A REVIEW ON CANCER MULTI DRUG RESISTANCE AND ITS THERAPY

Hemangi Rawal* and Vidhi Doshi

Student, Department of Pharmacy, NSHM Knowledge Campus – Kolkata Group of Institutions, Kolkata, West Bengal, India.

ABSTRACT

Chemotherapeutics are the most effective means for the treatment for metastatic tumours. However, the ability of cancer cells to become simultaneously resistant to different drugs a trait known as multidrug resistance remains a significant impediment to successful chemotherapy. There are various mechanisms through which cancer cells develop resistance to anticancer drugs which may vary depending on the type of drugs used, type of cells involved and even depending on an individual patient. But some patients are cured by these drugs and others respond transiently or incompletely, this may be due to host and tumour genetic alterations, epigenetic changes and tumour environment all of which may contribute to the complexity of cancer multidrug resistance. Conventional cancer chemotherapy is seriously limited by tumor cells exhibiting Multidrug Resistance (MDR), caused by changes in the level or activity of membrane transporters that mediate energy-dependent drug efflux and of other proteins that affect drug metabolism and/or drug action. Identification of several mechanisms of acquired multidrug resistance has led to the development of chemosensitizing agents that counter specific mechanisms of multidrug resistance. Therefore to overcome this disappointing therapeutic failure, there are various approaches evolving to reverse or circumvent cancer multidrug resistance. These include p-glycoprotein inhibitors and other drugs that target cancer multidrug resistance. This article highlights the various mechanisms of multidrug resistance and the ways with which we can combat it.
KEYWORDS: Chemotherapeutics, multidrug resistance, genetic alterations, p-glycoprotein inhibitors.

INTRODUCTION
Cancer cells survive and multiply due to the decreased intracellular concentration of anti-cancer drugs. The solution to this problem is to block the activity of proteins (ABC transporters) that are responsible for the drug extrusion. The inhibition of transporter protein can preserve the activity of anticancer chemotherapeutic drugs given simultaneously.\(^1\) There are different proteins that are involved in cancer multi drug resistance. These includes p-glycoproteins, multi drug resistance associated proteins and lung resistance proteins.\(^2\) However, there are currently different agents suggested to be used managing cancer multidrug resistance, including p-glycoprotein inhibitors, lipid bilayer modulators, Nitric Oxide, Mifepristone, Trabectedin, Agosterol A,\(^3\) and others discussed in this article.

MECHANISM OF CANCER MULTIDRUG RESISTANCE

![Diagram](image)

Fig. 1- Various mechanisms through which cancer cells develop resistance to anti-cancer drugs
### TABLE 1: Various mechanisms through which resistance occurs to various antineoplastic drugs[^2]

<table>
<thead>
<tr>
<th>Drugs Developing Resistance</th>
<th>Various Causes Of Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Mechanism Of Resistance</td>
<td>Repeated exposure to single antineoplastic agents will generally result in cross-resistance to some related agents of the same drug class due to shared drug transport carriers, drug metabolizing pathways, and intracellular cytotoxic targets of these structurally and biochemically similar compounds. Emergence of cross resistance to multiple, apparently structurally and functionally unrelated drugs, to which the patient or cancer cells were never exposed during the initial drug treatment. Despite apparent differences in the families of drugs associated with multi-drug resistance (MDR) phenotypes, mechanisms underlying these phenotypes involved antineoplastic agents share common metabolic pathways, efflux transport systems, or sites of cytotoxic action. Thus, the targets of MDR mechanisms are similar to the targets of single agent resistance mechanisms.</td>
</tr>
<tr>
<td>Resistance To Microtubule inhibitors</td>
<td>Nonspecific mechanisms of drug resistance—overexpression of drug efflux pumps (e.g., P glycoprotein, multidrug resistance protein). Specific mechanisms to antimicrotubule agents include alterations in tubulin through mutation, differential expression of tubulin isotypes, post-translational tubulin modifications and altered expression of microtubule regulator proteins.</td>
</tr>
<tr>
<td>Resistance To Alkylating Agents</td>
<td>Resistance to alkylating agents occurs through three broad mechanistic categories including— Decreased drug accumulation, Increased drug inactivation, and Enhanced repair of DNA damage</td>
</tr>
<tr>
<td>Resistance To Antibiotics</td>
<td>Resistance to anti-topoisomerase drugs like dactinomycin can result from decreased levels of the enzyme in tumor cells. This phenomenon is termed atypical multidrug resistance [at- MDR] since it differs from classical MDR which involves enhanced cellular efflux of drug.</td>
</tr>
<tr>
<td>Resistance To Antimetabolite</td>
<td><strong>Antifolates</strong> - MTX  Reduced MTX uptake via a defective folate transport system, Increased export Reduced polyglutamation leading to decreased drug retention as well as reduced inhibition of thymidylate synthase and Either elevated levels of DHFR or reduced affinity of DHFR for MTX.  <strong>Thiopurine Antimetabolites</strong>.  Deficiency or complete lack of the activating enzyme, HGPRT. Decreased drug transport; Alteration in allosteric inhibition of ribosylamine 5-phosphate synthase; Increased activity of multidrug resistance protein, which exports nucleoside analogs.</td>
</tr>
</tbody>
</table>
Fig. 2: The efflux of the antineoplastic drugs through pgp transporters and the role of its inhibitors in treating the resistance caused due efflux of the drug

NOVEL APPROACHES TO CANCER MULTIDRUG RESISTANCE THERAPY

Overexpression of ATP-binding cassette (ABC) transport proteins, including P-glycoprotein (Pgp), multidrug resistance protein (MRP-1) and breast cancer resistance protein (BCRP), is a well characterized mechanism of multidrug resistance (MDR). The emerging complexity of the MDR phenotype has engendered several alternative approaches to MDR therapy, designed either to inhibit MDR in novel ways or to cleverly circumvent MDR mechanisms altogether.[2]

TABLE 2: The various drugs and their mechanism to treat multidrug resistance[2]

<table>
<thead>
<tr>
<th>Name Of The Drug</th>
<th>Mechanism Of Action To Treat Multidrug Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Cytotoxic Taxanes</td>
<td>The cytotoxic taxanes paclitaxel and docetaxel are substrates for P gp mediated efflux, whereas the semi-synthetic taxane analog, ortataxel, by inhibiting Pgp-mediated transport, is not. Ortataxel also modulates drug efflux mediated by MRP-1 and BCRP. Because the cytotoxic properties of ortataxel are less favorable for development as an MDR modulator.</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>Doxorubicin is a substrate of P gp; it has been suggested that its ability to induce synthesis of nitric oxide (NO) could explain, at least in part, its cytotoxic effects.</td>
</tr>
</tbody>
</table>
A doxorubicin-resistant (HT29-dx) cell population: these cells accumulated less intracellular doxorubicin, were less sensitive to the cytotoxic effects of doxorubicin over expressed Pgp and MRP3, and exhibited a lower NO production. The resistance to doxorubicin could be reversed when HT29-dx cells were incubated with inducers of NO synthesis (cytokines mix, atorvastatin). An experiment conducted on this suggested that onset of MDR and impairment of NO synthesis are related.

Mifepristone

Mifepristone is a potent antiprogestin agent (the termination of early pregnancy). It exerts markedly anticancer effects and reversal effects on MDR in some cancer cells with no serious side-effects. Mifepristone exerts potent reversal effect on MDR via inhibiting MRP- and P-gp mediated drug transporter which can be used on MDR in human gastric cancer cells.

Trabectedin

Trabectedin is a tetrahydroisoquinoline alkaloid that binds to the minor groove of DNA inhibiting transcription activation of key genes, nucleotide excision repair pathways and cell proliferation leading to apoptosis of cancer cells. It also inhibits over expression of the multi-drug resistance-1 gene coding for the Pglycoprotein that is a major factor responsible for cells developing resistance to cancer drugs. Trabectedin is approved for the treatment of advanced soft tissue sarcoma.

Agosterol A

inhibits the efflux of anticancer agents by interaction with Pglycoprotein and multiple drug-resistant associated protein (MRP1), thus reversing multidrug resistance.

Antisense Oligo-nucleotide

Downregulation of MDR transporters has been suggested as a more specific way to overcome MDR than the use of inhibitors as they suppress P-gp expression using antisense oligonucleotides with improved stability and cellular permeability.

CIRCUMVENTING CANCER MDR MECHANISMS

MDR mechanisms reflect the innate adaptive potential of living cells and may thus prove to be intractable. Therefore, researchers have looked for various ways to circumvent rather than directly inhibit MDR mechanisms. [2]

- One approach has focused on developing anticancer drugs that are poor substrates for MDR transporters. Examples include anthracyclines such as idarubicin and annamycin.
- Tumors require an adequate blood supply in order to grow and are capable of inducing the formation of new blood vessels that provide them with oxygen and nutrients, a phenomenon called angiogenesis.
  - The angiogenic response requires proliferation of vascular endothelial cells which depends on angiogenic factors, and it can be inhibited by anti-angiogenic factors.
  - As anti-angiogenic factors do not target the tumor cells themselves but rather the endothelial cells, anti-angiogenic therapy should, in principle, be equally effective toward non-MDR and MDR tumors.
The effectiveness of thalidomide an antiangiogenic drug, in treating patients with refractory multiple myeloma.[4]

CONCLUSION
Multidrug resistance, the principal mechanism by which many cancers develop resistance to chemotherapy drugs, is a major factor in the failure of many forms of chemotherapy. Resistance to therapy has been correlated to the presence of at least two molecular "pumps"-P-glycoprotein and multidrug resistance–associated protein (MRP) in tumor-cell membranes that actively expel chemotherapy drugs from the interior. This allows tumor cells to avoid the toxic effects of the drug or molecular processes within the nucleus or the cytoplasm.

In the fight against cancer, a number of targets are being pursued with equal zeal. The resistance-mediating transporters discussed here represent a significant set of clinically relevant drug targets that have therapeutic as well as diagnostic potential. Cancer defends itself actively by using these mechanisms, and therefore their impairment is likely to have a significant therapeutic benefit. The science in this area is progressing very rapidly, and corporate involvement is likely to follow suit.[5]

REFERENCES