Cancer Drug Resistance

Overviews and Methods

Edited by

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Preface

The last few decades have been witness to a far-reaching transformation in the biomedical sciences in which genetics has been one amongst the main actors. Indeed, genetics casts a new light on our understanding of genes and their action, with genomic sciences enabling the rapid acquisition of knowledge of whole genome sequences, polymorphisms, and epigenomics’ mechanisms of regulation of gene expression, leading to the current era of the “omics” with all its component members: the genome, the transcriptome, the proteome, the metabolome, or the variome. Other terms could enter this lexicon reflecting the increased ability of a more accurate diagnosis and characterization of the neoplastic cell types, but not still necessarily a cure.

The present impact of the major noncommunicable diseases is startling, inasmuch as it shows a strong tendency to rise and tends to increase proportionally in low-income countries. Cancer as well as other major non-communicable diseases displays an unbridled growth both in incidence and in mortality. The global burden of cancer continues to increase largely because of the aging and the growth of the world population [1] alongside a failure of cancer therapy associated with acquired and intrinsic resistance mechanisms. Indeed, of the 7.6 million cancer deaths that occur every year worldwide, [2] many are due to cancer drug resistance.

This problem is not negligible since the number of new cases is projected to rise from the 13.3 million new cases of cancer in 2010 to 21.5 million in 2030 [3]. In the European Region alone, cancer is the most important cause of death and morbidity after cardiovascular diseases, with more than three million new cases and 1.7 million deaths each year. Overall, more than 70 % of all cancer deaths occur in low-income and middle-income regions with little or no resources for the prevention, diagnosis, and treatment of cancer. The proportion of cases diagnosed in less developed countries is projected to meagerly increase from about 56 % in 2008 to a little more than 60 % in 2030 [4]. Cancer is inextricably linked with economic wealth.

Cancer care costs are a financial burden to patients, their families, and society as a whole. The importance of the effectiveness of new drugs is also illustrated by financial figures, and the global pharmaceutical market with their approximately 30 % profit margins epitomizes the costs involved in the search for new effective drugs due to acquired and intrinsic resistance mechanisms. And those costs are growing.

Although stemming from a single account of evidence and to make a long story short, the importance of developing new cancer drugs when older ones become less effective may be well illustrated by remembering imatinib and nilotinib, both functioning as competitive inhibitors at the ATP-binding site of BCR-ABL of chronic myelogenous leukemia (CML). Although imatinib is a first-line treatment for CML and might also be of interest, for instance, for glioblastoma multiform, having generated sales of more than US$2.5 billion worldwide in 2006, its less favorable therapeutic results in CML led, in a few years, to the development of the second-generation drug nilotinib which showed a relatively more favorable safety profile and is active in imatinib-resistant CML [5]. In 2012 nilotinib generated US$998 million and a 44 % growth gaining market segment share as a potent second-generation
targeted therapy for chronic myeloid leukemia (CML). Although it is a truism that cancer treatment is inextricably linked to economical factors, we live in a time to invest boldly in new ways of understanding and predicting new cancer drugs’ effects and their potential to induce resistance. The new era of the “omics” is poised to face the problem, and the current book was a timely initiative of Springer, Humana Press, which intends to review and update the available knowledge and mechanisms on cancer drug resistance.

Cellular resistance to drugs can develop from a variety of mechanisms which are intended to be dealt in this book, not necessarily thoroughly, which would be an impossible task.

Resistance to a particular drug, or a class of drugs with similar mechanisms of action (multi-drug resistance [MDR]), might arise from an alteration in the drug’s cellular target (e.g., a mutation in the target molecule) or by an increase in the repair of drug-induced DNA damage, or a rapid metabolic biotransformation of the drug rendering it ineffective. In the last few years, the importance of DNA repair pathways in resistance to chemotherapy has been increasingly recognized, yet translation to the clinic is residual. Since many classical cancer therapies target DNA, the influence of DNA repair systems in response to DNA damage from chemotherapy and radiotherapy is critical to cell survival. The use of inhibitors of DNA repair or DNA damage signaling pathways (NER, BER, MMR, HR, and NHEJ) provides an interesting opportunity to target the genetic differences that exist between normal and tumor tissue. On the other hand, the study of genes involved in the metabolism of drugs and xenobiotics, in particular CYPs, CYPOR, and Cytb5 which may mediate the effectiveness of drugs and also drug resistance, is central to the development of next-generation therapies.

However, the most common mechanism of resistance to cancer drugs may rely on the efflux of drugs from the cell by one or more adenosine 5′-triphosphate (ATP)–binding cassette (ABC) transporters. In healthy cells, ABC transporter proteins display a variety of roles in several organs, i.e., the liver, kidneys, gastrointestinal tract, or the nervous and reproductive systems, increasing the excretion of toxins from the body. In cancer cells, the ABC transporters work to eject chemotherapeutics from the cell to nontoxic concentrations, thus decreasing their therapeutic effects. Of the more than 48 membrane proteins that comprise the ABC transporters family, at least 15 have been associated with drug resistance. Although much progress has been made to elucidate the molecular mechanism of these resistance-conferring ABC transporters, this knowledge is not sadly at a routine stage of translational to clinical relevance. It thus seems paramount to search for an integrative view of membrane transporters as mediators of the entry, distribution, and excretion of medicines and genotoxic xenobiotics in the human organism, namely the superfamilies of membrane transporters ABC and SLC (and there are some 55 families in the human SLC gene superfamily) and their involvement in the membrane traffic of cancer drugs. Also, as elusive as it might still be if the Warburg effect is causal or is an effect in tumorigenesis, the fact is that cancer cells are avid for glucose and thus the two different types of membrane carrier proteins, the Na+-coupled glucose transporters (SLC5A/SGLT2) and the glucose transporter facilitators (SLC2A/GLUT1), are paramount to glucose inflow and have been shown to be upregulated in some cancers. Besides their role as main players in PET scan diagnostic procedures, they may constitute potential targets for new drugs blocking the entrance of glucose in cancer cells inasmuch as those drugs may exhibit cancer cell tropism.

Moreover, genome-wide association studies (GWAS) have been extremely successful in identifying regions of the genome that are linked to a specific trait and could also be applied in detecting the most probable marker/gene responsible for a certain resistance to a drug or patient’s germ line genetic variation that may also affect drug response. Furthermore,
NGS-based approaches as applied to the exome of cancer cells may open new ways to the early identification of mutated genes whose protein products are targets to new drugs.

The study of the variome of repair genes and the levels and allocation of epigenetic regulators, in particular noncoding RNAs (e.g., microRNAs) and methylation patterns, as well as the DNA lesions and the regulation of gene expression, all have a central interest in the etiology of cancer. These aspects will contribute to the increase in the effectiveness and safety of new drugs and their therapeutic use and thus will certainly be among the major players in the future treatment of cancer.

Not more important than all the above-mentioned aspects, but still overriding, is the use of methods like proteomics which are essential in evaluating protein markers that can guide us in the search for the genomic variants or mutations responsible for cancer drug resistance.

Finally, the development of databases and in silico methodologies and their use in helping to de-emphasize individual medical hunches by supplying the criteria of evidence-based medicine will surely improve the rationale of the use of new cancer drugs and their potential resistance as well as play an interesting trade-off of individual medical ethics against the social ethics (and biopolitics) of the efficient use of scarce health resources.

Had it not been for the kind invitation of Professor John M. Walker, Professor Emeritus, School of Life and Medical Sciences, University of Hertfordshire, we would never have had the boldness of entangling ourselves in the task of organizing a book on resistance to cancer drugs. Also without the prompt and supremely competent contribution of all the prestigious authors of the various chapters who kindly accepted our invitation, the book would never be here. Our gratitude is proffered to all of them.

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