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CIRCUMVENTION OF CHEMO-RESISTANCE: AN OVERVIEW

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Rational circumvention of chemo-resistance in cancer requires knowledge of the underlying mechanisms and this is currently not available. Nevertheless, a number of approaches have been pursued, and this illustrates the frustrations felt by clinicians treating a range of tumour types. In this symposium several avenues will be explored.

Multi-drug resistance, mediated by P-glycoprotein, is a laboratory observation of uncertain clinical relevance; however, its reversal can easily be achieved experimentally and a number of clinical trials have been pursued. To date a key feature has been the important pharmacokinetics interaction between the modulating agent and the cytotoxic drug under study. Multidrug resistance (MDR) may be mediated by other cellular means, which may be amenable to alternative modulators; these may also be effective for agents other than those classically involved in MDR.

Factors which could underly resistance to other important drugs, e.g. cisplatin, include defective drug transport, enhanced drug inactivation and increased DNA repair. Potential means for modulation for each of these include the development of platinum analogues, intracellular glutathione depletion, and the use of repair inhibitors; to date their clinical value is unclear. A key determinant for resistance to many agents, including cisplatin, could be the failure of tumour cells to engage the process of apoptosis. As the genetic controls for this process are increasingly being understood, the possibility exists for rational new means for resistance circumvention, provided that the clinical relevance of this pathway is confirmed.

As well as 'cellular' factors, chemoresistance can be due to 'pharmacological' factors, which include considerations of dose and schedule. This may be particularly relevant for antimetabolites, such as 5-fluorouracil and cytosine arabinoside, whose activity does seem to be schedule-dependent. However, modulation of chemo-resistance based on the single manoeuvre of increasing dose has not yet made a major impact in solid tumors, and it is possible that the most successful strategy will be to employ a number of modulation techniques.

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CIRCUMVENTION OF MULTIDRUG RESISTANCE

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Two members of the superfamily of ABC transport proteins, Mr 170.000 PGP and Mr 190.000 MRP, have been identified as multidrug resistance genes. Both genes can act as cellular efflux pumps for natural product anticancer drugs, like anthracyclines, Vinca alkaloids, and epipodophyllotoxins. Pgp and MRP are expressed in a variety of tumours, including haematological malignancies. Pharmacological intervention by competitive inhibition of PGP and MRP has been studied *in vitro*, and clinical studies have been performed with the aim to circumvent (primarily PGP-mediated) MDR. In summary, these attempts have not been very successful, so far, in solid tumours (e.g. kidney and colon cancer) with de novo expression of PGP. For haematological malignancies the results obtained encouraged randomized phase III trials (which are ongoing). The effects of the so-called reversal agents on clinical tumour responses seen in pilot studies, are likely due to specific inhibition of PGP in tumour cells and to altered pharmacokinetics of the cytotoxic drugs. The general idea is that more effective and less toxic reversal agents are needed for clinical trials. However, mdr-knockout mice appeared to be extremely sensitive for xenobiotics. Thus, upon clinical use of highly effective, second generation reversal agents, altered (life-threatening) toxicity profiles should be anticipated.

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CIRCUMVENTION OF MDR: ALTERNATIVES TO THE AFFLUX PUMP

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Various genes responsible for multidrug resistance have been characterized. Factors involved are overexpression of the P-glycoprotein (P-gp) pump, an overexpression of the multidrug resistance related protein (MRP), altered topoisomerase II enzyme and increased detoxification of the drug. With (RT)-PCR, Northern and Western blotting, immunohistochemistry, and functional assays it is possible to detect the presence of the factors in human tumors. The exact role of each of these factors in the tumors of patients is unknown. Within a human tumor more than one factor plays a role and within a tumor there can be regional differences. Modulation in the clinic is performed with P-gp blockers such as verapamil. It is unknown whether the drugs for e.g. P-gp blocking do reach an effective tumor concentration and do indeed block the pump in patient's tumors. Currently, clinical studies with functional detection methods to localize MDR pumps are ongoing with e.g. ^{99m}Tc-Sestamibi. For the MRP pump, which was found to be the glutathione-conjugate pump, no modulators are available. Therefore, insight in glutathione metabolism may be of increasing value. Topoisomerase II, drug target for a number of drug measurements, may be another options to rationalize chemotherapy treatment. It is increasingly realized that modulation of more than one MDR mechanism is required in the clinic.

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PLATINUM RESISTANCE AS PARADIGM OF PRECLINICAL AND CLINICAL CONCEPTUAL DIFFERENCES

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Resistance to anticancer agents is the subject of intensive basic and applied research. Its definition is quantitative and expressed as n times the concentration of the agent in question, mostly *in vitro*. Schedule dependency, and concentration × time effects are seldom studied. No standards of normal sensitivity exist, since in most cases the resistance level is gauged against the parental line, seldom of human cancer origin. The medical oncologist perception of the resistance phenomenon is relative to both the quantitative aspects of antitumor response evaluation and qualitative respect to dynamics tumor progression. Clinical resistance definition is adhoc for every tumor type, and undergoes continuous evolution with new drugs and putative manipulations for its circumvention (modulation, dose, schedule). Resistance to platinum compounds has been studied through basic research and the main mechanisms have been elucidated. Only recently the relevance of the different mechanisms is being correlated to disease and natural history specific clinical settings. Non cross resistance between distinct platinum compound families has been perceived for over two decades, but its clinical potential was never implemented. Dose response and dose intensity delivery issues are also a long standing subject in Platinum efficacy assessment. The association of Cisplatin and Carboplatin, dose intensive schedules (weekly administration), the interaction with other agents, and the availability of Oxaliplatin, a non cross resistant DACH compound offer tools for the medical oncologist that will expand further the therapeutic role of Platinum compounds. Applied research preparing a solid rational for this horizon should be adapted to clinically relevant targets.

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CIRCUMVENTION OF RESISTANCE TO 5-FLUOROURACIL BY SCHEDULE-ORIENTED BIOCHEMICAL MODULATION IN ADVANCED COLON CANCER PATIENTS

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We have recently demonstrated that bolus FUra treatments of human colon carcinoma cells, HCT-8, produce resistance via an RNA-related mechanism, while prolonged exposures to the fluoropyrimidine is responsible for a DNA-related mechanism of resistance. In addition, cells