MODULATION OF P-GLYCOPROTEIN MEDIATED MULTIDRUG RESISTANCE (MDR) IN CANCER USING CHEMOSENSITIZERS

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ABSTRACT:

Multidrug resistance (MDR) is one of the main obstacles in the chemotherapy of cancer. MDR is associated with the over expression of P-glycoprotein (P-gp), resulting in increased efflux of chemotherapy from cancer cells. Inhibiting P-gp as a method to reverse MDR in cancer patients has been studied extensively, but the results have generally been disappointing.

First-generation agents were limited by unacceptable toxicity, whereas second-generation agents had better tolerability but were confounded by unpredictable pharmacokinetic interactions and interactions with other transporter proteins. Third-generation inhibitors have high potency and specificity for P-gp. Furthermore, pharmacokinetic studies to date have shown no appreciable impact on drug metabolism and no clinically significant drug interactions with common chemotherapy agents.

Third-generation P-gp inhibitors have shown promise in clinical trials. The continued development of these agents may establish the true therapeutic potential of P-gp-mediated MDR reversal.

KEYWORDS: Multidrug resistance, P-glycoprotein, P-gp modulators,P-gp inhibitors

INTRODUCTION:

Every year, more than 6 million cancer deaths were reported in the world. Of the 10 million new cases each year, more than half occur in developing countries. WHO predictions show that, out of 15 million cases, 66% will occur in developing countries, by 2015.

Drug resistance is the major cause of death in cancer. 30 to 80% of cancers can become resistant to cytotoxic drugs, leaving patients and doctors with few options when treatment fails.

Multidrug resistance is a phenomenon whereby tumor cells exposed to one cytotoxic agent develop cross-resistance to a range of structurally and functionally unrelated compounds. The drug resistance that develops in cancer cells often results from elevated expression of particular proteins, such as cell-membrane transporters, which can result in an increased efflux of the cytotoxic drugs from the cancer cells, thus lowering their intracellular concentrations[1, 2].

Resistance to the drugs may be primary where the tumor does not respond to drugs from the start or secondary in which case the tumor initially responds but slowly acquires resistance[3].

The cytotoxic drugs that are most frequently associated with MDR are hydrophobic, amphipathic natural products, such as the taxanes (paclitaxel and docetaxel), vinca alkaloids (vinorelbine,vincristine, and vinblastine), anthracyclines (doxorubicin, daunorubicin, and epirubicin), epipodophyllotoxins (etoposide and teniposide), antimetabolites (methorexate, fluorouracil, cytosar, 5-azacytosine, 6-mercaptopurine, and gemcitabine) topotecan, dactinomycin, and mitomycin C[4,5,6].

Development of resistance to a wide spectrum of drugs occurred through a variety of mechanisms. Number of mechanisms have been proposed to explain the development of multidrug resistance (MDR). These include modulation of genes, alteration in DNA repair capacity, altered target enzyme levels, detoxification involving glutathion conjugation and MDR through efflux pumps such as P-glycoprotein (p-gp) protein[7, 8].

Although several mechanisms are proposed for drug resistance, the best-studied mechanism of MDR is related to the over expression of P-Glycoprotein (P-gp), a 170 KDa ATP dependent membrane transporter that acts as a drug efflux pump (Fig.1) [1, 9].

In addition to cytotoxic drugs, P-gp also transports several other exogenous compounds, including digoxin, opiates, polycyclic aromatic hydrocarbons, technetium (99mTc) sestamibi, and rhodamine 123.
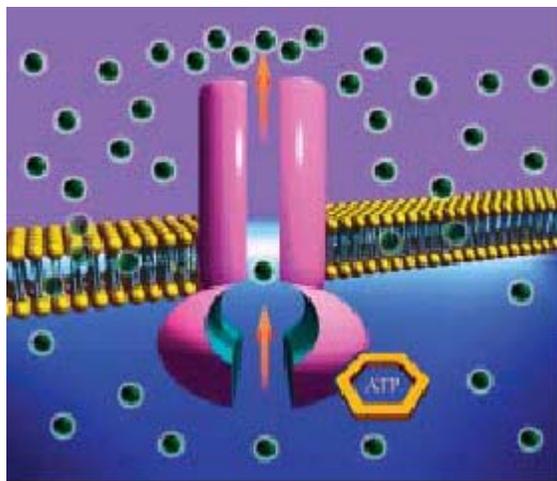

Fig.1. Normal P-gp function in the plasma membrane of a cancer cell during chemotherapy. Activation of the efflux pump by the hydrolysis of a bound ATP molecule drives the cytotoxic drug molecules out of the cell.

P-gp belongs to the ATP-binding cassette (ABC) family of transporters, currently numbering 48 members that share sequence and structural homology. It is believed that, while this class of transporters has a large number of members, only 10 or so are reported to confer the drug-resistant phenotype[1]. These transporters use the energy that is released when they hydrolyze ATP to drive the transport of various molecules across the cell membrane[10, 11]. In addition to their physiologic expression in normal tissues, many are expressed and, importantly, over-expressed, in human tumors[1]. A number of ABC transporters and the chemotherapy drugs to which they have been shown to confer resistance are listed in the Table No.1.

P-gp consists of four distinct domains. Two of these are highly hydrophobic, integral membrane domains, each of which spans the membrane six times by alfa-helices. The other two are hydrophilic nucleotide-binding domains (NBDs).

Recently, a 2.5 nm resolution structure of P-gp was obtained by electron microscopy and single-particle image analysis[12,13]. In the P-gp molecule there is a large central pore, ~5 nm in diameter, which is closed at the inner (cytoplasmic) side of the plasma membrane. A gap may be present in the protein ring; this could allow substrates to access the central pore from the lipid phase. P-glycoprotein is predicted to act as a flippase with drug substrates, gaining access to their binding sites from the inner leaflet of the lipid bilayer [14].

P-gp is a broad-spectrum multidrug efflux pump that has 12 transmembrane regions and two ATP-binding Sites (Fig. 2)[15].The transmembrane regions bind hydrophobic drug substrates that are either neutral or positively charged, and are probably presented to the transporter directly from the lipid bilayer [16]. Two ATP hydrolysis events, which do not occur simultaneously, are needed to transport one drug molecule1[17]. Binding of substrate to the transmembrane regions stimulates the ATPase activity of P-gp, causing a conformational change that releases substrate to either the outer leaflet of the membrane (from which it can diffuse into the medium) or the extracellular space[18, 19,20].

In cancerous tissue, the expression of P-gp is usually highest in tumors that are derived from tissues that normally express P-gp, such as epithelial cells of the colon, kidney, adrenal, pancreas, and liver, resulting in the potential for resistance to some cytotoxic agents before chemotherapy is initiated. In other tumors, the expression of P-gp may be low at the time of diagnosis but increases after exposure to cytotoxic agents, thereby resulting in the development of MDR in those cells[21].
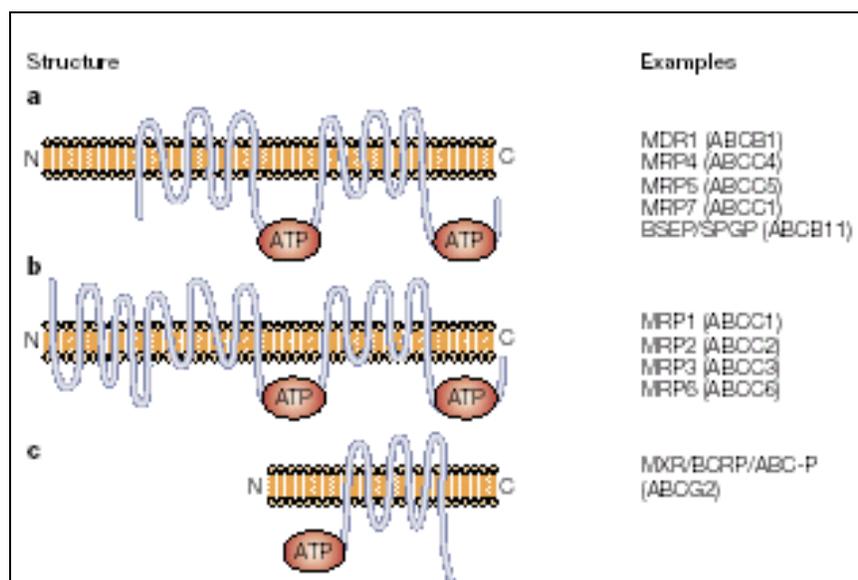

Figure 2 Structures of ABC transporters known to confer drug resistance.

The structures of three categories of ABC transporter. **a** | ABC transporters such as multidrug resistance MDR1 and multidrug-resistance-associated protein 4 MRP4 have 12 transmembrane domains and two AT binding sites. **b** | The structures of MRP1, 2, 3 and 6 are similar in that they possess two ATP binding regions. They also contain an additional domain that is composed of five transmembrane segments at the amino-terminal end, giving them a total of 17 transmembrane domains. **c** | The 'half-transporter' ABCG2 contains six transmembrane domains and one ATP-binding region — in this case, on the amino-terminal side (N) of the transmembrane domain. In other 'half-transporters', such as the transporter associated with antigen processing (TAP), the ATP-binding cassette is found on the carboxy-terminal (C) side of the transmembrane domain. Half-transporters are thought to homodimerize or heterodimerize to function.

Table No.1: P-Glycoprotein and other ATP-Binding Cassette Transporters associated with classic Multidrug Resistance and the Cytotoxic Substrates they transport.

Common Name	Other Names	Systematic Name	Cytotoxic Substrates
P-gp	MDR1	ABCB1	actinomycin-D bisantrene daunorubicin docetaxel doxorubicin etoposide homoharringtonine mitoxantrone53 paclitaxel teniposide topotecan vinblastine vincristine vinorelbine
MDR2	—	ABCB4	paclitaxel vinblastine
MRP1	—	ABCC1	doxorubicin epirubicin etoposide methotrexate vincristine vinorelbine
BCRP	MXR, ABC-P	ABCG2	daunorubicin doxorubicin mitoxantrone SN-38 topotecan

P-gp = p-glycoprotein
MDR = multidrug resistance
MRP = multidrug resistance protein
CMOAT = canalicular multi-organic anion transporter
BRCP = breast cancer resistance protein
MXR = mitoxantrone resistance
ABC = ATP-binding cassette

P-gp MODULATORS:

There are many studies to overcome MDR by inhibiting MDR transporters, to suppress or circumvent MDR mechanisms. The use of anticancer drugs that could escape from the ABC transporters might be a solution to avoid drug resistance. Anticancer drugs which are not the substrates of ABC transporters are alkylating drugs (cyclophosphamide), antimetabolites (5-fluorouracil), and the anthracycline modified drugs (annamycin and doxorubicin-peptide)[8].Another method to overcome resistance to anticancer drugs is to administer compounds that would not be toxic themselves, but would inhibit ABC transporters [8,22]. The compounds that would reverse resistance against anticancer drugs are called MDR inhibitors, MDR modulators, MDR reversal agents or chemosensitizers.

The process by which these agents circumvent MDR is referred as chemosensitization[23.]

Most modulators identified interfere with P-gp by competitive or noncompetitive inhibition of its drug effluxing activity. They are normally P-gp substrates, some of them are only able to bind to the protein but are not effluxed from the cells, and can thus be considered as pure antagonists.

It has been shown that various MDR type substrates and Chemosensitizers compete at a common drug-binding site present in P-gp[24].

Many agents that modulate the P-gp transporter, including verapamil, cyclosporin (cyclosporin A), tamoxifen, and several calmodulin antagonists, were identified in the 1980s. These agents often produced disappointing results *in vivo* because their low binding affinities necessitated the use of high doses, resulting in unacceptable toxicity[25, 26,27]. Many of the initial chemosensitizers identified were themselves substrates for P-gp and thus worked by competing with the cytotoxic compounds for efflux by the P-gp pump; therefore, high serum concentrations of the Chemosensitizers were necessary to produce adequate intracellular concentrations of the cytotoxic drug[2]. In addition, many of these chemosensitizers are substrates for other transporters and enzyme systems, resulting in unpredictable pharmacokinetic interactions in the presence of chemotherapy agents. To overcome these limitations, several novel analogs of these early chemosensitizers were tested and developed, with the aim of finding P-gp modulators with less toxicity and greater potency[25, 28].

The second-generation P-gp modulators include dexverapamil, dexniguldipine, valspodar (PSC 833), and biricodar (VX-710). These agents are more potent than their predecessors and also less toxic[25]. The best characterized and most studied of these agents is valspodar, a nonimmunosuppressive derivative of cyclosporin D that inhibits P-gp with 10 to 20 fold greater activity than cyclosporin A[29, 30].

Second-generation P-gp modulators have a better pharmacologic profile than the first-generation compounds, but they also retain some characteristics that limit their clinical usefulness. In particular, these compounds significantly inhibit the metabolism and excretion of cytotoxic agents, thus leading to unacceptable toxicity.

Many of the cytotoxic agents that are substrates for P-gp are also substrates for the cytochrome P450 isoenzyme 3A4. It is not surprising then that the agents that are affected by the development of MDR are also metabolized by cytochrome P450 3A4. Several of the second-generation P-gp modulators, including valspodar and biricodar, are substrates for this enzyme[5].

The competition between cytotoxic agents and these P-gp modulators for cytochrome P450 3A4 activity has resulted in unpredictable pharmacokinetic interactions. For example, valspodar inhibits the cytochrome P450 3A4-mediated metabolism of paclitaxel and vinblastine[31, 32] resulting in increased serum concentrations of the cytotoxic agents and potentially putting patients at risk of cytotoxic drug overexposure[33] Similarly, in a pharmacokinetic study in patients with solid tumors, biricodar administered in a 24-hour intravenous infusion decreased the clearance of paclitaxel in a dose-dependent manner. It has been suggested that this interaction may be due in part to the inhibition of cytochrome P450 3A4 by biricodar, thereby interfering with the metabolism of paclitaxel[34].

In addition to inhibiting P-gp, many second-generation modulators also function as substrates for other transporters, particularly those of the ABC transporter family, inhibition of which could lessen the ability of normal cells and tissues to protect themselves from cytotoxic agents. Many of these transporters have well defined physiologic roles, often involving the elimination of xenobiotics[25, 5].

Many of the early-generation P-gp modulators inhibited several other ABC transporters as well as the P-gp transporter. For instance, valspodar and biricodar are not specific solely to P-gp; both of these agents affect MRP1[22,36]. It is possible that this inhibition of non-target transporters may lead to greater adverse effects of anticancer drugs, including neutropenia and other myelotoxic effects[37,35].

Third-generation molecules that specifically and potently inhibit P-gp function have been developed by using structure-activity relationships and combinatorial chemistry to overcome the limitations of the second generation P-gp modulators. These agents do not affect cytochrome P450 3A4 at relevant concentrations. Similarly, third-generation agents typically do not inhibit other ABC transporters[38, 39].

The third generation P-gp inhibitors currently in clinical development include the anthranilamide derivative tariquidar (XR9576), diketopiperazine derivative XR9051[40], the cyclopropyldibenzosuberane zosuquidar

(LY335979)[41] and the substituted diarylimidazole ONT- 093[42]. Despite having diverse chemical structures and origins, these agents have in common a high potency and specificity for the P-gp transporter.

One of the most promising third-generation P-gp inhibitors is tariquidar, which binds with high affinity to the P-gp transporter and potently inhibits its activity[43,44]. Second-generation P-gp modulators compete as a substrate with the cytotoxic agent for transport by the pump (Fig 3). In contrast, tariquidar specifically and noncompetitively binds to the pump (Fig 4) with an affinity that greatly exceeds that of the transported substrates[45] It is not clear whether the binding of XR9576 on P-gp is indeed to that of the ATP binding site, but like other modulators such as GF120918, it inhibits the ATPase activity of P-gp[46].

The cyclopropyldibenzosuberane modulator LY335979 was shown to competitively inhibit the binding of vinblastine to P-gp[47]. In clinical studies in both solid and hematologic malignancies, LY335979 showed no significant pharmacokinetic interactions with doxorubicin, etoposide, daunorubicin, vincristine, or paclitaxel.[48-51], R101933 and ONT-093 are two other third-generation P-gp inhibitors that have been shown to be effective in inhibiting P-gp with no effect on the pharmacokinetics of docetaxel[35] and paclitaxel[42].
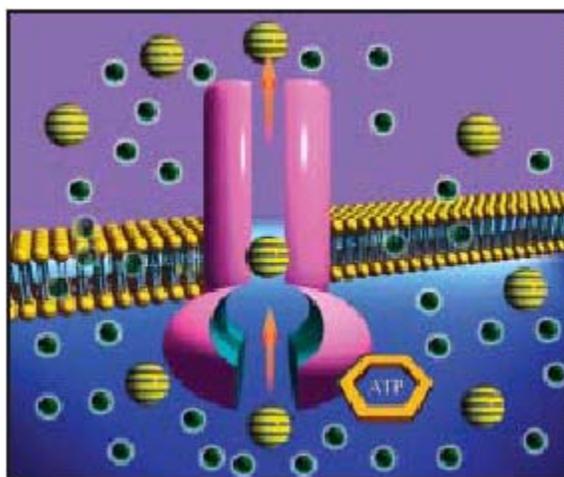

Fig 3. Competitive inhibition of the P-glycoprotein transporter. First and second-generation modulators compete as a substrate with the cytotoxic agent for transport by the pump. This limits the efflux of the cytotoxic agent, increasing its intracellular concentration.
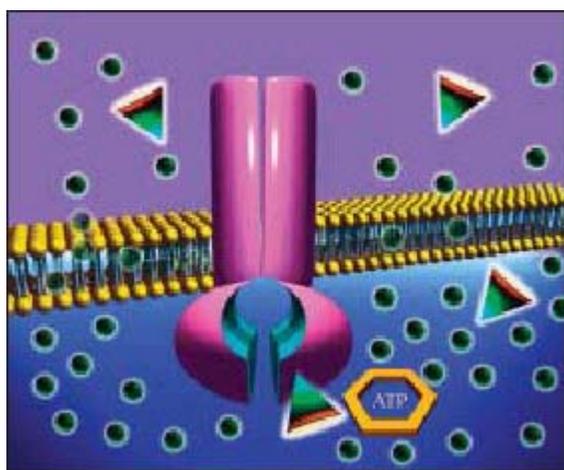

Fig 4. Noncompetitive inhibition of the P-glycoprotein transporter.

Third-generation inhibitors of P-gp, such as tariquidar, bind with high affinity to the pump but are not themselves substrates. This induces a conformational change in the protein, thereby preventing ATP hydrolysis and transport of the cytotoxic agent out of the cell, resulting in an increased intracellular concentration.

Conclusion:

Because of their specificity for P-gp transporters and lack of interaction with cytochrome P450 3A4, third-generation P-gp inhibitors offer significant advantages over the second-generation agents.

Ongoing clinical trials with third-generation P-gp inhibitors should show whether this approach will result in greater survival in patients with cancer. So far, this objective has not been demonstrated, due in part to the unpredictable pharmacokinetic effects of second- generation P-gp modulators on the coadministered chemotherapy agents. The preliminary results with third-generation P-gp inhibitors offer new hopes that this goal might be realized.

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