical assessment of rational therapeutic drug combinations and the use of biomarkers. Attempts to overcome resistance involves the use of combination drug therapy, p-glycoprotein modulators, epigenetic drugs, gene knockout using antisense oligonucleotides or ribozymes, interference and metronomic chemotherapy.

KEYWORDS: Cancer, Resistance, Chemotherapy.

INTRODUCTION

The advent of in silico models, cell based therapies, high throughput screening has marked a new era of cancer therapeutics by tailoring therapy to precision. Also stringent treatment strategies such as combination chemotherapy, repeated multiple cycles chemotherapy, ideal drug scheduling and dose intensification are employed to overcome chemotherapeutic resistance they still pose a threat to chemotherapy. The mechanism of drug resistance differs for various cancer types due to its location, genetics type of drug used. Drug resistance in addition to reducing clinical effectiveness, result in early termination of treatment and refractory cancer.[1] This review focuses on the various current strategies employed to overcome chemotherapeutic resistance.

Genetics: Anticancer drug efficiency depends on the genetic makeup of the individual For instance prostate tumour cell lines with high level of proto-oncogenes exhibited significant resistance to adriamycin. Studies of methotrexate resistance revealed the phenomenon of gene amplification of dihydrofolate reductase genes.[2]

Histone deacetylase inhibitors HDACi are epigenetic drugs that can be used to sensitize drug-resistant cancer cells. One study has shown that HDACi treatment demethylates and re-expresses tumor suppressor genes, leading to the sensitization of cancer cells to other cytotoxic drugs. Additionally, HDACi in combination with calpeptin has been shown to enhance anti-cancer activity on breast and ovarian cancer cells.[3]

Cancer stem cells

Cancer stem cells (CSC) account for cancer initiation, progression, remission, metastasis and chemoresistance. They affect 3 key pathways, namely Wnt, notch and hedgehog pathways. Vitamin D3 and cucurmin has been shown to inactivate Wnt pathway and has been effective in certain carcinoma. Mk0752, RO4929097 target secretase of notch signalling pathway. IPI-926 targeting hedgehog pathway is undergoing clinical trials for CSC molecular targets. Increased aldehyde dehydrogenase activity is characteristics of CSC and aldehyde dehydrogenase inhibitors namely disulfiram has shown to exhibit anti-cancer stem cell potential by inhibiting aldehyde dehydrogenase, proteasome, DNA demethylation.[4,5]

Drug efflux

Over expression of mdr1 gene encoding P glycoprotein, an efflux transporter leads to multi drug resistance (MDR) by decreasing intracellular drug concentration of drugs such as taxanes, vinca alkaloid, anthracyclines, dactinomycin and mitomycin.[6] Thus MDR modulations may prevent clinical drug resistance. However, clinical data show that most first, second and third generation MDR inhibitors are not providing major improvements. There is current interest in exploring the use of natural components such as flavonoids as fourth generation P glycoprotein modulators. Other clinical approaches to overcome MDR in cancer cells include the use of chemotherapeutics that are not substrates of p-glycoprotein such as cyclophosphamide, 5-fluorouracil. Another mode of MDR reversal is by using monoclonal antibodies targeting both MDR protein and cancer epitopes.[7]

Drug target

Resistance to drugs that target microtubule system could be due to slowing cell cycle kinetics thus making them less susceptible to cell cycle specific anti-mitotic drugs. To overcome this resistance epothilones with anti-angiogenic properties are currently being developed and evaluated in clinical trials. Many potential telomerase inhibitors such as oligonucleotides, hammerhead ribozymes, reverse transcriptase inhibitors targeting malignancy and resistance are still under research and clinical trials.[8,9]

Apoptosis

Chemotherapeutic agents kill cancer cells by inducing apoptosis. Inhibitors of apoptosis (IAP) can suppress apoptosis leading to drug resistance. Antagonist to IAP such as antisense oligonucleotides, and small molecule IAP are in clinical trials. Interestingly, the naturally occurring dietary compound resveratrol was also found to sensitize a number of established and primary cancer cell lines to the action of cytotoxic agents including DOX, cisplatin, cytosine arabinoside, and etoposide by down regulating surviving (an IAP) through transcriptional and posttranscriptional mechanisms.[10,11]

Anti-malarial drugs such as chloroquine and hydroxychloroquine play a role in inhibiting autophagy-dependent resistance to chemotherapy. For instance, fluorouracil in combination with chloroquine is more effective in treating cancer cells than fluorouracil alone. Also hydroxychloroquine has been shown to inhibit autophagy in cancer cells and restore sensitivity with tamoxifen in breast cancer.[12]

Drug inactivation

Drug inactivation or lack of drug activation is other important reason for drug resistance. For instance the conversion of drugs such as 5-fluorouracil and methotrexate to their active forms does not occur when the relevant cellular enzyme activities are absent. Capecitabine is converted into 5-FU by thymidine phosphorylase. Epigenetic silencing of the gene encoding thymidine phosphorylase leads to capecitabine resistance. Studies show that this epigenetic silencing can be reversed by DNA methyltransferases inhibitors.[13] Studies indicate that presence of high level of glutathione leads to resistance and the clinical use of buthione sulfoximide, decreases intracellular level of glutathione and overcome resistance to alkylating agents.[2]

Metabolism

Cancer cells exhibit abnormal metabolic properties leading to resistance. Targeting these pathways open new avenues for cancer therapy and overcoming resistance.[14] Since cancer cells rely on glucose transporters for glucose uptake under hypoxia for their survival and drug resistance, inhibition of glucose transporters may preferentially sensitizes cancer cells to chemotherapeutic agents under hypoxia.[15] Studies show that phloretin, a GLUT 1 inhibitor enhances daunorubicin effects by increasing daunorubicin induced apoptosis only under hypoxia in colon cancer and leukaemia. Ritonavir, a GLUT 4 inhibitor, enhances doxorubicin sensitivity by decreasing glucose consumption and proliferation by inducing apoptosis in

multiple myeloma. 2-deoxy glucose, a hexokinase inhibitor increases efficacy and overcomes trastuzumab resistance in ErbB2 positive breast cancer cells by glycolytic inhibition. Oxamates a lactate dehydrogenase inhibitor promoted paclitaxel induced cellular apoptosis in breast cancer. Rapamycin (mTORC1 inhibitor) reverted chemoresistance of cisplatin by reducing mTORC activity in leukemia.[14]

A new therapeutic strategy namely metronomic chemotherapy which consist of administrating anti-neoplastic agents continuously at low doses are expected to limit the appearance of drug resistance, by targeting vascular endothelial cells instead of tumor cells which are genetically unstable leading to resistance.[16] More recent innovations targeting chemotherapeutic resistance such as antisense oligonucleotides or ribozymes, interference are gaining momentum.[7]

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