Current Cancer Drug Targets

The international journal for timely in-depth & mini-reviews on Drug Targets for Cancer
EDITORIAL

It was with great pleasure that I accepted the invitation to be Guest Editor for this issue of Current Cancer Drug Targets. This volume collates reviews by experts on a wide range of research topics relevant to anti-cancer drug sensitivity and resistance, considering both traditional chemotherapeutic agents and newer, targeted therapies.

The use of chemotherapy to treat cancer began in 1943 following the observation of leukopenia in those exposed to mustard gas (alkylating agent) after the explosion of a battle ship in Bari harbor during World War II. This alkylating agent was adapted for i.v. application and produced dramatic, if short-lived, responses in lymphoma and leukemia patients. Advancing on this, an extensive range of anti-cancer chemotherapeutic agents have been developed and are used in the oncology clinic. Such anti-cancer drugs aim to destroy cancer cells by stopping them from growing or multiplying. Unfortunately, due to the relative non-specific effects of some of these drugs, healthy cells (especially those that divide quickly) can also be harmed, resulting in undesirable side-effects. Based on our increasing understanding of normal versus cancer cells, in recent years the specific design and targeting of anti-cancer treatment is becoming increasingly sophisticated. The initially crude chemotherapy poisons which have since been continuously fine-tuned to increase efficacy and reduce side-effects and the newer “targeted agents” (which more specifically target features of cancer cells, with more limited side-effects) are set to revolutionise cancer treatment.

Most types of cancer show some response to traditional chemotherapy and/or newer targeted agents, but only a limited number of forms of cancer can be completely cured by these approaches. In fact, the successful treatment of cancers varies greatly depending upon the specific malignancy. Some cancers, such as testicular seminoma, leukemias and malignant lymphomas, are highly responsive to anti-cancer treatment; others, less devastates diseases, showing limited, if any, response to currently available therapies. Unfortunately, intrinsic and acquired resistance to anti-cancer agents still represents a serious obstacle to success as patients refractory to treatment often exhibit resistance to multiple anti-cancer agents of differing structures and, often, differing functions. This clinical resistance, comparable to the experimental phenomenon termed multiple drug resistance (MDR), is likely to be multifactorial and heterogeneous, with many molecular mechanisms potentially contributing to the drug-resistance phenotype. This resistance—whether inherent or acquired—of cancer cells to the effects of such agents is a serious problem, which we need to better understand and overcome.

Studies on mechanisms of cancer drug resistance have yielded, and continue to yield, important information about how to circumvent this problem to improve response. Applying both basic and advanced analytical technologies, genome-wide studies correlating drug response phenotypes with large DNA, RNA, and miRNA microarray and proteomic datasets are being performed to identify the genes, RNAs, and proteins involved in drug sensitivity or resistance. The goal is to identify panels of sensitive- and/or resistance-associated genes, that are predictive of treatment response, for each anti-cancer agent/treatment regime. The hope is that such emerging panels of biomarkers will offer the potential for the selection of optimal treatment regimens for individual patients and also for the identification of novel therapeutic targets to overcome drug resistance.

In light of this, in a timely manner, the topics addressed in this volume of Current Cancer Drug Targets span the field of anti-cancer drug sensitivity and resistance, considering both traditional chemotherapeutic agents and newer, more targeted therapies. The review by Hegedüs, Özvegy-Laczka, Szakács, and Sarkadi details classical MDR drug transporters, discussing protein kinase inhibitors (PKIs) in modern cancer chemotherapy, and proposes how combinations of classical chemotherapeutic drugs and PKIs may be advantageous for currently untreatable metastatic cancer. Laboratory and clinical efforts at circumventing MDR, together with emerging knowledge leading to new strategies which may augment the activity of both conventional cytotoxic drugs and newer targeted anti-cancer agents, is reviewed by O’Connor. The article by Goda, Bacsó and Szabó more specifically evaluates MDR associated with the very relevant drug efflux pump, P-glycoprotein, while Mayur, Peters, Rajendra Prasad, Lemos and Satish provide an overview of various drugs being developed to overcome MDR in cancer cells, focussing -in particular- on acridine derivatives. Other very important mechanisms of MDR in cancer which must be considered are the anti-apoptotic mechanisms. These are comprehensively reviewed through two articles by expert groups in this field – including Wilson, Johnston, and Longley who review apoptosis and the mechanisms by which it can become dys-regulated in cancer and, subsequently, they outline novel therapeutic strategies that target key components of the apoptotic machinery. Giménez-Bonafé, Tortosa and Pérez-Tomás discuss therapeutic interventions and strategies to lower the apoptosis-threshold of tumour cells (which may become useful anti-cancer approaches), placing particular emphasis on targeting tumour stem cells. Kasper and Barth report caveolin-1 involvement in bleomycin-induced apoptosis in lung cells and propose further research to elucidate the specific role of caveolin-1 and so the potential for development of a new targeted treatment approach. Again, mining more specifically on MDR to frequently used anti-cancer agents, Stordal and Davey extensive review genes involved in the inverse resistance relationship to cisplatin and paclitaxel, proposing BRCA1 as the first of a panel of cellular biomarkers to predict the inverse cisplatin/paclitaxel resistance phenotype, while Balandiran outlines the mechanism of daunorubicin action and explains a method to improve its effectiveness by modulating AKR1B10 activity. Considering hormone-based approaches for the treatment of appropriate cancers, such as sub-groups of breast tumours, Keely and Meegan discuss developments in estrogen receptor targeting approaches; including estrogen receptor ligand conjugates containing a variety of cytotoxic agents, photodynamic therapeutic agents and radioligands, and they evaluate the potential advantages of these conjugates in the discovery of more effective anti-cancer agents. Hypoxia and its contribution to gliomas which, unfortunately, are notorious resistance to chemotherapy and radiation, is reviewed and detailed by Amberger-Murphy. Considering another example of notoriously resistant cancers, la Porta reviews molecular mechanisms involved in melanoma drug resistance; the relationship
between cancer stem cells - which have constitutive MDR- and the efficacy of therapy; and potential strategies to overcome such resistance. Significant advances have been made in the area of breast cancer research recently, through the identification of 5 intrinsic tumour sub-groups. With this in mind, Germano and O'Driscoll discuss sensitivity and resistance to chemotherapy and targeted therapies to aid in personalised medicine. Advancing on the pioneering work of Dennis Slamon and colleagues, significant advances - giving optimism also for other solid tumour types - have been made in the treatment of subgroups (HER-2) of breast tumours through the use of the monoclonal antibody, Trastuzumab (Herceptin™). As detailed by Browne, O'Brien, Duffy, Crown and O'Donovan, while not all HER-2-overexpressing patients respond to trastuzumab and most that initially respond develop resistance within one year of treatment, through molecular dissection of the pathways contributing to this resistance and the application of other relevant targeted therapies (such as the dual HER-2 and EGFR tyrosine kinase inhibitor, lapaatinab; Tykerb™) progressive tailoring of treatment regimes to meet the patients needs can realistically increase both quality of life and overall survival. Undoubtedly, identification of individuals who are likely to respond to such targeted treatment is of utmost importance to avoid over- or under-treatment. Another very important example of this is comprehensively overviewed by Konings, Verweij, Wiemer and Steijger, when considering the use of mTOR inhibitions. This review very elegantly addresses the mechanism-of-action and current clinical experience with mTOR-inhibitors and their role in over-coming resistance to conventional therapies, as well as discussing potential predictors of outcome to mTOR-inhibition.

With more than 10,000,000 new cases of cancer diagnosed world-wide each year, cancer remains a challenge to optimally treat, based on the individual patient's needs. Unfortunately, resistance to treatment regimes contributes to this being a major cause of morbidity and mortality. However, as will be evident from the reviews presented here, through the concerted efforts of scientific and medical researchers, working together with patient groups, collaborating with the pharma industry, and with the very welcome support of national and international funding agencies, every effort is being made to improve cancer treatment; and very exciting advances are being made. Collectively, we still have many hurdles to clear and very much to achieve, but I truly believe that there is reason to be optimistic and that the continued translation of our concerted efforts will lead to much improved tailored treatments and significantly better survival rates for individual cancer patients.

I hope that this collection of critical reviews will be helpful to researchers working in clinical, pharmacological, cellular and molecular fields of cancer treatment; to patient groups; and to others who want to review progress in this field. Mostly I hope it will contribute, in some way, to advancing progress towards better cancer treatments with few side-effects, improved quality of life and, ultimately, cures for more patients suffering from cancer.

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