Regional Cancer Therapy

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Regional Cancer Therapy

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Foreword by

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Foreword

Regional cancer therapies remain important options in the management of malignant disease, in spite of the venue of more targeted agents for systemic therapies. New technologies and better guidance systems for radiofrequency ablation and intrastitial laser therapies, highly selective intravascular approaches with improved catheters and guidance systems, improved agents for embolizations, and new vasoactive drugs for isolated limb and liver perfusions are just a few of the new developments in a field that is alive and progressing.

Regional Cancer Therapy, so well put together by the editors Peter M. Schlag and Ulrike S. Stein, presents an overview of today's realities and tomorrow's possibilities. Regional cancer therapy models provide ways to make new discoveries about tumor biology and new agents that may be used regionally as well as systemically. This book should therefore be of interest to all clinicians and scientists with an interest in tumor biology as well as clinical advances.

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PREFACE

The treatment of malignant tumors has been substantially improved in recent years due to developments in clinical medicine and technology as well as by advances in molecular biological research. Modern molecular and genetic techniques allow the characterization of molecules that are decisive for tumor development and progression. Considerable success has been achieved in selected solid tumors using molecular-targeted therapies, e.g., for GIST treated with Gleevec or breast cancer treated with Herceptin. These remain, perhaps, the most successful examples of molecular-targeted systemic cancer therapies. Avastin, acting to inhibit VEGF signaling, is another example with apparently wider utility, owing to the more general importance of angiogenesis in tumor biology. Therapies directed against the process of metastasis could potentially provide an additional dimension to therapeutic regimens in the future.

Curative treatment requires control of both local and systemic disease. Advances in diagnostic procedures have made it possible to more accurately assess the distribution and extent of malignant disease and define a role for both surgery and regional therapy in modern cancer treatment. The concept of regional cancer therapy aims at a targeted destruction of a tumor disease that is not accessible by classical surgical tumor resection or radiotherapeutic ablation. Modern regional tumor therapy, based on progress in technology and research, will contribute to new dimensions in this exciting field of oncology.

Regional Cancer Therapy describes findings and technical features of regional tumor therapy with diverse facets considered for various tumor entities and locations. New developments and conceptual formulations are presented with respect to both tumor biology and technical aspects. Clinical trial concepts and treatment protocols currently employed to improve regional tumor therapy are discussed in this book in detail. Thus, the book represents not only a therapeutic vade mecum for the current possibilities for effective regional tumor therapy, but also provides numerous suggestions for future advances. The book will be of value not only for clinical oncologists, but also for scientists who are interested in the fundamentals of regional tumor therapy as it relates to optimizing translational approaches.

Regional tumor therapy, in general, is an excellent example of an interdisciplinary strategy. Thus, not only the classical oncological disciplines, such as surgical oncology, radiotherapy, and medical oncology, but also interventional radiology and nuclear medicine, and medical students and other medical support staff will benefit from reading *Regional Cancer Therapy.*

The editors are very thankful to all authors for their valuable contributions, which provide a thorough description of the concepts of regional cancer therapy. This enabled us to bring the reader a balanced book where all sides of the regional cancer therapy issues are covered fairly. We hope that *Regional Cancer Therapy* will stimulate interest and rapid advances in the important field of regional cancer therapy for the improved treatment of patients.

Peter M. Schlag, *MD, PhD*
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I Background

1 Biological Background

Multidrug Resistance—Clinical Implications

Ulrike S. Stein, PhD, Wolfgang Walther, PhD, and Peter M. Schlag, MD, PhD*

CONTENTS

SUMMARY

Drug resistance of human tumors to a variety of chemotherapeutic agents remains the major cause of cancer treatment failure. Although multiple mechanisms of drug resistance may occur in parallel or sequentially at all different levels of drug action, one resistance mechanism was identified within the last two decades that very likely represents the most frequent cause for the development of drug resistance in cancer cells: the phenomenon of multidrug resistance (MDR). MDR, the simultaneous resistance toward structurally and functionally unrelated cytostatic drugs, depends mainly on the presence of different transporter proteins, their genetic polymorphisms, and their regulation/deregulation. Thus, decreased uptake and/or increased efflux, lowered net accumulation, and, in consequence, less efficiency of anticancer drugs is the clinical hurdle.

The biology of the most prominent members of the MDR-associated, membrane-spanning ATP-binding cassette (ABC) transporter proteins (MDR1, MRP1, and BCRP), their transport mechanisms, and the spectra of cytostatic drugs are summarized in this chapter. The clinical importance of these MDR-associated molecules (their basal and therapy-induced expression) is discussed for different solid tumors with respect to clinical outcome parameters. Resistance profiling and response prediction as essential prerequisites for tailor-made, patient-individual MDR reversal as

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well as intervention strategies targeting functional, translational, and transcriptional levels are evaluated.

Key Words: Multidrug resistance; MDR1; MRP1; BCRP; prediction; reversal; inhibitors.

1. INTRODUCTION: DRUG RESISTANCE AND CANCER

Treatment of most locally confined malignant tumors is presently based on surgical and radiotherapeutic approaches. For advanced and metastatic tumors, chemotherapy is the most effective treatment, with clinical success differing from patient to patient. Some patients are cured, others respond transiently, and a third group has incomplete responses. Furthermore, clinical oncologists have noted that cancer patients treated with multiple anticancer drugs developed cross-resistance to many other chemotherapeutics to which they had never been exposed. As a consequence, the possibility of curing these patients with chemotherapy is dramatically reduced *(1,2)*.

Multiple mechanisms of drug resistance may occur in parallel or sequentially at all different levels of drug action, leading to intrinsic (without any treatment) or acquired (therapy-induced) resistance toward cytotoxic drugs. Anticancer drugs have different ways to enter the cell. Uptake of hydrophilic drugs into the cell depends on transporters, carriers, or channels, since these drugs are not able to cross the cell membrane by themselves. Defects in drug uptake proteins lead to reduced influx, resulting in lowered intracellular drug concentration, and the cell becomes resistant to a single drug. Natural anticancer products such as anthracyclines, vinca alkaloids, epipodophyllotoxins, and taxanes are hydrophobic and enter the cell by diffusion across the cell membrane. Resistance toward these drugs develops by increased drug efflux depending on the activity of efflux pumps, such as transmembrane energy (ATP)-dependent transporter proteins. Thus, intracellular drug concentration is reduced; the cell becomes resistant to a panel of hydrophobic drugs. Furthermore, activation of proteins that are involved in metabolism or detoxification of drugs may cause drug resistance without affecting drug accumulation. Intracellular drug redistribution, e.g., the nucleocytoplasmic drug transport by vaults, may contribute to drug resistance. Moreover, cytostatic-induced activation of nuclear proteins such as mismatch repair genes involved in enhanced repair of drug-induced DNA damage may lead to drug resistance. Cells may also become resistant to drug-induced cell death by activation of anti-apoptotic proteins and by affecting the cell cycle and checkpoints *(1–3)*.

Although several mechanisms might be able to contribute to a drug resistance phenotype, one resistance mechanism was identified within the last two decades that very likely represents the most frequent cause for the development of drug resistance in cancer cells: the phenomenon of multidrug resistance (MDR). MDR reflects the ability of a tumor cell to resist typically lethal or sublethal doses of multiple usually cytotoxic drugs. MDR is defined as the simultaneous resistance to structurally and functionally unrelated natural product anticancer drugs. To date, MDR of human tumors to a variety of chemotherapeutic agents still represents the major cause of failure of cancer chemotherapy. Therefore, the need to identify those tumors with high intrinsic and/or therapy-inducible MDR is desired. Patient-individual response prediction and tailor-made reversal of MDR are the ultimate goals to improve cancer chemotherapy.

2. MULTIDRUG RESISTANCE, ABC TRANSPORTERS, AND DRUG TRANSPORT

The development of the MDR phenotype is dependent on expression of MDR-associated genes encoding energy-dependent transmembrane transporter proteins *(4)*. They act as drug efflux pumps, thereby lowering the intracellular concentration of cytotoxic drugs through increased drug efflux. These drug efflux pumps belong to the intensively studied protein superfamily of ATP-binding cassette (ABC) transporter proteins representing the largest gene family of transmembrane proteins *(5)*. The normal physiological functions of these transporters are the protection of epithelial cells (e.g., those of the gastrointestinal tract, liver and kidney) and brain capillaries for the uptake of xenobiotics and the promotion of their excretion in the bile and urine. They also transport multiple classes of anticancer drugs such as anthracyclines, vinca alkaloids, epipodophyllotoxins, taxanes, and others out of the cell, making it multidrug resistant. ABC transporter-mediated drug transport is energy dependent, driven by hydrolysis of ATP *(4)*.

In the human genome, 48 ABC transporters have been identified so far *(5)*. Based on sequence similarities—they share common features such as nucleotide binding sites and transmembrane domains—they have been classified into seven subfamilies by phylogenetic analysis. Important ABC transporters associated with the MDR phenotype are encoded by the following genes:

1. The multidrug resistance gene 1 (MDR1, or ABCB1; subfamily ABCB) encodes P-glycoprotein, causing the so-called classical, P-glycoprotein-mediated MDR.
2. The genes for the multidrug resistance-associated proteins 1, 2, and 3 (MRP1–3, or ABCC1–3; subfamily ABCC) as well as the gene for the breast cancer resistance protein (BCRP); also called ABC transporter in placenta [ABCP] and mitoxantrone resistance gene [MXR or ABCG2; subfamily ABCG] lead to the so-called atypical, non-P-glycoprotein-mediated MDR.

For some of these MDR-associated ABC transporters, a causal role for generation of the MDR phenotype has been demonstrated, e.g., MDR1, MRP1, BCRP; for others, an ability to transport multiple cytotoxic compounds has been shown. The spectrum of anticancer drugs transported by the ABC transporters includes anthracyclines such as doxorubicin, daunorubicin, epirubicin, and mitoxantrone, vinca alkaloids such as vincristine and vinblastine, epipodophyllotoxins such as etoposide and tenoposide, and taxanes such as paclitaxel and docetaxel. Interestingly, the drug spectra of single MDR-associated ABC transporters are overlapping but not identical. Moreover, it has been shown for several transporters that their substrate specificities might vary owing to defined point mutations within their genes.

2.1. MDR1/P-Glycoprotein

The ABCB subfamily of ABC transporters harbors 12 members, with the most prominent being, the MDR1 gene, which was first described about three decades ago *(6,7)*. MDR1/P-glycoprotein is the first cloned human ABC transporter, for which direct generation of the MDR phenotype was shown by gene transduction *(8,9)*. The MDR1 gene encodes P-glycoprotein, a multidrug efflux pump with two nucleotide binding sites and two transmembrane domains each consisting of 12 membrane-spanning α-helices that is

believed to determine the substrate specificity of the drug transported. P-glycoprotein is able to bind a wide spectrum of hydrophobic, neutral, or positively charged substrates, such as anthracyclines, vinca alkaloids, epipodophyllotoxins, and taxanes. After binding of the drug, ATP hydrolysis leads to conformational changes in the protein as an essential prerequisite for release of the substrate out of the cell. Then ATP hydrolysis is necessary for resetting of the transporter molecule *(4,5)*.

MDR1 gene expression has been analyzed in an enormous number of studies. In humans, high expression levels have been repeatedly detected in normal tissues with excretory or secretory functions, such as on the apical surface of columnar epithelial cells of small and large intestines, the biliary canalicular membrane of hepatocytes, the apical surface of epithelial cells of the proximal tubules of the kidney, the apical surface of epithelial cells of the placenta, and the apical surface of endothelial cells in blood capillaries of the brain *(10,11)*. Interestingly, MDR1 expression appears to increase progressively over the total length of the gastrointestinal tract, with low levels in the stomach, intermediate levels in the jejunum, and high levels in the colon *(12)*.

In tumors of these tissues, such as colon, kidney, adrenocortical, and hepatocellular cancers, P-glycoprotein expression is inherently overexpressed, making them primarily chemotherapy-resistant toward a wide panel of anticancer drugs *(12)*. This basically is a major reason for the limited selection of chemotherapeutics to tumors of these organs, e.g., for therapy of gastrointestinal cancer *(1,12–15)*.

Furthermore, in addition to basal expression levels of MDR1, external factors such as components of multimodal cancer therapy are able to induce expression of the MDR1 gene. Thus, cytostatics, but also heat or radiation, might lead to elevation of MDR1 gene expression (e.g., refs. *16–20*). Several studies have shown that in approx 50% of all treated tumors, induction of MDR1 expression has been observed *(21)*. By identification of the MDR1 gene promoter and generation of promoter deletion mutants, drug- and heat-responsive elements have been identified, mediating therapy-caused stress signals into transcriptional activation of the MDR1 gene *(22)*. This is in agreement with the chemotherapy- or hyperthermia-induced elevation of MDR1 gene expression that have been detected in patients. However, single-nucleotide polymorphisms, either of the MDR1 promoter *(23,24)* or of the MDR1 gene *(25)* may alter basal expression levels as well as drug inducibility. Mutations mainly affecting positions 2677 and 3435 of the MDR1 gene were associated with altered P-glycoprotein expression and function. Thus, MDR1 gene polymorphisms may also play a role in patients who do not respond to drug treatment.

Tumors that are more sensitive to chemotherapy show low or intermediate basal MDR1 expression but develop upregulation of MDR1 expression following chemotherapy, which results in the acquired type of drug resistance *(26,27)*. For example, expression of P-glycoprotein was increased after treatment in myeloma (pretreatment/posttreatment 6%/43%), in breast cancer (14%/43% and 11%/30%), and in ovarian (15%/48%) and cervical cancer (39%/88%) *(29–32)*. Moreover, in patients with unresectable pulmonary sarcoma metastases, who underwent isolated single lung perfusion with doxorubicin, relative MDR1 expression was measured in metastatic tumor nodules after initiation of chemoperfusion. Increases in MDR1 expression (up to 15-–fold) were detected 50 min after administration of doxorubicin. This observation demonstrates that MDR1 expression can be activated very rapidly in human tumors after transient exposure to chemotherapy *(33)*. Heat, as an external stress factor, may also induce MDR1 gene expression. However, hyperthermic isolated limb perfusion of sarcoma and melanoma

patients did not lead to induction of ABC transporters, probably because of the mild temperatures applied. Interestingly, expression of the major vault protein, a component of vault-mediated drug resistance, was induced *(34,35)*. On the other hand, regional cancer therapy techniques for organ-specific administration of drugs, such as lung perfusion, isolated limb perfusion, hepatic arterial infusion, intrathecal therapy, hyperoxygenation, and hyperthermia, are all strategies aiming at increasing drug delivery. However, this goal of an elevated drug accumulation at the tumor site must be evaluated in the context of the treatment modalities/external stress factors such as radiation, hyperthermia, or chemotherapy itself, balancing the increased organ-site drug accumulation with risk of MDR induction.

For nonsolid cancers, e.g., acute myelogenous leukemia, the most reproducible results on MDR1 expression levels, treatment-caused inductions, and correlations to clinical outcome have been reported (e.g., ref. *36*). Although the prognostic implications of MDR1 expression are controversial, the value of P-glycoprotein as marker for poor prognosis has been repeatedly supported (e.g., ref. *37*). For a variety of solid tumors, in particular for those more chemosensitive to drug treatment, acquired chemoresistance was accompanied with upregulated levels of MDR1 after exposure to chemotherapy. Correlation of clinical outcome parameters with MDR1 expression have been reported for bone and soft tissue sarcomas *(38–40)*, breast cancer *(41,42)*, and others.

2.2. The MRP Family

The ABCC subfamily of ABC transporters consists of 11 members with 9 MRP-related gene-associated proteins (MRP1–9 or ABCC1–6 and ABCC10–12). The most studied member, MRP1, was identified more than a decade ago in a non-P-glycoprotein-expressing, but multidrug-resistant human tumor cell line *(43)*. MRP1 is structurally similar to P-glycoprotein, however, with an amino-terminal extension of five membrane spanning α-helices. Like MRP1, MRP2, MRP3, and MRP6 harbor these extra amino-terminal transmembrane domains when compared with P-glycoprotein.

The spectrum of transported hydrophobic natural anticancer drugs overlap those transported by P-glycoprotein and also includes compounds of anthracyclines, vinca alkaloids, and epipodophyllotoxins. Like P-glycoprotein, the substrate specificity of MRP1 is altered owing to single amino acid substitutions within the respective transporter protein. However, the mechanism of drug transport is different. The MRPs transport anionic and neutral drugs conjugated to acidic ligands, such as glutathione, glucuronate, or sulfate. Alternatively, they can cause resistance to neutral drugs without conjugation but by cotransporting these drugs with free glutathione *(3,44–46)*. MRP4, MRP5, and MRP7 lack the additional helical regions but show higher sequence similarities to MRP1 than to P-glycoprotein or other ABC transporters. Both MRP4 and MRP5, are also organic anion transporters, like MRP1, -2, and -3, which have been identified to pump nucleotide analogs.

Gene transduction has shown that MRP1 plays a causal role in conferring the MDR phenotype on previously chemosensitive cells. Basal expression of MRP1 has been found to be ubiquitous in human tissues. Moreover, in almost all malignant tissues, basal MRP1 expression levels have been determined *(47)*, as reported, for example, in myeloma (in 100% of the tumors analyzed), breast cancer (100%), lung cancer (88% for small cell lung cancer [SCLC], 100% for non-small cell lung cancer [NSCLC]), sarcomas (80%) *(48–51)*. High MRP1 expression levels have been observed for lung, breast, and

ovarian cancer *(26)*. Moreover, for several tumor entities, correlations of high MRP1 expression with clinical outcome parameters such as response to chemotherapy and disease-free survival have been reported, e.g., for mammary, lung, and ovarian carcinomas, as well as for leukemias; in refractory hematological malignancies, increases in MRP1 have also been observed *(52)*. Moreover, a prognostic significance of MRP1 expression has been reported for primary breast cancer *(53)*. However, the clinical importance of MRP1 is still a matter of discussion, since studies have both confirmed and rejected a correlation of MRP1 expression level and outcome.

2.3. BCRP

BCRP (also called ABCP and MXR) was originally identified in a mitoxantrone-resistant, but P-glycoprotein and MRP1-negative human carcinoma cell line and was given three names because of its almost simultaneous discovery by three independent groups *(54–56)*. BCRP also encodes an ABC transporter and, together with four additional members, constitutes the ABCG subfamily. By contrast, this so-called half-transporter harbors only one nucleotide binding site and only one transmembrane domain with six membrane-spanning α-helices; full transporters such as P-glycoprotein and the MRPs contain two nucleotide binding sites and two transmembrane domains, suggesting BCRP homodimerization to gain full transport activity *(55)*.

Transduction of BCRP cDNA also caused the resistance phenotype. The drug spectra of BCRP considerably overlap with those of P-glycoprotein, including mitoxantrone, topotecan, and doxorubicin, with differing efficiences, however. High levels of BCRP were mainly detected in several mitoxantrone-resistant mammary, colon, ovarian, and gastric human cell lines *(57–61)*. Thus, BCRP showed high affinities for mitoxantrone, representing the long-sought transporter for this cytotoxic compound. Further BCRP substrates are methotrexate and flavopiridol. Tyrosine kinase inhibitors such as imatinib and gefitinib are also transported by BCRP (and also by P-glycoprotein). Vincristine and taxanes, typical P-glycoprotein substrates, are not included in the BCRP drug spectrum. It has been shown for P-glycoprotein and MRP1 that defined point mutations leading to amino acid substitutions, particularly within the transmembrane domains, alter substrate specificity and transport efficiency. This has also been confirmed for BCRP, e.g., for substitutions of arginine at position 482 for threonine or glycine, occurring during drug selection *(62,63)*.

BCRP was mainly detected in human tissues such as intestine, colon, mammary, liver canaliculi, and renal tubules and is highly expressed in placenta and the blood-brain barrier *(1,2,13)*. Intrinsic BCRP expression was frequently observed in human tumors of different entities. So far, high BCRP expression levels have been published for carcinomas of the digestive tract, for lung carcinomas, and for melanomas *(64)*. Its clinical relevance of high and/or therapy-induced BCRP expression in the context of clinical parameters such as response to chemotherapy and survival remains to be elucidated.

3. PREDICTION OF CHEMOSENSITIVITY AND TREATMENT RESPONSE

Different mechanisms and genes contribute to intrinsic and/or acquired drug resistance. For patients to qualify for a respective treatment regime, and for tailor-made patient-individual therapies, knowledge of the expression and function of genes and

proteins related to drug resistance represents an essential prerequisite. Since single individual markers have shown limited predictive value, the simultaneous analysis of a panel of resistance-associated genes is desired.

However, up to now clinical tests for predicting cancer chemotherapy response are not available. So far, several reports have described the generation of expression profiles for the prediction of chemosensitivity. For three human cell lines, expression profiles of 38 ABC transporters have been generated by using low-density microarrays combined with quantitative real-time polymerase chain reaction (PCR) *(65)*. For the 60-cell line panel of the National Cancer Institute (NCI), expression profiles of the known 48 ABC transporters have been created by means of quantitative real-time reverse transcription (RT)-PCR *(66)*. Furthermore, doxorubicin sensitivity in human breast tumors was predicted on the basis of microarray-generated and quantitative real-time RT-PCR-validated expression profiles and correlated with patient survival *(67)*. These approaches demonstrate the significance of in vitro experiments and may serve for the development of diagnostic tools for cancer response prediction in clinical samples.

4. INTERVENTION STRATEGIES FOR REVERSAL OF MDR

The failure of certain cancer chemotherapies was primarily linked to basal and/or induced expression of P-glycoprotein. The identification of MDR1/P-glycoprotein and its correlation with parameters of clinical outcome gave rise to the following optimistic assumption: "The high hope of P-glycoprotein was that here was a single protein that confers resistance to a whole array of structurally unrelated anticancer drugs. That was a very attractive idea. It raised the possibility that drug resistance could be overcome, because if a single mechanism is responsible, all you have to do is learn to understand that mechanism, find strategies to overcome it, and you could cure people of cancer" *(68)*. Thus, the inhibition of P-glycoprotein aiming at reversal of the MDR phenotype has been extensively studied for more than two decades. Several approaches have been made to target the function and the expression of MDR-associated genes and proteins, such as the employment of specific antibodies, inhibiting drug transport, the introduction of antisense oligonucleotides and ribozymes, or, one of the newest developments, the transduction of small interfering RNA (siRNA) molecules. However, the most promising attempts to reverse the MDR phenotype have been made with inhibitory compounds targeting P-glycoprotein function.

4.1. Approaches Targeting the Function of MDR-Associated ABC Transporters

4.1.1. Inhibitors

Based on this early optimism, numerous approaches have been made with so-called first-generation inhibitors of P-glycoprotein representing antagonists that have already been used for other indications, such as the calcium channel blocker verapamil and the immunosuppressive agent cyclosporine A. First-generation inhibitors are themselves substrates for P-glycoprotein and compete with the cytotoxic drug for binding and efflux by the P-glycoprotein pump, thereby limiting the efflux of the drug. As a consequence, intracellular drug concentrations increase, leading to elevated cytotoxicity; the cell becomes chemosensitive. These inhibitors worked with great success on cultured cells to overcome MDR. In the clinic, however, they produced disappointing results. A variety

of problems slowed down the optimism of the early years: different intrinsic and/or therapy-induced expression profiles in certain tumors/tissues, or varying correlations of expression and clinical response in certain cancers following chemotherapy. Both might be owing to nonstandardized techniques for expression analysis. Moreover, sequence polymorphisms may also have led to modulated drug transport. In particular, in order to reverse MDR, extremely high inhibitor concentrations were needed, causing unacceptable toxicity. Furthermore, these inhibitors are not transported exclusively by P-glycoprotein, resulting in unpredictable pharmacokinetic interactions when coadministered with the drug.

In addition to the major player, P-glycoprotein, a variety of further MDR-associated genes/proteins have been identified in recent years, mainly the discovery of MRP1 with its family members, or the discovery of BCRP, and, of course, relatives of P-glycoprotein itself *(69)*. The phenotype of MDR could nolonger be attributed to a sole, even well-characterized protein but had to be understood as the net effect of a multifactorial process of an entire panel of resistance genes controlling an array of alternative resistance mechanisms.

Second-generation P-glycoprotein inhibitors, also acting as competitive substrates, were created with the aim of overcoming specifically the P-glycoprotein-mediated resistance. Compared with first-generation inhibitors, they showed less toxicity and greater potency for inhibition of P-glycoprotein. Examples of second-generation inhibitors are valspodar (PSC833, Novartis), a nonimmunosuppressive cyclosporine analog, and biricodar (VX710, Vertex Pharmaceuticals), both designed to restore the effectiveness of chemotherapeutic agents in multidrug resistant tumors. Clinical trials have demonstrated that administration of second-generation inhibitors together with the anticancer drug might lead to reversal of the MDR phenotype, e.g., when one is treating refractory cancers *(26,70)*. However, certain limitations, as seen with the early inhibitors, could not be resolved, such as unacceptable toxicity and interaction with additional transporter molecules.

Third-generation inhibitors were developed based on structure-activity relationships *(70)*. These newly generated compounds inhibit P-glycoprotein more specifically and with greater potency and do usually not interact with other transporter molecules. They are not substrates for a defined ABC transporter, as is described for first- and second-generation inhibitors. Inhibitors of the third-generation bind noncompetitively to the pump. Thereby conformational changes of the transporter protein are caused, hindering ATP hydrolysis. Consequently, drug transport out of the cell is prevented, leading to increased intracellular concentration of the cytotoxic drug and enhanced cytotoxicity. For example, the chemosensitizer zosuquidar (LY335979, Eli Lilly) reversed mitoxantrone resistance in part and vinorelbine resistance completely in P-glycoprotein-overexpressing cells; in MRP1- or BCRP-overexpressing cells, however, drug resistance was not modulated *(71)*. To date, tariquidar has been one of the most potent MDR-modulating agents (XR-9576, Xenova Group plc/QLT Inc). It was applied very successfully, achieving complete MDR reversal at low concentrations, and it holds a long duration of activity in a panel of resistant tumor cells. Tariquidar is now under evaluation in several clinical trials (*see* **Subheading 4.1.2.**).

These results demonstrate the specificity of third-generation inhibitors with respect to the ABC transporter P-glycoprotein. Moreover, it was demonstrated for several newly created inhibitors that the pharmacokinetics of classical MDR-associated drugs such as

doxorubicin, vincristine, etoposide, and paclitaxel were not affected in patients. Based on these first findings obtained with the third-generation inhibitors, MDR of cancer cells might be overcome. If the mechanisms of resistance can be overcome, the spectrum of traditional agents and of treatable tumor entities will certainly be extended.

4.1.2. Clinical Trials

So far, nine randomized clinical studies have been conducted to evaluate the impact of P-glycoprotein inhibitors *(72)*. However, only three of these have shown statistically significant differences in overall survival, those performed in acute myeloid leukemia (AML) *(73)*, breast cancer *(74)*, and lung cancer patients *(75)*. One reason for the disappointing results has been the need for dose reduction of the chemotherapeutic drug in the context of the inhibitor. At present, the U.S. National Institutes of Health (NIH) is recruiting patients for three clinical phase I and II trials to evaluate the impact of the third-generation P-glycoprotein inhibitor tariquidar in solid tumors such as brain tumors, Ewing sarcomas, neuroblastomas, and rhabdomyosarcomas in children, in adrenal cortex neoplasms, as well as in lung, ovarian, and cervical neoplasms, with respect to the anticancer drugs doxorubicin, vinorelbine, vincristine, docetaxel, and etoposide (www.ClinicalTrials.gov). Most of these studies use Tc-99m sestamibi for expressional and functional control of P-glycoprotein.

4.1.3 Surrogate Assay: Tc-99m Sestamibi

To evaluate the expression and, in particular, the function of MDR1/P-glycoprotein with respect to clinical settings, Tc-99m sestamibi is employed. Tc-99m sestamibi harbors two main features in that context: it is a radionucleotide imaging agent, already in clinical use to determine cardiac dysfunction. Moreover, it is also a substrate and thus is transported by P-glycoprotein. Using this imaging agent, normal tissues and tumor areas with high P-glycoprotein expression can be identified; furthermore, the impact of P-glycoprotein inhibitors, measured as increased intratumoral drug accumulation, can be evaluated. It has been observed, e.g., in normal liver and kidney, that the uptake of Tc-99m sestamibi is increased following treatment with the inhibitors valspodar, biricodar, and tariquidar *(76–78)*. For hepatocellular carcinoma, a correlation of Tc-99m liver imaging with P-glycoprotein expression was reported *(79)*. Furthermore, increased Tc-99m sestamibi accumulation was reported for metastastic cancers following treatment with tariquidar *(78)*. For NSCLC, Tc-99m was used to predict the response to paclitaxel-based chemotherapy on the basis of P-glycoprotein detection, as demonstrated by chest images *(80)*. These findings confirm that MDR inhibitors are able to increase the accumulation of the respective substrate in P-glycoprotein-expressing normal and tumor tissues of patients. Moreover, the inhibitor concentrations achieved at the tumor site are sufficient to modulate P-glycoprotein function and thereby the MDR phenotype *(72,81)*.

At present, the NIH is recruiting patients for a clinical phase II trial to evaluate the use of sestamibi for imaging drug resistance in solid tumors (www.ClinicalTrials.gov). Patients are also being recruited for clinical trials to evaluate the impact of third-generation P-glycoprotein inhibitors in combination with chemotherapy; the monitoring of P-glycoprotein expression and function is carried out by administration of Tc-99m sestamibi. In addition, a correlation of Tc-99m imaging with expression of MRP1 in patients with hepatocellular carcinoma has been shown recently, possibly extending the use of imaging agents to MRP1-mediated MDR *(82)*.

4.1.4. Tyrosine Kinase Inhibitors

Several new molecular cancer therapeutics have been developed in recent years, such as a large variety of tyrosine kinase inhibitors. These agents are known to inhibit malignant cell growth and metastasis. Their therapeutic potential, however, depends on their access to the intracellular target, which might be disturbed by MDR-associated ABC transporters. Iressa (gefitinib), an epidermal growth factor tyrosine kinase inhibitor, as well as Gleevec (imatinib), a BCR-Abl, platelet-derived growth factor receptor (PDGFR) and c-kit tyrosine kinase inhibitor, belong to these recently developed compounds. Both Iressa and Gleevec might interact with MDR1 and also with BCRP as competitive ATP inhibitors; for both, the reversal of chemotherapy resistance has been demonstrated *(83,84)*.

4.1.5. MRP1 and BCRP Inhibitors

Although MDR1/P-glycoprotein is the central molecule in the context of MDR, the aforementioned P-glycoprotein inhibitors may also target additional ABC transporters with different affinities, e.g., biricodar also targetting MRP and BCRP and tariquidar also targetting BCRP in addition to P-glycoprotein *(85,86)*. Specific inhibitors, e.g., MK-571 for MRP1 *(61,87)* or fumitremorgin C for BCRP *(61,88)*, were used in experimental studies and worked successfully in terms of the respective transporter. However, their ability to increase accumulation of anticancer drugs associated with the MRP1- or BCRP-mediated MDR must be determined in a clinical setting.

4.1.6. Antibodies and Immunotoxins

Antibody-directed approaches might represent alternative stragegies for reversal of MDR. Monoclonal P-glycoprotein-specific antibodies have been shown to affect the proliferation of P-glycoprotein-expressing tumor cells *(89,90)*. However, the best chemosensitizing results were achieved when the monoclonal antibodies were applied in combination with inhibitors *(91,92)*. An interesting approach is the use of immunotoxins, consisting of monoclonal antibodies coupled to cytotoxic agents. After binding to the antigen and internalization, cytotoxic activity toward P-glycoprotein-expressing cells was demonstrated *(93,94)*.

4.2. Approaches Targeting Transcription, Posttranscription, and Posttranslation

Further interventional strategies affect the control of expression of MDR-associated genes. Several approaches have been used to prevent or disturb transcription of the MDR1 gene, e.g., by using MDR1-specific transcriptional repressors, by cytostatic blocking of induced but not constitutive MDR1 expression, or by targeting MDR1 transcription factors *(86,95–97)*. Moreover, alternative approaches interfere with translational expression by targeting the MDR1 or MRP1 mRNA. These intervention strategies use, e.g., complementary oligodeoxyribonucleotides to form complexes with the target mRNA, so-called antisense RNAs *(98–101)*. Catalytic RNAs, so-called ribozymes, hybridize to a complementary mRNA, thereby catalyzing site-specific cleavage of the substrate. A panel of ribozymes specific for several MDR-associated ABC transporters (MDR1, MRP1, and BCRP) has been successfully applied, leading to reduced expression and reversal of MDR in vitro *(102–104)*. One of the most interesting approaches is the employment of siRNA, also known as posttranscriptional gene silencing. For MDR1 and

BCRP, some promising reports have been published, demonstrating specific expression inhibition by degradation of the complementary mRNA using siRNA as well as by vector-based transfection in vitro and in vivo *(105–108)*.

N-glycosylation and phosphorylation are posttranslational modifications for P-glycoprotein, as well as for other MDR-associated ABC transporters. With the use of glycosylation inhibitors, such as tunicamycin, it turned out that N-glycosylation may contribute to correct folding and/or stabilization of P-glycoprotein; the MDR transport function, however, was not affected *(109)*. Since the phosphorylation of P-glycoprotein is an essential prerequisite for its transporter function, protein kinases represent a potential target for overcoming MDR. Because protein kinase C is known to phosphorylate and thereby activate P-glycoprotein, inhibitors of that enzyme have been used to reverse MDR *(110)*. More selective inhibitors targeting P-glycoprotein directly will certainly improve this approach *(111)*. Although all expression-based intervention approaches work well in experimental settings, we have no data so far for clinical application.s

5. PROSPECTS

MDR, caused by ABC transporter molecules, remains the major cause of inadequate responses in cancer chemotherapy. Forty-eight ABC transporters have been identified through the Human Genome Project. Sixteen of them have known functions, and 14 are discussed in the context of human diseases. Physiological functions are mainly the transport of lipids, bile acids, toxic compounds, and peptides for antigen presentation. Since it is unlikely that many new ABC transporters will be discovered, the phenotype and development of MDR must be elucidated further in the context of the about 10 already known MDR-associated ABC transporters.

Detailed knowledge of these transporter molecules, their sequence polymorphisms, their transcriptional, translational, and posttranslational regulation, and functional features of substrate binding and transport represent the basis for the development of specific and thus successful intervention strategies for MDR reversal in the clinic. Moreover, a patient-individual resistance profiling is desired that will provide the scientific basis for selection and application of specific chemotherapeutic drugs in defined therapy regimes; it would also provide the rationale and essential prerequisite for tailor-made approaches to overcome drug resistance. Therefore, patient-individual response prediction, MDR reversal, and possibly MDR prevention strategies are the ultimate goals to improve chemotherapy, in particular when applied as regional cancer therapy.

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2 Pharmacological Background

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CONTENTS:

SUMMARY

The pharmacological rational for regional cancer therapy is based on delivering a high dose intensity of the chemotherapeutic drug, resulting in an advantageous tumor cure/normal tissue complication differential (high therapeutic ratio). Only patients with an anatomically confined tumor and technical feasibility of antitumor therapy administration are expected to reach clinical benefit. Specific pharmacological characteristics of the delivered drug are of potential additional benefit. The pharmacological background of intraperitoneal chemotherapy, isolated hepatic perfusion, and isolated extremity perfusion are given as an example of the advantages and opportunities of regional anticancer therapy.

Key Words: Intraperitoneal; chemotherapy; isolated hepatic perfusion; extremity perfusion; pharmacology; regional cancer therapy.

1. INTRODUCTION

Regional cancer therapy is based on the concept of delivering a high dose intensity to an anatomically confined tumor site. The effectiveness of the procedure depends on the biology of the tumor (*see* Chapter 1), the technique (*see* Chapter 3), and the pharmacology

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