Patients who have cancer that does not respond to local excision or radiation (about 50% of total cancer cases), and patients with haematological malignancies, are treated with chemotherapy, immunotherapy and biological-response modifiers. But why can some patients be cured by these approaches and others respond transiently or incompletely? Host and tumour genetic alterations, epigenetic changes and tumour environment all seem to contribute to the complex story of cancer drug resistance.

Cellular mechanisms of multidrug resistance

There are two general classes of resistance to anticancer drugs: those that impair delivery of antitumour therapies to tumour cells, and those that arise in the cancer cell itself due to genetic and epigenetic alterations that affect drug sensitivity. Impaired drug delivery can result from poor absorption of orally administered drugs, increased drug metabolism or increased excretion, resulting in lower levels of drug in the blood and reduced diffusion of drugs from the blood into the tumour mass. Recent studies have emphasized the importance of the tumour vasculature and an appropriate pressure gradient for adequate drug delivery to the tumour. In addition, some cancer cells that are sensitive to chemotherapy as monolayer cells in culture become resistant when transplanted into animal models. This indicates that environmental factors, such as the extracellular matrix or tumour geometry, might be involved in drug resistance. Cancer cells grown in culture as three-dimensional spheroids, mimicking their in vivo geometry, have also been shown to become resistant to cancer drugs. Much remains to be learned about this type of drug resistance and its role in clinical oncology.

Cellular mechanisms of multidrug resistance have been intensively studied, as experimental models can be easily generated by in vitro selection with cytotoxic agents. Cancer cells in culture can become resistant to a single drug, or a class of drugs with a similar mechanism of action, by altering the drug's cellular target or by increasing repair of drug-induced damage, frequently to DNA. After selection for resistance to a single drug, cells might also show cross-resistance to other structurally and mechanistically unrelated drugs — a phenomenon that is known as multidrug resistance. This might explain why treatment regimens that combine multiple agents with different targets are not more effective.

As illustrated in Fig. 1, different types of cellular multidrug resistance have been described. Resistance to natural-product hydrophobic drugs — sometimes known as classical multidrug resistance — generally results from expression of ATP-dependent efflux pumps with broad drug specificity. These pumps belong to a
Multidrug resistance of cancer cells is a potentially surmountable obstacle to effective chemotherapy of cancer.

- ATP-binding cassette (ABC) transporters, including MDR1 (ABCB1), MRP1 (ABCC1) and ABCG2, can confer multidrug resistance to cancer cells in vitro.
- MRP2 (ABCC2), MRP3 (ABCC3), MRP4 (ABCC4), MRP5 (ABCC5), ABCA2 and BSEP (ABCB11) are capable of transporting drugs; future studies are needed to determine a role in drug resistance.
- ABC transporters such as MDR1 and MRP1 are expressed in many human cancers, including leukemias and some solid tumours; in some studies, expression of these transporters has been shown to correlate with response to therapy and survival.
- Inhibitors of ABC transporters such as MDR1/P-glycoprotein have been tested in clinical trials with a suggestion of benefit, especially in acute myelogenous leukaemia.
- Interpretation of clinical trials using inhibitors of MDR1/P-glycoprotein has been confounded by their effects on the pharmacokinetics of anticancer drugs.
- Development of inhibitors of ABC transporters should focus on potency and specificity to minimize unexpected pharmacokinetic effects.
- Efficacy should be confirmed using surrogate assays.
- Normal tissues might be protected from toxicity by gene transfer of drug-resistance genes.
- Prevention of ABC transporter induction in cancer cells might help to avert drug resistance.

**Summary**

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**MULTIDRUG RESISTANCE**

Simultaneous resistance to several structurally unrelated drugs that do not have a common mechanism of action.

**VINCA ALKALOIDS**

A family of natural-product anticancer drugs, extracted from the periwinkle family, that depolymerize microtubules. Examples include vincristine and vinblastine.

**ANTHRACYCLINES**

Semi-synthetic anticancer derivatives of anthraquinone that intercalate into DNA and inhibit DNA topoisomerase II. Examples include daunorubicin and doxorubicin.

**CYTOCHROME P450**

A group of enzymes that are located on the endoplasmic reticulum, and are involved in drug metabolism and detoxification. They are primarily expressed in the liver and small intestine.

**MULTIFACTORIAL MULTIDRUG RESISTANCE**

Multidrug resistance caused by several different mechanisms of resistance that operate simultaneously.

Family of ATP-binding cassette (ABC) transporters that share sequence and structural homology. So far, 48 human ABC genes have been identified and divided into seven distinct subfamilies (ABCA–ABCG) on the basis of their sequence homology and domain organization.

Resistance results because increased drug efflux lowers intracellular drug concentrations. Drugs that are affected by classical multidrug resistance include the vinca alkaloids (vincristine and vincristine), the anthracyclines (doxorubicin and daunorubicin), the RNA transcription inhibitor actinomycin-D and the microtubule-stabilizing drug paclitaxel.

Resistance can also be mediated by reduced drug uptake. Water-soluble drugs that ‘piggyback’ on transporters and carriers that are used to bring nutrients into the cell, or agents that enter by means of endocytosis, might fail to accumulate without evidence of increased efflux. Examples include the antifolate methotrexate, nucleotide analogues, such as 5-fluorouracil and 8-azaguanine, and cisplatin.

Multidrug resistance can also result from activation of coordinately regulated detoxifying systems, such as DNA repair and the cytochrome P450 mixed-function oxidases. Indeed, coordinate induction of the multidrug transporter P-glycoprotein (PGP) and cytochrome P450 3A has been observed. This type of multidrug resistance can be induced after exposure to any drug. Recent evidence indicates that certain orphan nuclear receptors, such as SXR, might be involved in mediating this global response to environmental stress.

Finally, resistance can result from defective apoptotic pathways. This might occur as a result of malignant transformation; for example, in cancers with mutant or non-functional p53. Alternatively, cells might acquire changes in apoptotic pathways during exposure to chemotherapy, such as alteration of ceramide levels or changes in cell-cycle machinery, which activate checkpoints and prevent initiation of apoptosis.

An important principle in multidrug resistance is that cancer cells are genetically heterogeneous. Although the process that results in uncontrolled cell growth in cancer favours clonal expansion, tumour cells that are exposed to chemotherapeutic agents will be selected for their ability to survive and grow in the presence of cytotoxic drugs. These cancer cells are likely to be genetically heterogeneous because of the mutator phenotype. So, in any population of cancer cells that is exposed to chemotherapy, more than one mechanism of multidrug resistance can be present. This phenomenon has been called multifactorial multidrug resistance.

**ATP-dependent transporters**

Selection of cancer cells in culture with natural-product anticancer drugs, such as paclitaxel, doxorubicin, or vinblastine, frequently results in multidrug resistance that is due to expression of the ABC transporter PGP, the product of the ABCB1 (or MDR1) gene. PGP is a broad-spectrum multidrug efflux pump that has 12 transmembrane regions and two ATP-binding sites (Fig. 1). 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. Two ATP hydrolysis events, which do not occur simultaneously, are needed to transport one drug molecule. Binding...
of substrate to the transmembrane regions stimulates the ATPase activity of PGP, 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. Hydrolysis at the second ATP site seems to be required to "re-set" the transporter so that it can bind substrate again, completing one catalytic cycle.

PGP efficiently removes cytotoxic drugs and many commonly used pharmaceuticals from the lipid bilayer. Its broad substrate specificity presumably reflects a large, polymorphous drug-binding domain or domains within the transmembrane segments. Because PGP binds many different hydrophobic compounds, it has been easy to find potent PGP inhibitors. Two inhibitors that are used in the laboratory and in clinical trials that attempted to reverse drug resistance are the calcium channel blocker verapamil and the immunosuppressant cyclosporin A.

As not all multidrug-resistant cells express PGP, a search for other efflux pumps was initiated, leading to the discovery of the multidrug-resistance-associated protein 1 (MRP1, or ABCC1). MRP1 is similar to PGP in structure, with the exception of an amino-terminal extension that contains five-membrane-spanning domains attached to a PGP-like core (FIG. 2). MRP1 recognizes neutral and anionic hydrophobic compounds, and transfers glutathione and other conjugates of these drugs, or, in some cases — such as for vincristine — co-transports unconjugated glutathione. The discovery of MRP1 stimulated a genomic search for homologues, leading to the discovery of eight additional members of the ABCB subfamily of transporters, of which six have been studied in some detail. Like MRP1, some of these MRPs have the five-transmembrane amino-terminal extension (ABCC2, ABCC3 and ABCC6, also named MRP2, 3, and 6), whereas others do not. Many MRP family members transport drugs in model systems and therefore have the potential to confer drug resistance.

Some anticancer drugs, such as mitoxantrone, are poor substrates for MDR1 and MRP1. Selection for mitoxantrone resistance results in multidrug-resistant cells that produce a more distant member of the ABC transporter family, ABCG2 — also known as MXR (mitoxantrone-resistance gene), BCRP (breast cancer resistance protein) or ABC-P (ABC transporter in placenta). This transporter is thought to be a homodimer of two half-transporters, each containing an ATP-binding domain at the amino-terminal end of the molecule and six transmembrane segments (FIG. 2). The first two original ABCG2 genes that were cloned from resistant cells encoded proteins with either a threonine or glycine substituted for arginine at amino acid 482, giving them much broader substrate specificity, including the ability to transport doxorubicin. This finding, together with many well-documented mutations in PGP, shows that even single amino-acid substitutions can change substrate specificity.

Other ABC family members have been associated with drug resistance. For example, the bile salt export protein (BSEP, also known as ABCB11), first reported as the "sister of PGP" (SPGP), is expressed at high levels in liver cells, and in transfection experiments it confers low-level resistance to paclitaxel. MDR3 (sometimes called MDR2), a phosphatidylcholine flippase that is closely related to PGP, normally transports phospholipids into bile, but can transport paclitaxel and vinblastine, albeit inefficiently unless it is mutated. Finally, ABCA2 is overexpressed in estramustine-resistant cells. Estramustine is a nitrogen mustard derivative of oestradiol, so ABCA2 — which is expressed intracellularly in endosomal/lysosomal vesicles — might participate in steroid transport.

Although the lung resistance protein (LRP) is not an ABC transporter, it is frequently included in discussions of drug resistance, as it is expressed at high levels in drug-resistant cell lines and some tumours. LRP is a major vault protein found in the cytoplasm and on the nuclear membrane. Vaults are large ribonucleoprotein particles that are present in all eukaryotic cells. Their shape is reminiscent of the nucleopore central plug, and the major vault proteins account for 70% of their mass. Although their role in normal physiology is not yet established, vaults may confer drug resistance by redistributing drugs away from intracellular targets.

**ABC transporters in normal cells**

Although many ABC transporters have been identified as drug-resistance proteins, they are all expressed in normal tissues. Consistent with their wide distribution, it is becoming clear that in addition to exogenously administered drugs, ABC proteins transport numerous endogenous substrates.
ABC transporters have an important role in regulating central nervous system permeability. The brain is protected against blood-borne toxins by the blood–brain barrier (BBB), and the blood–cerebrospinal-fluid (CSF) barrier. The BBB is formed by the endothelial cells of capillaries, with PGP located on the luminal surface, preventing the penetration of cytotoxins across the endothelium\(^\text{29,30}\). MRP proteins such as MRP1 are localized to the basolateral membrane of the choroid plexus, where they serve to pump the metabolic waste products of CSF into the blood\(^\text{24,60–63}\). ABC transporters also seem to protect testicular tissue and the developing fetus in a similar manner. In the testis, as in the brain, PGP transports toxins into the capillary lumen. MRP1, on the other hand, is localized on the basolateral surface of Sertoli cells, protecting sperm within the testicular tubules. In the placenta, PGP is localized on the apical syncytiotrophoblast surface, where it can protect the fetus from toxic cationic xenobiotics\(^\text{31}\). MRP family members and the half-transporter ABCG2 are also localized in placenta\(^\text{32,34}\). MRP1 and other isoforms might be involved in protecting fetal blood from toxic organic anions and excreting glutathione/glucuronide metabolites into the maternal circulation\(^\text{35}\).

Whereas ABC transporters are expressed in the brain, testis and placenta to protect these ‘sanctuaries’ from cytotoxins, the liver, gastrointestinal tract and kidney use them to excrete toxins, protecting the entire organism. PGP is localized in the apical membranes of hepatocytes, where it transports BILIRUBIN-glucuronide and other organic anions into bile\(^\text{55}\). Mutations that disrupt MRP2 function cause bilirubin accumulation.
and jaundice in rats60,61 and in patients with Dubin–Johnson syndrome26,65. Mutations in BSEP are associated with progressive familial intrahepatic cholestasis type-2, which is characterized by reduced secretion of bile salts and hepatic failure64,65. Finally, MDR2 functions as a phosphatidylcholine trans-locase, which reduces the toxicity of bile salts66. Loss of MDR2 function results in progressive familial intrahepatic cholestasis type-3 (REFS 31, 67).

In the gastrointestinal tract, PGP is localized in apical membranes of mucosal cells, where it extrudes toxins, forming a first line of defence. Increased tissue concentrations of PGP substrates in Pgp substrates in Mdr1a/Mdr1b-knockout mice indicate that PGP might have a significant role in determining oral drug bioavailability. Studies have shown increased tissue absorption of putative PGP substrates following oral administration when a PGP inhibitor is administered concurrently66–70. Additionally, PGP actively secretes intravenously administered drugs into the gastrointestinal tract67. In contrast to PGP, Mrp1 is located in the basolateral membrane of mucosal cells, and therefore transports substrates into the interstitium and the bloodstream, rather than across the apical surface into the intestinal lumen2. Consistent with the absence of expression on the apical surface, Mrp1-null mice have not been found to have alterations in drug pharmacokinetics72. Mrp2, on the other hand, localizes to the canalicular membrane of hepatocytes and the apical surface of epithelial cells, and has a primary role in the excretion of bilirubin-glucuronide. Studies confirmed that Mrp2 was capable of mediating drug efflux, and a recent study showed increased bioavailability of a food-derived carcinogen — 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine — in Mrp2-null rats8. This indicates that Mrp2, like PGP, might also regulate drug bioavailability.

**ABC transporters in human cancers**

Although it seems likely that cancer cells use several different types of ABC transporter to gain drug resistance, most clinical studies have focused on PGP. Early studies showed that PGP was highly expressed in colon, kidney, adrenocortical and hepatocellular cancers73,74. Initially, there was hope that increases in PGP expression alone would explain cancer drug resistance. However, the failure of these cancers to respond to drugs that are not PGP substrates indicated that other factors are involved, and attention turned to cancers that acquire resistance following chemotherapy. In seeking to define the role of PGP in drug resistance, researchers have assumed that PGP expression is highest in tumours that are dependent on expression for survival, that expression impairs response to chemotherapy, and that expression levels increase as tumours become drug resistant. On the basis of these assumptions, clinical trials aimed at increasing chemotherapy sensitivity in drug-resistant tumours, through inhibition of PGP, have been implemented.

So, does PGP expression confer drug resistance in human cancer? Most studies that correlate PGP expression with clinical outcome have been small, retrospective, single-institution studies with insufficient power to draw reliable conclusions8. One problem with designing a study that provides statistically valid results is that methods for detecting PGP expression are imperfect. This is primarily due to the lack of specificity of many commonly used anti-PGP antibodies. To complicate matters, researchers also use different methods to quantify expression, to control for tumour heterogeneity, and to account for the presence of normal tissue in tumour biopsies8. Despite efforts to bring uniformity to PGP quantification, it is still difficult to discern valid from invalid data.

Expression of Mrp1 has also been analysed in clinical samples. Antibodies against Mrp1 seem to be more specific than those that recognize PGP9, and Mrp1 is highly expressed in leukaemias, oesophageal carcinoma and non-small-cell lung cancers8. Conclusions about expression levels of other ABC transporters in human tissue await more extensive analysis.

**Leukaemia.** The most uniform associations between MDR1/PGP expression and drug resistance have been reported in acute myelogenous leukaemia (AML). PGP expression has been reported in leukaemic cells from about one-third of patients with AML at the time of diagnosis, and more than 50% of patients at relapse; higher levels occur in certain subtypes, including secondary leukaemias81–85. PGP expression is correlated with a reduced complete remission rate, and a higher incidence of refractory disease — a surprising finding, as treatment regimens include not only the PGP substrate daunorubicin, but also AraC, which is not a PGP substrate62,64–66. Recent studies report that PGP expression is associated with a poorer prognosis, although the magnitude of the effects on response and survival is probably not as great as initially thought. These clinical results are supported by ex vivo studies of leukaemic cells, which have shown that PGP expression reduces the intracellular accumulation of daunorubicin60,65. In addition, administration of a PGP inhibitor increases daunorubicin accumulation in leukaemic cells8.

Mrp1 and LRP expression have also been evaluated in leukaemia. Increased Mrp1 expression has been reported in chronic lymphocytic and prolymphocytic leukaemia cells86. Expression levels are less frequently elevated in AML cells (10–34%)81,82,89, and these studies lead to different conclusions about whether Mrp1 confers a poor prognosis. So far, the largest trial in untreated patients found no correlation between Mrp1 or LRP expression and prognosis, but observed a correlation between PGP expression and prognosis81. Finally, low expression levels of BCRP/ MXR have been observed in AML cells81. Taken together, the clinical data support a role for PGP in drug resistance in AML patients, and for Mrp1 expression in chronic lymphocytic and prolymphocytic leukaemias. Additional studies are needed to confirm and extend these findings.

**Breast cancer.** Detection of transporters in solid tumour samples has been more difficult. A 1997 meta-analysis of 31 reports from 1989–1996 found that 41%
of breast tumours expressed PGP^21. PGP expression increased after therapy and was associated with a greater likelihood of treatment failure. However, there was considerable interstudy variability—a finding that has persisted in the reports since 1996 (REFS 93,96,97,159–161), preventing a solid conclusion about the role of PGP in breast cancer. Recent imaging studies using ^99m^Tc (technetium)-sestamibi (Cardiolite), a transport substrate recognized by PGP, indicate that its activity is increased in breast carcinomas^95–97.

Whether the MRP1 expression levels associated with breast cancer are enough to confer drug resistance is not yet resolved^98,99. As MRP1 is expressed ubiquitously, it is not surprising that using reverse transcriptase polymerase chain reaction (RT—PCR), MRP1 mRNA can be detected in all breast cancer samples at levels comparable to that in normal tissues. One immunohistochemical analysis of a series of resected invasive primary breast carcinomas reported a correlation between relapse-free survival and MRP1 expression^98.

**Other solid tumours.** Variability in expression is also a problem for other solid tumours. In ovarian cancer samples, 16–47% were found to express PGP, as measured by immunohistochemistry^162–164. Critical analysis of these data reveals that PGP is expressed by only about 20% of ovarian cancers when samples were taken at diagnosis. This makes it difficult to demonstrate a correlation between expression and outcomes, such as disease-free survival, particularly given the importance of cisplatin in therapy.

In lung cancer samples, *MDR1* mRNA expression was reported to be increased in 15–50% of tumours^99–101. The incidence of MRP1 expression is much higher (about 80%) in small-cell lung cancer (SCLC) samples. MRP1 expression was detected in 100% of non-small-cell lung cancers (NSCLC), with higher levels noted in 30% of the samples — this might not be surprising, given its ubiquitous expression in normal lung tissue^101,102. Immunohistochemical studies confirmed the predominantly plasma-membrane localization pattern of MRP1 (REF 103). Given the low levels of *MDR1* expression and the nearly ubiquitous expression of MRP1, lung cancer should be an excellent model in which to evaluate the role of MRP1-specific inhibitors.

**Sarcomas** represent another malignancy in which PGP expression seems to be important for drug resistance. Immunohistochemical studies of both soft-tissue sarcomas and osteosarcomas revealed a strong association between PGP expression, relapse-free survival and overall survival^104,105. Other methodologies, however, have used to substantiate and refute these findings, and there has been no consensus regarding the effect of PGP on survival in sarcomas^106–110.

**Pharmacokinetic interactions.** Interpretation of clinical trials involving inhibitors of MDR1/PGP has been confounded by their effects on the pharmacokinetics of anticancer drugs. Because PGP inhibitors increase serum levels of anticancer drugs^112,113, researchers reduced the doses of anticancer drugs given to patients. The hope was that these dose reductions would result in similar drug concentrations. However, two studies administering paclitaxel in combination with FSC-833 found that a significant fraction of patients were undertreated^117,118. Further evidence for
A subset of circulating lymphocytes, known as natural killer cells, that express the CD56 antigen. They are used to test drug effectiveness in clinical studies because they express high levels of MDR1/P-glycoprotein.

underdosing can also be inferred from other trials. If these are representative of most studies, and there is no reason to believe otherwise, it indicates that a significant fraction of patients have been underdosed. In a disease such as AML, this would have adverse consequences. Furthermore, another fraction of patients were probably overdosed, increasing the morbidity and mortality in those individuals receiving the PGP inhibitor.

The pharmacokinetic complications associated with PGP inhibitors might be due to the fact that they inhibit other proteins involved in drug metabolism, such as cytochrome P450. Or, for example, PSC-833 and cyclosporin A inhibit BSEP and reduce the secretion of bile salts, so they might reduce bile flow and slow hepatic excretion of chemotherapeutic agents.

Pharmacokinetic interactions seem to be most pronounced in patients treated with PSC-833 and cyclosporin A, although they have been reported in patients treated with verapamil, dexamethasone, nifedipine and VX-710. The effect varies depending on the anticancer drug used in conjunction with the inhibitor, or even whether the parent drug or a metabolite is administered.

After nearly 15 years and dozens of studies, there is no definitive answer to the question: can a PGP inhibitor effectively reverse drug resistance in humans? The pharmacokinetic interactions observed with these agents have made it difficult to interpret efficacy. PGP inhibitors with fewer pharmacokinetic interactions are being developed, and surrogates are being used to determine the optimal dose of PGP inhibitor needed (Box 1).

A surrogate assay for PGP inhibition.

This assay uses flow cytometry to test the ability of human CD56+ cells — which express high levels of the efflux pump P-glycoprotein (PGP) — to retain the PGP substrate rhodamine after exposure to the efflux pump inhibitor PSC-833. The number of cells is indicated on the y axis, and intracellular rhodamine fluorescence intensity is indicated on the x axis. a Cells that were never incubated in rhodamine have very low levels of fluorescence (blue line). When cells taken from a patient who has not yet been treated with PSC-833 are incubated in rhodamine, and then allowed a 30-min period of efflux in rhodamine-free medium, they begin to lose fluorescence (yellow line). When the same cells are loaded with rhodamine and also treated with the PGP inhibitor PSC-833, they are highly fluorescent after 30 mins in rhodamine-free medium (red line). b Cells taken from the same patient have high levels of intracellular fluorescence (red line) 2 and 24 hours after initiation of a continuous intravenous infusion of PSC-833.
Several studies show a correlation between PGP expression in cancer patients and increased 99mTc-sestamibi accumulation in tumours has been observed following administration of PGP inhibitor XR-9576 (Tariquidar). However, it is important to remember that 99mTc-sestamibi is a substrate for MRP as well as for PGP.

Future prospects

Detailed knowledge about the causes of drug resistance might make it possible, in the future, to predict the response of a human cancer to chemotherapy. Once all the main causes of drug resistance have been catalogued and molecular probes have been defined, it should be possible to determine their expression in individual cancer cells, obtained by either microdissection or from pathological sections. Even specific mechanisms of resistance expressed in a subpopulation of cells might be ascertained in this way. By enhancing detection capabilities, the likelihood of predicting the sensitivity or resistance of a cancer might be improved. DNA microarray analysis will improve our ability to determine which drug-resistance and drug-metabolizing genes are upregulated in different tumours, and these results can then be correlated with clinical responses to specific types of chemotherapy.

The primary goal of clinical trials has been to reverse existing drug resistance. A trial approach that has not been thoroughly examined is one that aims to prevent the emergence of drug resistance. In the laboratory, selection of resistant cells usually begins with low drug concentrations, which are then gradually advanced. Using high concentrations at the outset markedly reduces the number of resistant clones that are isolated. Because drug transporters effectively reduce drug exposure, they can facilitate development of drug resistance without themselves conferring high levels of resistance. So, a potentially effective strategy to prevent the emergence of drug resistance is to increase the intracellular concentration of chemotherapeutic agents by administering a transport inhibitor at the beginning of treatment. Several in vitro models support such a strategy. For example, in single-step selections, co-administration of an inhibitor has been shown to reduce the rate of mutations that cause doxorubicin resistance to a tenth of the rate in the absence of an inhibitor, while suppressing the emergence of PGP-expressing resistant cells.

It must be emphasized, however, that in a trial design that aims to prevent the emergence of drug resistance, significant differences in patient response rates might not be observed. Instead, only differences in the rate of relapse and time to progression would be anticipated. The latter would occur because a prevention strategy does not target most of the cells in a tumour, but only a small subpopulation, and hence does not significantly alter the initial cell kill. Such an outcome has been reported in a study in which cyclosporin A was added to daunorubicin and Ara-C in the initial treatment of patients with AML. Although this combination regimen had no impact on the complete remission rate, the overall survival and the disease-free survival were improved.

Clinical evidence indicates that PGP expression can be induced by drug exposure. In one study in which biopsies were obtained surgically at the beginning and end of a lung perfusion with doxorubicin, PGP levels increased 3–15-fold, showing that tumours adjust rapidly to anticancer drugs. Similar observations have been made in patients receiving the histone deacetylase inhibitor vorinostat.
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