JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 1067–1081

Received January 29, 2004
Accepted June 22, 2004
DOI 10.1211/0022357044265
ISSN 0022-3573

Review Article

A review of selected anti-tumour therapeutic agents and reasons for multidrug resistance occurrence

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Abstract

It is assumed that proteins from the ABC family (i.e., glycoprotein P (Pgp)) and a multidrug resistance associated protein (MRP) play a main role in the occurrence of multidrug resistance (MDR) in tumour cells. Other factors that influence the rise of MDR are mechanisms connected with change in the effectiveness of the glutathione cycle and with decrease in expression of topoisomerases I and II. The aim of this review is to characterize drugs applied in anti-tumour therapy and to describe the present state of knowledge concerning the mechanisms of MDR occurrence, as well as the pharmacological agents applied in reducing this phenomenon.

Introduction

The main reason for failures of anti-tumour therapy is intrinsic or acquired resistance of tumours to drugs applied during chemotherapy (Stefanska et al 2003). This phenomenon of simultaneous tumour resistance to several groups of cytostatic drugs, differing in chemical structure and effects, has been called multidrug resistance (MDR) (Sonneveld & Segeren 2003). A few independent mechanisms are responsible for MDR: the membrane mechanism determining the low drug level in resistant cells, connected with the existence of specific membrane proteins (glycoprotein P, Pgp, and multidrug resistance associated protein, MRP) (Higgins 2001; Dean 2002; Sparreboom et al 2003); the mechanism connected with change in the effectiveness of the glutathione cycle; the mechanism connected with the decrease in DNA topoisomerases expression (Naito et al 2000; Gottesman 2002). The mechanisms of action of these factors are not yet fully known and they are still being investigated by methods such as spectroscopy (Dey et al 1997), circular dichroism (CD), transmission electron microscopy (TEM) and atomic force microscopy (AFM) (Diociaiuti et al 2002).

Among the new anti-tumour drugs, STI571 (also known as Glivec (Westwell 2003)), a tyrosine kinase inhibitor (Weisberg & Griffin 2001; Cohen et al 2002), evokes much interest. It is one of the most active drugs in chronic myeloid leukaemia (CML) and in gastrointestinal stromal tumours (GIST) (Bakalova et al 2003; Roskoski 2003). Promising results have been reported in phase II trials of topotecan, a specific topoisomerase I inhibitor (Fioricia 2003; Herzog 2003). It has anti-tumour activity against relapsed ovarian cancer (Morris 2003) and endometrial cancer (Holloway 2003). Many research centres concentrate on ciclosporin and verapamil – Pgp and MRP modulators (Cocker et al 2000; Fu et al 2002) – but the results of the research are quite controversial (Davidson et al 2002; Garraway & Chabner 2002).

The subject of this work is to present the current state of knowledge of the mechanisms of MDR and the pharmacological agents used in anti-tumour therapy.

Drugs in cancer therapy

An application of anti-tumour drugs involves replacing the natural chelators that bind to natural cellular receptors (McKay & Hirano 2002). The drugs may imitate natural regulative agents (they are called agonists or analogues), or they may inhibit the activity of natural ligands through blocking the receptor spot. Some drugs are introduced into the tissue in an inactive form and they become biologically active

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Acknowledgement and funding:
This work was supported with the 4 PO5F 014 19 Grant from the KBN (State Committee for Scientific Research) and Technical University in Biatystok (S/IIS/24/04). We also thank Hanna Lewandowska for her help in the preparation of this paper.

compounds as a result of interaction with the cytoplasmic reticulum. For example, adriamycin and mitomycin become active only after having undergone the process of reduction in the cytoplasmic reticulum. The antitumour drugs may be divided into the following groups: alkylating agents, antimetabolites, cytostatic antibiotics, alkaloids and lignans (Table 1) (Espinosa et al 2003). The drugs show some structural and functional similarities (Esser et al 2000), such as small size, biplanar molecules, particle hydrophobicity or presence of nitrogen atoms in their aromatic rings. The compounds enter a cell by passive diffusion.

The characteristics of selected drugs causing multidrug resistance

In the next part of this paper we focus on two chemotherapeutic agents, which, despite their dangerous side effects and a tendency to induce multidrug resistance, are the most often applied. Moreover, combination of these drugs with other agents shows promising results in clinical treatment.

Doxorubicin Though not completely elucidated, the mechanism of action of doxorubicin consists of: intercalation with DNA causing inhibition of nucleic acid (RNA and DNA) synthesis; DNA strands scission by affecting topisomerase II activity; alteration of membrane fluidity and ion transport; semiquinone free radical generation, which can, in turn, react with molecular oxygen to generate highly reactive cytotoxic compounds, such as superoxide, hydroxyl radicals and hydrogen peroxide (Nygren & Lundgren 1997; Salmon & Sartorelli 1998).

Doxorubicin is applied in myeloblastic leukaemia, lymphoblastic leukaemia (Wondergem et al 1998; Ibrahim et al 1999), breast cancer (Nielsen et al 2000), ovarian tumour, urinary bladder cancer, small-cell lung tumour, bone and soft tissue sarcoma, lymphomas and thyroid and stomach cancer treatment (Gnewuch & Sosnovsky 2002). After intravenous injection, the antibiotic quickly disappears from the plasma, which indicates a dynamic distribution of doxorubicin to the organs and tissues. Doxorubicin does not cross the blood–brain barrier and very slightly penetrates the placental barrier and gets into the mother's milk (Grandjean et al 2002). Doxorubicin is metabolised in the liver (inter alia to the form of active doxorubicinol) and it is excreted with the bile (up to 50%) and in small quantities in the urine (Nygren & Lundgren 1997).

Some of the adverse effects of this drug are bone marrow depression and cardiotoxicity, which result primarily from the generation of damaging free oxygen radicals but might also be partly due to the inhibition of topoisomerase II (Hande 1998; Wu et al 2001). Radiation therapy to the mediastinum (Wondergem et al 1998), advanced age and pre-existing cardiac disorders (Ibrahim et al 1999) augment the cardiotoxicity. To increase the safety of doxorubicin, combination with other drugs has been investigated (Herman et al 2000). Pretreatment with tamoxifen alters the metabolic profile of doxorubicin either by inhibiting the formation of its toxic metabolite doxorubicinol or by reducing the enzymes that are responsible for its biotransformation (Vaidyanathan & Boroujerdi 2000b). Pre-treatment with dexrazoxane prevents free radical formation, lipid peroxidation and cardiotoxicity (Vaidyanathan & Boroujerdi 2000a). Compared with dexrazoxane, amifostine provides a similar degree of protection against the nephrotoxicity of doxorubicin, but seems to be less cardioprotective (Sargent et al 2001). These differences may be related to the fact that amifostine may act as a scavenger of reactive oxygen species, whereas dexrazoxane may prevent their formation (Herman et al 2000). The separate application of doxorubicin and paclitaxel at about a 16-h interval decreased the cardiotoxicity of doxorubicin in patients with locally advanced breast cancer. On the other hand, when doxorubicin and paclitaxel were applied at a shorter interval the cardiotoxicity increased (Moreira et al 2001). At present, there are more than 2000 safer and more effective synthetic analogues of doxorubicin, which are potential anti-tumour compounds, but only a small percentage of them have reached the registration or marketing phases (e.g., epirubicin, pirarubicin, idarubicin, valrubicin, Da-125) (Figure 1) (Kim et al 2001; Grynkiewicz et al 2002).

Resistance to doxorubicin occurs through multiple mechanisms, the best known of which is connected to the over-expression of Pgp (Grandjean et al 2002) (see below). Several modifications in mitochondrial oxido-reductase activity have been encountered in human K562 leukaemia cells resistant to doxorubicin. They are characterized by a significant increase in the activity of the DNA–topoisomerase II complex in contrast with a decrease in the COX (cytochrome c oxidase) activity and the cytochrome aa3 contents during the stationary growth phase. Moreover an increase in expression of antioxidants, such as glutathione and glutathione-dependent proteins, causes an increase in glutathione peroxidase activity and a reduction in doxorubicin activity (Grandjean et al 2002).

Platinum-based anti-cancer agents Platinum-based anticancer agents contain oxidized platinum Pt(II) and Pt(IV). The chemicals are electroneutral (except the group called platinum pigments). The cisplatin analogues, containing chlorine ligands, exhibit much stronger therapeutic features than the analogues in which the ligands are azides, cyanides, iodides or rhodanates. Moreover, only platinum complexes coordinating ammonium molecules and 1′- and 2′-amines have cytostatic properties, while platinum compounds with 3′-amine groups exhibit practically no therapeutic features (Rosenberg et al 1969). Cisplatin (*cis*-diamminedichloroplatinum II) is effective in the treatment of a variety of cancers, especially testicular cancer for which it has a greater than 90% cure rate (Jamieson & Lippard 1999) and human head and neck cancer (Yang et al 2000).

The mechanism by which cisplatin is taken up by the cells is not fully understood. It has been suggested that cisplatin enters the cells by passive diffusion (Jamieson & Lippard 1999) and also, as recently discovered, by active transport mediated by the copper transporter Ctr1p in yeast and mammals (Ishida et al 2002; Lin et al 2002).

Table 1 Division of selected anti-tumour drugs on the basis of the structure, mechanism of action, and the phase of the cell cycle in which they operate

Compound	Chemical structure	Representatives (exemplary drugs)	Mechanism of action	Phase(s) of the cell cycle in which the drugs interact	References
Alkylating agents	Structurally different classes of chemical compounds, small size	Nitrogen mustards (chlorambucil, cyclophosphamide, ifosfamide, melphalan) Ethylenimine derivatives (thiotepa, triaziquone) Sulfic acid esters (busulfan) Nitrosoureas derivatives (fotemustine, semustine, lomustine, streptozocin) Triazenes (dacarbazine, temozolomide) Other alkylating agents (degranol, myelobromol, dibromodulcitol, cisplatin)	The main reaction is alkylation of a nitrogen group in guanine. It causes disturbances and errors in transcription and translation, breaks a DNA strand nucleotide chain, induces crosslinks between DNA strands, and breaking of the DNA strand.	All phases in the cell cycle, mostly in phase S of the cell cycle	Hurley 2002; Yam et al. 2002; Kartalou & Essigmann 2001; Nygren & Lundgren 1997
Antimetabolites	Structural analogues of natural metabolites or coenzymes occurring in cellular biological systems	Folic acid derivatives (methotrexate, edatrexate) Purine derivatives (cladribine, mercaptopurine, thioguanine) Pyridine derivatives (capecitabine, cytarabine, floxuridine, 5-fluorouracil, gemcitabine) Urea derivatives (hydroxyurea) Adenosine analogues (pentostatin, fludarabine, cladribine)	Due to their chemical structure similar to that of natural metabolites, antimetabolites inhibit competitive enzymatic reactions or they are incorporated instead of metabolites as the construction unit essential for correct life processes. In consequence, it leads to inhibition of DNA and RNA synthesis.	S phase of the cell cycle	Espinosa et al 2003; Gnewuch & Sosnovsky 2002
Cytostatic antibiotics	One common feature of their chemical structure is the presence of a bond between the glycoside ring and the daunosamine aminosugar	Anthracycline (antibiotics produced by different strains of *Streptomyces* or received by chemical synthesis): I generation (daunorubicin, doxorubicin); II generation (mitoxantrone, epirubicin, idarubicin, pirarubicin) Other antibiotics (dactinomycin, plicamycin, bleomycin, mitomycin)	Binding of antibiotics with the DNA double helix, fragmentation of the DNA strand due to inhibition of catalytic activity of topoisomerase II, and in consequence inhibition of DNA and RNA synthesis.	All phases in the cell cycle, except bleomycin, which interacts with the G_1 phase	Espinosa et al 2003; Grandjean et al 2002; Skotnicki et al 1998; Gnewuch & Sosnovsky 2002
Alkaloids	Vinca rosea indol alkaloids; the complex structure is almost identical	Vincristine, vinblastine, vindesine, vinorelbine	Inhibition of the cell division during the metaphase stage. Alkaloids bind with tubuline, a component of microtubules that form a mitotic spindle. In consequence, the mitotic spindle is deformed, which causes the disruption of the chromosome arrangement. Chromosomes assemble in the cytoplasm in a pell-mell way, which leads to cell death.	M phase of the cell cycle	Davidson et al 2002; Espinosa et al 2003
Lignans	Different chemical structure	Etoposide (VP-16), teniposide (VM-26)	These drugs inhibit the entrance of a cell into the mitosis prophase. Moreover, they cause fragmentation of both DNA strands, inhibit the activity of topoisomerase II (which damages the DNA repair mechanisms), take part in the formation of free radicals and inhibition of nucleosides to be incorporated into DNA and RNA.	G_2 phase of the cell cycle	Gnewuch & Sosnovsky 2002

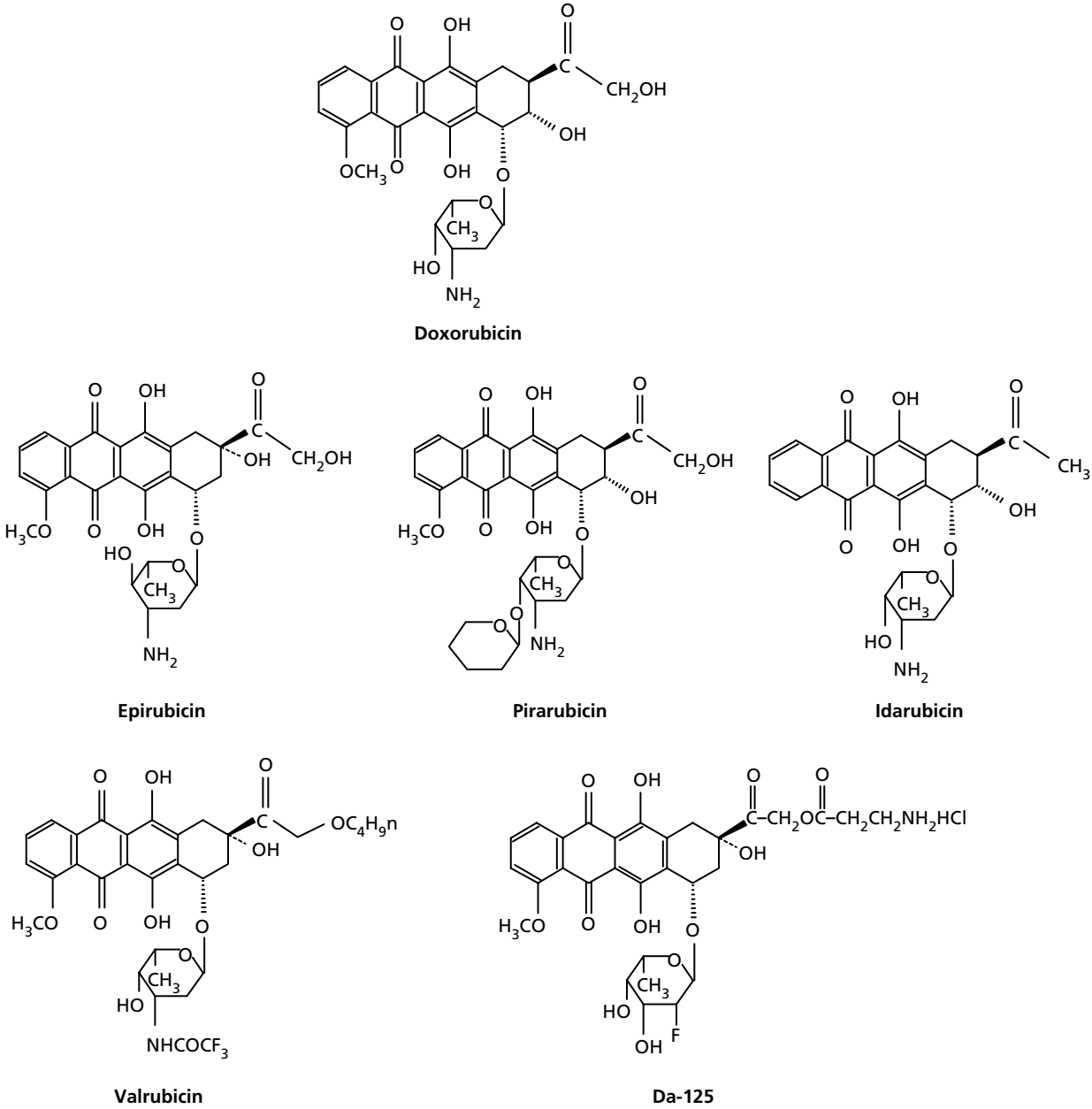

Figure 1 Structure of doxorubicin and selected synthetic analogues of doxorubicin.

Cisplatin's mechanism of action is as follows: cisplatin is administered intravenously, and while it circulates in the blood, where the chloride concentration is ~100 mM, Pt(II) remains coordinated to its chloride ligands. Upon entering the cell where the chloride concentration is low (~4 mM), the chloride ligands of cisplatin are presumably replaced by water molecules, generating a positively charged aquated species that can react with nucleophilic sites on intracellular macromolecules to form protein, RNA and DNA adducts. The reaction with the DNA yields monofunctional adducts, intrastrand crosslinks and interstrand crosslinks with the platinum atom coordinated to the N7 position of guanine or adenine. It results in the inhibition of the DNA replication and the RNA transcription, the G_2 phase of the cell cycle is arrested and programmed cell death ensues (Figure 2) (Holford et al 1998; Li et al 1999).

Due to significant adverse effects and cell resistance to cisplatin (especially for ovarian cancer), much attention has been paid to designing new platinum compounds with improved pharmacological properties and a broader range of anti-tumour activity (Zhang & Lippard 2003). Among them there is carboplatin (Figure 3), which has an effectiveness comparable with that of cisplatin, but it is better tolerated because of its lower nephro- and neurotoxicity (Kelland et al 1992; Goddard 1996). Oxaliplatin faster

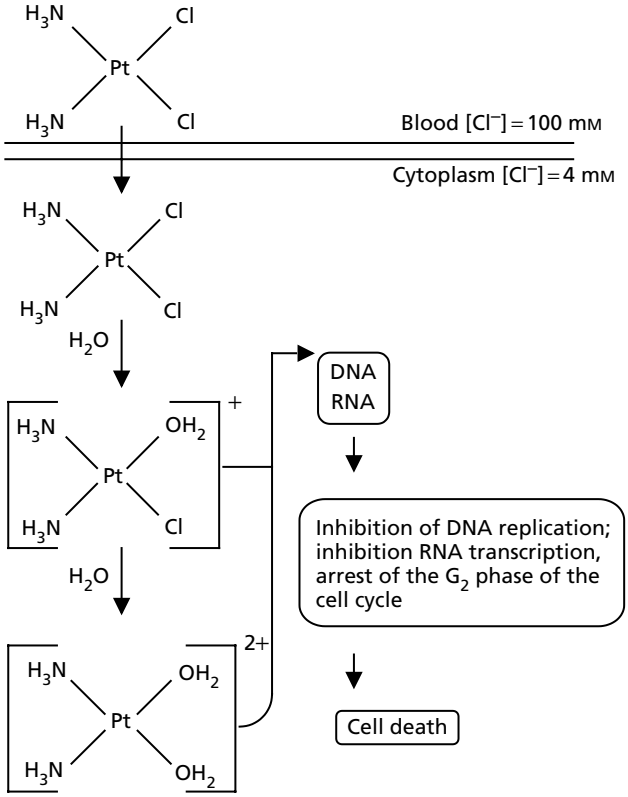

Figure 2 Mechanism of action of cisplatin.

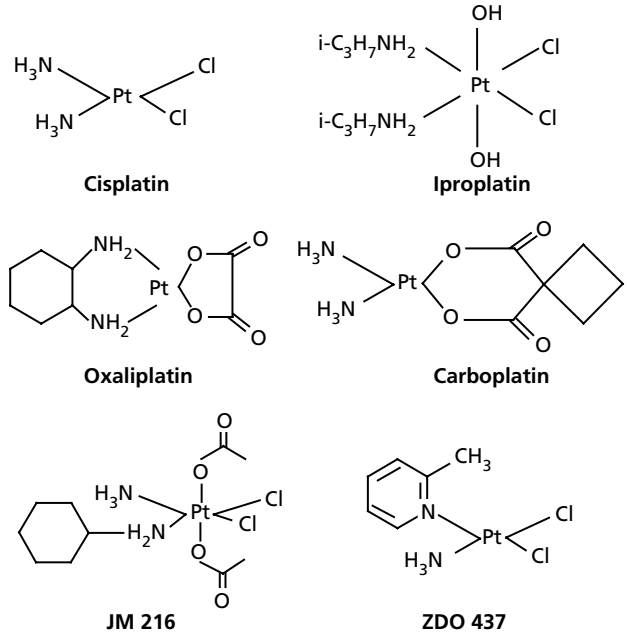

Figure 3 Selected platinum compounds that are in clinical use or have recently been approved for clinical use.

creates different structured adducts with DNA when compared with cisplatin-DNA adducts, and as a result, oxaliplatin is active against a whole series of cisplatin-resistant cellular lines (Ishibashi et al 2002; Ita et al 2003). Chemotherapy with nedaplatin and radiation is effective against the primary malignancy of oral squamous cell carcinoma (Masamichi et al 2003). Priebe has examined cisplatin complexes with polyaminosaccharide ligands containing a modified doxorubicin carbohydrate molecule (Fuks et al 2003; Samochocka et al 2003). The saccharides create complexes of great stability and easily modifiable lipophilicity. Combination of cisplatin with estrogens (Wysokinski 1998) or some anti-tumour drugs (Szachowicz-Petelska et al 2001) has been also studied. Cisplatin combined with etoposide and bleomycin is 95% effective in testicular cancer treatment (Kartalou & Essigmann 2001).

The invulnerability of cells to cisplatin toxicity has been attributed to several processes including: the inhibition of drug uptake; an increase in the production of cellular thiols (methallothioneins and glutathione); enhanced replicative bypass of the cisplatin–DNA adducts; changes in the concentration of regulatory proteins; an increase in the repair of cisplatin–DNA adducts (Chu 1994). A factor that plays a critical role in cellular resistance to cisplatin is an increase in DNA repair, which could be caused by enhanced expression of proteins involved in DNA repair (Zamble & Lippard 1995). ERCC1 is one of the essential components of the mammalian nucleotide excision repair (NER) pathway. When relative expression of the gene encoding for ERCC1 was monitored in tumour tissue from ovarian cancer patients, the mRNA levels were significantly higher in tissue from patients who were clinically resistant to cisplatin therapy than in tissue of patients who responded favourably to treatment (Van Vuuren et al 1995; Lan et al 2004; Wu et al 2003). Proliferating cell nuclear antigen (PCNA) is another protein that is required for the NER pathway to function and this protein was also found to be overexpressed in cell lines that showed resistance to cisplatin exposure (Zamble & Lippard 1995; Kartalou & Essigmann 2001). C-fos and C-myc are proto-oncogenes that have both been correlated with cisplatin resistance following drug exposure. Activating the transcription of these genes may lead to a cascade of gene expression that, in turn, stimulates the activity of proteins having a direct role in DNA repair (Yokoyama et al 1998). p53 is a tumour suppressor gene product that has been linked to the ability of DNA repair to confer cisplatin sensitivity. Disruption of the gene encoding for p53 in human breast cancer cells increases their sensitivity to cisplatin, possibly because of a decrease in DNA repair (Wetzel & Berberich 2001; Yazlovitskaya et al 2001; Fojta et al 2003).

Factors responsible for multidrug resistance

Multidrug resistance proteins – Pgp and MRP

Glycoprotein P (Pgp) The protein from the ABC family transports drugs by removing them to the outside

Table 2 Selected anti-cancer drugs that are substrates for the factors responsible for multidrug resistance

Name	Substrates
Pgp	Doxorubicin, daunorubicin, epirubicin, etoposide, paclitaxel, docetaxel, vincristine, vinblastine, rhodamine-123, chloroquine, quinidine, aldosterone
MRP1	Vincristine, daunorubicin, doxorubicin, etoposide
MRP2	Methotrexate, etoposide, cisplatin, vinca alkaloids
MRP3	Etoposide, teniposide, estrogen derivatives, methotrexate, Vinca alkaloids
MRP4	Purine analogues, estrogen derivatives
MRP5	Thiopurines, cyclic nucleotides
GSTs	Chloroethylnitrosoureas, cisplatin, anthracyclines, phosphamides
Topo II	Chloroethylnitrosoureas, epipodophyllotoxins, cisplatin, anthracyclines

(Garraway & Chabner 2002; Teodori et al 2002; Leonessa & Clarke 2003; Sparreboom et al 2003).

of the cell, and it does not prevent the drugs from permeating (Juliano & Ling 1976; Leonessa & Clarke 2003); selected anti-cancer drugs that are substrates for Pgp are listed in Table 2. A distinct correlation has been shown between the amount of Pgp and the MDR intensification (Hendrikse & Vaalburg 2002; Kim et al 2003). This correlation has been observed in all the examined cells irrespective of the type of tumour (Nakanishi et al 1997).

Pgp is expressed in many healthy organs, such as a kidney, liver, intestine and adrenal gland (Zhang et al 1999; Van Bambeke et al 2003), where its normal physiological function is thought to involve the secretion of steroids and toxic metabolites (Schinkel et al 1997; Steinman & Muller 1998). Pgp, a 170 kDa membrane protein, can exist in a human body in two isoforms, Pgp1 and Pgp2, which are encoded by two genes, mdr1 and mdr2 (the latter also defined as mdr3). The products of the two human genes (mdr1, mdr2/3) contain 1280 and 1279 amino acids, respectively (Teodori et al 2002). Genes mdr1 and mdr2 are located on chromosome 7 (7q21.1) and are made up of 28 exons (Chen et al 1986); mdr2/3 codes a protein that has a different substrate profile to Pgp1 (Klopman et al 1997). Pgp consists of two homologous parts, each containing hydrophobic transmembrane domains (TMDs) and hydrophilic nucleotide-binding domains (NBDs) (Figure 4) (Jones & George 1998). Each NBD contains three elements: Walker A and B motifs and the so-called ABC signature sequence. Lys residue within the Walker A motif is directly involved in binding the ß-phosphate of adenosine 5′-triphosphate (ATP), while a highly conserved Asp residue within the Walker B motif serves to bind the Mg^{2+} ion. The

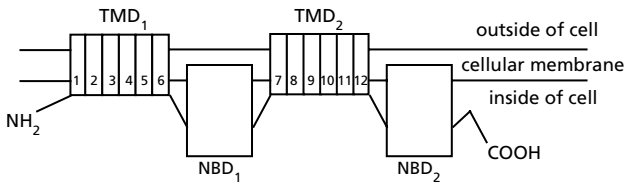

Figure 4 Structure of glycoprotein P (Jones & George 2000). NBD, nucleotide-binding domain; TMD, transmembrane domain; 1–12, transmembrane segments.

definitive role of the ABC signature sequence has not yet been elucidated (Naito et al 2000). On the basis of fluorescence resonance energy transfer (FRET) results, Sharom et al (1999) suggest that the two NBDs are both functionally and structurally identical and participate in ATP binding to the same extent. A model assuming the presence in each TMD of six α-helices engaged in drug binding and removing has been confirmed by several mapping studies. A Pgp structure model based on the double β-barrel motif has also been proposed (Kast et al 1996; Jones & George 1998). Using electron microscopy, X-ray and FRET analyses, Rosenberg et al (1997) proposed a cylindrical model for the Pgp structure (~100 Å in width and ~80 Å in depth) with two L-shaped NBDs partially embedded in the membrane and separated from each other by ~17 Å.

Experiments on mutations taking place in the transmembrane α-helices have revealed that the two last pairs of transmembrane segments (i.e., 5 and 6 in TMD_1 as well as 11 and 12 in TMD_2) constitute the main site of interaction with drugs (Gottesman et al 1995; Ambudkar et al 1999). A model for the drug-binding site emerging from cysteine-scanning mutagenesis and cross-linking experiments indicates a drug-binding site involving residues from the TMD domains – 4, 5, 6, 8, 9, 10, 11 and 12 (Loo & Clark 2002). Moreover, the authors suggest a hypothesis that this common pocket can allow diverse substrates to create their own binding sites, via a substrate-induced fit mechanism where the substrates use a combination of residues from the different TMDs.

In the first phase of removing drugs, Pgp yields phosphorylation with the participation of the highly energetic ATP molecule and this leads to a change in Pgp conformation (Endo et al 2002; Gnewuch & Sosnovsky 2002). A binding site showing great kinship to the transported compound is exposed on the peptide chain. After the binding, the molecule is transported to the other side of the membrane, and then dephosphorylation and consecutive conformation changes aimed at releasing the transported compound take place. When accepting such a hypothesis it should be assumed that binding of the compound, which is transported by Pgp, is reversible and the glycoprotein has different drug-binding sites. The research conducted in that field has shown that Pgp has two

I-iodoarylazidoprazosin-binding sites, while fluorescent spectroscopy analysis revealed that Pgp shows single-site binding for daunorubicin and two-site binding for vinblastine and verapamil (Sharom et al 1999). The results of the experiments show that Pgp contains two substrate binding sites with different affinities, and that a particular drug may interact with one or both of these sites. Shapiro & Ling (1997) have labelled these binding sites within Pgp as the H site and the R site. Martin et al (2000) describe the existence of at least four binding sites within Pgp. The recognition pattern of the compound transported by Pgp is hitherto unknown. A hypothesis has been presented that the substrates removed from the cell by Pgp are marked by the intermolecular conjugates (e.g., glutathione under the influence of glutathione transferase) (Yang et al 2001).

There are at least three possible mechanisms of action for Pgp. The first hypothesis assumes that Pgp acts as a transporting channel. According to the second, Pgp acts as a flippase and removes hydrophobic substances from the cytoplasm to the outer site of the lipid bilayer of the cellular membrane from where they can diffuse to the extracellular space (Roepe 1995). Moreover, using Hoechst 33342 dye, Ling has shown that Pgp might also act as a so-called hydrophobic vacuum cleaner, enabling drug removal from the lipid phase. Using a protonophore and measuring the intraliposomal pH while transporting drugs, the hypotheses of indirect mechanisms of Pgp action, such as intracellular pH changes or membrane potential modifications, have been rejected (Shapiro & Ling 1997; Krishna & Mayer 2000).

Multidrug resistance associated protein – MRP (MRP1)

As opposed to Pgp, which usually over-expresses when the concentration of chemotherapeutics is high, MRP over-expresses under the influence of a lower drug concentration (Cole et al 1992; Burger et al 1994; Hart et al 1994); selected anti-cancer drugs that are substrates for MRP are listed in Table 2. MRP protein is thought to play a role in protecting cells from chemical toxicity and oxidative stress and to mediate inflammatory responses involving cysteinyl leukotrienes (Twentyman & Bagnij 1998). MRP transports drugs that are conjugated to glutathione (e.g., chlorambucil, melphalan and etacrynic acid) (Zaman et al 1995).

Six homologues of MRP have been described, which are labelled MRP1 to MRP6 (Borst et al 2000). MRP1 has been detected in the plasma membrane of many cell types, including erythrocytes, and is encoded by a gene, which has been mapped to chromosome 16 (16p13.1) (Cole & Deeley 1998). MRP2 (canalicular MRP, cMRP, or canalicular multispecific organic anion transporter, cMOAT) has been localized to the apical domain of polarized epithelial cells, including the hepatocyte canalicular membrane and the kidney proximal tubule membrane (Keppler & Konig 1997). MRP3–6 proteins are expressed in a variety of normal and tumour tissues (Young et al 1999; Van Bambeke et al 2003).

MRP, a 190 kDa protein, consists of 1531 amino acids, out of which 15% of sequences are identical to those of Pgp. The structure of MRP is similar that of Pgp in that MRP is made up of two transmembrane segments (TMD_1 and TMD_2, each comprising six membrane-spanning α-helices submerged in the lipid bilayer) separated from each other by two segments protruding into the cytoplasm: the nucleotide-binding domain (NBD) and the link area. Additionally, there is a TMD_0 area (Bakos et al 1996) formed by five transmembrane domains linked with the core by an L_0 loop. The function of TMD_0 is not fully known at present. It seems that the function of the L_0 loop is more important than TMD_0 – the lack of this loop in the protein causes its disfunctionality and the protein remains in the intracellular structures (Almquist et al 1995).

Transfection by the MRP gene causes a decrease in the intracellular accumulation of drugs to which cells become resistant, and causes an outflow of these compounds from the cells through a mechanism dependent on ATP (Cole & Deeley 1998). This suggests that MRP, similarly to Pgp, is an active transporter removing chemotherapeutics out of the cells. Nevertheless, H69/AR line cells, where MRP has been cloned, have not shown any decrease in the intracellular concentration of anti-tumour drugs. It has been suggested that MRP may not pump drugs outside the cellular membrane, but to the cytoplasmic granulations and the drugs are further removed through the process of exocytosis (Dzieduszycka et al 2002). In some cells the presence of MRP has been reported not only in the cytoplasmic cellular membrane, but also in the Golgi apparatus and other intracellular structures, which might confirm the above hypothesis (Meister 1983).

Changes in the effectiveness of the glutathione cycles or related enzyme cycles

Glutathione S-transferases (GSTs), a multiple gene family of phase II enzymes, catalyse detoxifying endogenous reactions with glutathione and protect cellular macromolecules from damage caused by cytotoxic and carcinogenic agents (O'Brien & Tew 1996; Wang et al 2003). Based on their amino acid sequences, the different GSTs are separated into five classes: alpha (GSTA), mu (GSTM), theta (GSTT), pi (GSTP), omega (GSTMO) and one membrane-associated microsomal GST (Hayes & Pulford 1995; Pastore et al 2003). The mu class comprises five different isoenzymes groups, namely GSTM1 to GSTM5, among which the M1 is particularly polymorphic. The relationship between the increased frequency of the GSTM1 mutations and a higher risk of cancer occurrence has been discussed (Pastore et al 2003). It is particularly the case in lung cancer for which the occurrence seems to be dependent on the cytochrome P450- and GSTM1-mediated capacity to detoxify the chemical carcinogens found in tobacco smoke. Nevertheless, it is still a matter of discussion whether GSTM1 polymorphism alone could confer an increased risk of lung cancer. Indeed, several recent studies reported significant differences in the polymorphism frequency between lung cancer patients and a control population, while others failed to show any connection (Harrison et al 1997; Sun et al 1997). GSTT1 and GSTP1 are members of the family characterized by a high frequency of polymorphism (Pastore et al 2003; Su et al

2003). GSTP1 is the most abundant GST isoform in lung tissue (Wang et al 2003). Few studies on GSTT1 and lung cancer have been reported and the GSTT1 genotype has been only occasionally associated with lung cancer (El-Zein et al 1997), with most studies to date reporting no dependence (Saarikoski et al 1998; Malats et al 2000). The role of GSTM1, GSTT1 and GSTP1 as markers for the risk of cancer is still under intense investigation and numerous further clinical studies are needed to clarify their role (Pastore et al 2003).

Alterations in topoisomerase levels and properties

DNA topoisomerases are nuclear enzymes responsible for controlling, preserving and modifying the structure of DNA during replication and translation of the genetic material (Cortés et al 2003). They change the number of the DNA thread strands through catalysis of the three-phase process: cutting one or both DNA threads; weaving the cut DNA segment through the gap created this way; joining the cut DNA segments together (Wijnholds et al 2000). Two classes of DNA topoisomerases are known, topo I and topo II, which differ in some aspects, namely topo II activity depends on the participation of ATP, while the activity of topo I does not. Topo I, as opposed to topo II, is an enzyme that does not depend on the cellular cycle. Moreover, topo I induces cutting of only one DNA helix thread, and topo II induces cutting of one or both of them (Husain et al 1994; Son et al 1998; Minderman et al 2000). There are two isoforms of topo II, the first, topo IIa, weighs 170 kDa, and the second, topo IIß weighs 180 kDa (Krishna & Mayer 2000). Topo IIα and topo IIβ are coded by genes characterized by great homology, located on chromosomes 17q and 3q, respectively (Yamazaki et al 1997). Although the catalytic mechanisms of topo IIα and topo IIβ appear to be the same, there is considerable evidence to suggest that the physiological functions of the two isoforms are different (Jensen et al 1996; Isaacs et al 1998). For example, topo IIα and topo IIβ differ in their expression throughout the cell cycle (Lok et al 2002) and in their tissue distribution both during the development and in adult vertebrates (Austin & Marsh 1998; Mirski et al 2003). Both isoforms accumulate in the nucleoplasm, but only topo IIβ is excluded from nucleoli during interphase (Meyer et al 1997). Topo IIα is essential for cell division, whereas only a minor fraction of topo IIβ becomes chromosome-associated late in the mitosis (Christensen et al 2002).

Topoisomerases are valuable targets for cancer chemotherapeutic agents (Sonneveld 1996). Several topoisomerase inhibitors have been introduced into cancer clinics as potent anti-cancer compounds (Hsiang et al 1985; Pommier et al 1998). Two general classes of topoisomerase inhibitors have been described (Umemura et al 2003): classical topoisomerase poisons (Liu et al 2000; Denny & Baguley 2003) that stabilize the cleavable complexes and stimulate single- or double-stranded DNA cleavage, such as camptothecin and its derivatives, indolocarbazoles for topo I, and TAS-103 for topo I and topo II; and catalytic inhibitors that prevent the catalytic cycle of the enzymes at steps other than cleavage intermediates, such as aclarubicin (Jensen et al 1991), intoplicine (Riou et al 1993) and F11782 (Jensen et al 2003).

Mutations that reduce the catalytic activity or nuclear content of topo I and topo II result in drug resistance (Lang et al 1998; Snapka et al 2001), which may also be accompanied by an increase in Pgp content and glutathione cycle disorders (Nooter & Stoter 1996; Martinchick et al 1997). Some authors label this type of MDR as atypical MDR (at-MDR) (Fry et al 1991; Van der Zee et al 1991).

MDR reversing by pharmacological modulation

In 1981, Tsuruo et al were the first to report on the possibility of breaking multidrug resistance. They demonstrated that verapamil and trifluoropyrazin increase the cellular concentration of vincristine and vinblastine in resistant leukaemic cells in a mouse (Tsuruo et al 1981; Krishna & Mayer 2000). Since this discovery was made, the existence of numerous MDR-reversing agents has been reported (Barancík et al 2001; Kimura et al 2002; Norman et al 2002). Most of the chemosensitizers described until now may be divided into six groups according to their basic pharmacological activity (Ford 1996) (Table 3).

The structural diversity of these compounds suggests that several mechanisms of MDR modulation might exist. It is most commonly assumed that chemosensitizers block cytotoxic drug efflux by acting as competitive or non-competitive inhibitors, possibly by binding to similar drug substrate binding sites, or to other chemosensitizers binding sites, causing allosteric changes that result in the inhibition of binding or transport of the cytotoxic drug (Ford 1996). As a result, the efflux of drugs from the cell is inhibited and their intracellular concentration increases.

However, results in this field are controversial, and seem to be dependent on the modulators and cell lines used in the tests. Research has demonstrated that treatment with verapamil decreases the Pgp level in leukaemic multidrug resistant cell lines (Muller et al 1994), whereas verapamil, nifedipine and ciclosporin induce an increase in the Pgp level in the human colon carcinoma cell lines (Herzog et al 1993). The results of this research demonstrate that particular chemosensitizers display different mechanisms of action. Nowadays much research concentrates on ciclosporin and verapamil analogues with the assumption that such substances would be efficient MDR modulators and they would not cause side effects.

Ciclosporin Ciclosporin belongs to a family of lipophilic undecapeptides, which are common metabolites of fungi from the *Beauveria, Verticillium* and *Tolypocladium* generae (Podsiadlowski et al 1998). Ciclosporin is used in lower concentrations than other chemosensitizers ($\sim$0.5–3 μM) (Ford 1996; Ruiz et al 2000).

Bamdad et al (1999) have suggested that the accumulation of adriamycin, rhodamine-123, benzo(a)pyrene and 7,12-dimetylobenzoanthracene in ciliate cells, *Tetrahymena pyriformis*, is significantly enhanced in the presence of ciclosporin. Larrivée & Averill (1999) have proved that ciclosporin can increase the intracellular accumulation of melphalan in Chinese hamster ovary cells.

Table 3 Selected pharmacological agents with ability to reverse multidrug resistance

Calcium-channel blockers	Verapamil, dexniguldipine, gallopamil, Ro11-2933, PAK-200, diltiazem
Immunosuppressants	Ciclosporin, SDZ PSC 833, SDZ 280-446, FK506, rapamycin
Calmodulin antagonists	Trifluoroperazine, fluphenazine, *trans*-flupentixol, pimozide
Vinca rosa alkaloid analogues	Vindoline, thaliblastine
Inhibitors of protein kinase	Calfostin C, staurosporin, CGP 41251, NPC 15437, safingol
Steroidal agents	Progesterone, tamoxifen, toremifene, megestrol acetate
Different compounds	S 9788, GF120918, tolyporphin, dipyridamole, and others

(Ford 1996; Teodori et al 2002; Yu et al 2003).

Further findings suggest that the combination of ciclosporin and hyperthermia could be very useful in overcoming melphalan resistance by increasing intracellular drug accumulation in MDR cells. Ushigome et al (2000) have shown that the uptake of vinblastine, vincristine and digoxin into human placental choriocarcinoma epithelial cells (BeWo cells) was significantly enhanced in the presence of ciclosporin. Also, intracellular concentration of propanolol has increased after application of this chemosensitizer. Clinical trials conducted by Davidson suggest that a high dose of ciclosporin combined with epirubicin, vincristine and etoposide has caused cancer to regress in 6 of 12 patients with neuroblastoma (Davidson et al 2002).

Not all results have demonstrated efficacy of ciclosporin in overcoming multidrug resistance. According to certain papers, ciclosporin increases the concentration of doxorubicin in brain carcinoma cells (Saito et al 2001; Zhao et al 2002). Other studies have shown that ciclosporin does not modify the brain permeability of doxorubicin (Rousselle et al 2000; Zhao et al 2002). The reason for the discrepancies among these reports might be different methods used or too small a concentration of ciclosporin. It is also reported that doxorubicin in combination with Pgp inhibitor (S9788) induces disruption of the blood–brain barrier in-vitro (Fenart et al 1998). Therefore, the observed increase in the brain penetration of doxorubicin may also be partially explained by blood–brain barrier disruption after co-administration with ciclosporin. The ciclosporin-induced increase in the plasma and brain concentration of doxorubicin might also be caused by reduction of Pgp-mediated biliary and renal excretion of doxorubicin since it is known that Pgp plays a role in the biliary and urinary excretion of doxorubicin (Van Asperen et al 2000; Saito et al 2001).

A large problem in therapy with ciclosporin is its toxicity, which depends on the dose used and is manifested through extended myelosuppression, nausea, vomiting and hyperbilirubinaemia (Kochi et al 2000). That is why second-generation drugs are promising in tumour treatment; in the majority of cases they are characterized by lowered toxicity (e.g., SDZ PCS 833 and SDZ 280-446 preparations (Teodori et al 2002)). The substances are efficient in in-vitro tests in a concentration of approximately 0.1 μM (Litman et al 2001).

Verapamil Verapamil belongs to the family of calcium-channel blockers (Walles et al 2002). Nielsen et al (2002) and Muller et al (1994) reported a decrease in the expression of Pgp in a human MDR leukaemia cell line treated with verapamil. They found decreased transcription of mdr1 in leukaemic cells after treatment with verapamil. Similarly Futscher et al (1996) found that application of verapamil during therapy with doxorubicin caused inhibition of Pgp expression. These results contradict those of Chaudhary & Roninson (1993), which showed that treatment with verapamil increased the expression of the mdr1 gene in leukaemia cells. Similarly, Herzog et al (1993) reported an increase in the expression of mdr1 in human colon carcinoma cell lines treated with different calcium-channel blockers. These differences can be explained by the recent results of Yu et al (2003), who found that verapamil did not reverse drug resistance if administered together with other anti-cancer drugs, but was effective when used as a pre-treatment. The calcium-channel blocker took effect only after cells were exposed to it for a certain time. Studies have shown that application of low intakes of verapamil increases doxorubicin toxicity, most probably through the interaction of the two drugs (being Pgp substrates) with Pgp present in healthy tissues (Candussio et al 2002). For that reason, the researchers seek analogues that would not show such properties (e.g., dexverapamil, RO 11-2933 and RO11-5160 (Chandra et al 2002)).

Beside the toxic effect of chemosensitizers, there are other reasons for the failure of a MDR modulator in the clinical treatment, namely that the chemosensitizer may increase the toxicity of the co-administered anti-tumour drug, the chemosensitizer may not reach the tumour, the tumour may have multiple mechanisms of resistance, or inappropriate patients may have been used in clinical trials (Xia & Smith 2001).

Current research

Presently, different research centres are searching for other alternative MDR-breaking methods: development of new agents sensitive to drug resistance cancer cells; development of agents that show collateral sensitivity to drug resistance cancer cells; combination of other agents that modulate resistance markers and increase the

sensitivity of drug resistant cancer cells; development of anti-angiogenesis therapy and gene therapy for drug resistant cancer cells. These aims may be enhanced by the development of more appropriate experimental models for clinically relevant tumour resistance mechanisms. At the same time, it is important to develop technologies that facilitate measurement of target expression and activity within individual patients; this may simplify interpretation of clinical effects seen with resistance modulators (Garraway & Chabner 2002). Modalities that allow real-time, in-vivo analysis of transporter function may prove useful in determining in-situ activity of the resistance mechanism in question (Luker et al 1997). Finally, the advent of proteomics and other genome-scale approaches for the global analysis of cancer biology may accelerate the identification and characterization of previously unrealized mechanisms responsible for tumour drug resistance (Hutter & Sinha 2001).

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