

PREFACE

It all started with an accidental discovery in the laboratory of Dr. Barnet Rosenberg at Michigan State University in the mid 1960s. Now, thirty years from the landmark publication of the anticancer activity of cisplatin, this volume follows in the wake of the 8th International Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, held in Oxford, UK, in March 1999. From small beginnings, this quadrennial Symposium now attracts several hundred laboratory and clinical scientists from all corners of the world.

Although the chemical structure of the inorganic square planar platinum-based coordination complex had been known for over 100 years prior to Rosenberg's studies, the medical oncology and, indeed, the scientific community at large were unaware of the dormant giant that lay waiting to be discovered. From the beginning of its clinical trials in the early 1970s, cisplatin made an immediate impact in the treatment of a variety of cancers (especially testicular and ovarian), but there were also significant problems in terms of inducing severe side-effects (especially kidney damage and nausea/vomiting). At the preclinical level, the next 10 years or so saw the emergence of a band of scientists who began to put in place the multidisciplinary approach essential to modern anticancer drug discovery. Notable from those early days were Joe Burchenal, Mike Cleare, Tom Connors, Ken Harrap, Jim Hoeschele, Yoshinori Kidani, John Roberts, and the National Cancer Institute (NCI).

Initial efforts focused on understanding the chemistry and biochemistry necessary to produce improved (less-toxic) analogs and elucidate the mechanism by which cisplatin exerted its antitumor effects. During the 1970s and 1980s, hundreds of new platinum-containing agents were synthesized, the focus being largely on reducing side-effects while retaining the antitumor activity of the parent molecule. One of the most important collaborations was established between the Johnson Matthey Company and academia, at The Institute of Cancer Research in Sutton UK, which resulted in the discovery of several key agents for clinical testing, including JM8 (carboplatin) and JM9 (iproplatin). From these trials, carboplatin (Paraplatin[®]) emerged as a significant new platinum-based anticancer drug in being broadly equivalent to cisplatin in terms of its spectrum of antitumor activity, but producing markedly less patient morbidity. Carboplatin remains the only cisplatin analog to be widely registered for clinical use.

For the last 10 years, the major focus of platinum drug development has been on the critical clinical need to broaden the number of tumor types that respond to this class of drug. Laboratory-based studies have shed light on the mechanisms by which tumors are, or become, resistant to the effects of cisplatin, thus allowing for the rational design of improved analogs. Several interesting new classes of platinum agents have been identified, including active *trans* isomers, orally active platinum, improved diaminocyclohexane (DACH) platinum, and bi- and tri-nuclear platinum. In total, approximately 30 platinum-based drugs have entered clinical trial. Importantly, their structural diversity continues to expand and many important trials are still ongoing.

Some 30 years on from the discovery of cisplatin, it is pertinent to ask “Where do we go from here?” The multidisciplinary approach of anticancer drug research involves synthetic chemists, molecular biologists, pharmacologists, and clinical oncologists. This volume brings together all of these and provides a comprehensive state-of-the-art appraisal by a panel of international contributors on:

(1) Platinum Chemistry. This section includes information on the chemistry of cisplatin in aqueous solution, the molecular interaction of platinum drugs with DNA, and transplatin-modified oligonucleotides.

(2) Platinum Biochemistry. Herein, there is particular emphasis on the burgeoning new areas of DNA mismatch repair, replicative bypass, and apoptosis, as well the important issue of how platinum drugs are transported into tumor cells.

(3) Clinical Antitumor Activity and Toxicology. This part covers an overview of the clinical experience with cisplatin and carboplatin, the exciting recent studies combining platinum drugs with taxanes, and clinical experience with DACH-based platinum drugs, particularly oxaliplatin. Moreover, an appraisal of the toxicological aspects of platinum drugs from both a clinical and a regulatory perspective is provided.

(4) New platinum drugs of the future. The volume concludes with an ongoing and futuristic look at new platinum drugs, including orally active drugs (JM216, ZD0473) and novel polynuclear charged platinum, such as BBR3464, which take the field into a new paradigm.

We are no longer completely in the dark as to how cisplatin exerts its antitumor (and toxicological) effects and how tumors acquire resistance; the considerable challenge is to exploit this knowledge to the further benefit of cancer sufferers. The field is poised at an especially exciting phase, the essence of which is captured in these chapters.

We wish to thank each of the contributors to *Platinum-Based Drugs in Cancer Therapy*. We are indebted to the time and effort each has

provided to both the overall field of platinum anticancer drug development in making platinum-based chemotherapy more efficacious and more “patient-friendly” and for their particular input into this volume.

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