CLINICALLY RELEVANT RESISTANCE IN CANCER CHEMOTHERAPY
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CLINICALLY RELEVANT RESISTANCE IN CANCER CHEMOTHERAPY

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Over the last several decades, the introduction of new chemotherapeutic drugs and drug combinations has resulted in increased long-term remission rates in several important tumor types. These include childhood leukemia, adult leukemias and lymphomas, as well as testicular and trophoblastic tumors. The addition of high-dose chemotherapy with growth factor and hemopoietic stem cell support has increased clinical remission rates even further. For the majority of patients with some of the more common malignancies, however, palliation (rather than cure) is still the most realistic goal of chemotherapy for metastatic disease. The failure of chemotherapy to cure metastatic cancer is commonly referred to among clinicians as "drug resistance". This phenomenon can, however, often be viewed as the survival of malignant cells that resulted from a failure to deliver an effective drug dose to the (cellular) target because of any one of or combination of a multitude of individual factors. Clinically, this treatment failure is often viewed as the rapid occurrence of resistance at the single cell level. However, in experimental systems, stable drug resistance is usually relatively slow to emerge. Clinical "drug resistance" may be caused by some combination of: [a] resistance of individual cells to the delivered treatment; [b] unfavorable drug-host interactions: tumor cells may be exposed to a limited drug concentration because of a high rate of metabolic drug degradation and/or altered regional blood supply; in this case, individual tumor cells may still be sensitive to the used chemotherapy; and [c] unfavorable malignant cell-host interactions that result in the survival and proliferation of the neoplastic cells.

We as a scientific community have come to realize that inter-individual genetic differences are of major importance for metabolic drug handling, and that this may be of the utmost importance for clinical treatment outcome. Furthermore, as our knowledge of the molecular mechanisms that operate to confer drug resistance at the single-cell level increases, we are developing the ability to create probes that can be used to study malignant-cell drug resistance at the clinical level, in addition to studying the clinical pharmacology of anticancer drugs both at the patient level and (sometimes) at the tumor cell level. An integration of clinical and experimental investigations will improve the understanding of clinically relevant drug resistance, and ultimately it should also assist us in improving the treatment of human cancer.
Recently, rapid technological advances have enabled high-throughput studies of genetic polymorphisms and cellular proteomes. This has opened up entirely new approaches not only to the study of drug resistance in model systems but also to the individualization of chemotherapy in order to decrease clinical toxicity and optimize treatment results. This volume reviews clinically relevant aspects of both cellular/experimental resistance to commonly used anticancer agents and the importance of the pharmacokinetics of such agents, as well as some of the developments that can be expected over the next 5-10 years.

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