Platinum and Other Heavy Metal Compounds in Cancer Chemotherapy

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Editors

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Molecular Mechanisms and Clinical Applications

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This book is dedicated to the memory of Lloyd R. Kelland, Ph.D., a generous and thoughtful colleague whose careful investigating of the mechanisms by which the platinum-containing drugs kill tumor cells provided valuable insights into how to improve their use in the management of cancer.

Preface

Cisplatin, the first member of the family of platinum-containing chemotherapeutic agents, was discovered by Barnett Rosenberg in 1965 and approved by the FDA for marketing in 1978. After 30 years of use in the clinic, cisplatin remains a central element of many treatment regimens. Cisplatin is still an irreplaceable component of a regimen that produces high cure rates in even advanced nonseminomatous germ-cell cancers, and is widely used in the treatment of ovarian cancers and other gynecologic cancers, head and neck, and numerous other tumor types. The development of carboplatin has reduced some of the adverse events associated with cisplatin treatment, and the introduction of the DACH platinum compound oxaliplatin has broadened the spectrum of activity of the platinums to include gastro-intestinal cancers, especially colorectal cancer. The clinical importance of this family of drugs continues to drive investigation into how these drugs work and how to improve their efficacy and reduce their toxicity.

The papers in this volume were presented in Verona, Italy, during the tenth International Symposium on Platinum Coordination Compounds in Cancer Chemotherapy. The symposium was jointly organized by the Department of Oncology of the Mater Salutis Hospital – Azienda Sanitaria Locale 21 of the Veneto Region – and by the Department of Medicine and Public Health, Section of Pharmacology, the University of Verona. They reflect the vitality of this field and the increasing use of new molecular and cell biologic, genetic, and biochemical tools to identify approaches to further improve their use.

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Platinum Compounds: The Culmination of the Era of Cancer Chemotherapy

Franco M. Muggia

Abstract The history of cancer chemotherapy is considered part of a chapter of empiricism that is coming to a close. However, the effect of cisplatin on germ cell tumors and, to a lesser extent, on epithelial ovarian cancer has captivated scientists and oncologists, and continues to expand its therapeutic horizons as more is learned. This is the Tenth Symposium on Platinum and Other Metal Coordination Compounds in Cancer Chemotherapy, and its highlights provide further confirmation of the value of scientific investment in this area of therapeutic research.

Keywords Chemotherapy; Cisplatin; Carboplatin; Germ cell and testicular tumors; Ovarian cancer

Various reviews have recounted the history of cancer chemotherapy, and its dawn at the beginning of the twentieth century with the introduction of "the magic bullet" concept against infectious pathogens and tumors by the brilliant German pathologist, Paul Ehrlich. The introduction of sulfonamides against bacteria and the effects of hormones against certain tumors constituted early validation of this concept. Modern chemotherapy, however, is usually traced to the sensational 2 December 1943 incident (1, 2) that occurred at the harbor of Bari, Italy. An air raid destroyed 17 allied ships, including one containing mustard "bombs" (being stored as possible retaliation to the threat of chemical warfare); exposed personnel experienced the marrow hypoplasia and involution of lymphoid tissue previously reported with sulfur mustard gas during World War I (3–5). In fact, the medicinal studies of the related nitrogen mustard by the U.S. governmental agencies, in concert with biomedical researchers at academic institutions such as Yale, had already started in 1942 (6). Fleming's unique discovery of penicillin in 1928 – a powerful stimulus for drug development – was followed by the search for drugs effective against

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tuberculosis. This constellation of events led to the creation of the U.S. National Institutes of Health and the National Cancer Institute (NCI), which were to play a pivotal role in launching the era of anticancer chemotherapy. These government entities had the ability to sponsor scientific exchanges with other national and international institutions functioning largely unencumbered by profit motives. They succeeded as a clearing house of ideas to combat cancer, despite the rather primitive understanding of neoplastic cell and molecular biology.

The Initial Phases of Systematic Anticancer Drug Discovery

With the support of Congress and as a part of the U.S. government's Public Health Service, the NCI organized itself to utilize evolving knowledge of tumor biology for the bold idea of identifying drugs for cancer treatment. Activity against carcinogen-induced L1210 and P388 leukemias in mice became a criterion for selectivity of a drug against these rapidly dividing tumor cells, without irreparably harming the host (7). A number of drugs related to nitrogen mustard and biochemically designed antimetabolites were established to have clinical activity and, in spite of the shortcomings of random screening, successes could be claimed against some human malignancies (8). Collaboration with other governmental agencies (e.g., the Department of Agriculture) and the pharmaceutical industry also led to the selection of useful natural products such as the vincas, camptothecins, and taxanes – the vincas mostly developed by industry, and camptothecins, and taxanes through the perseverance of NCI-sponsored investigations. Another landmark achievement was the identification, by Heidelberger and colleagues, of 5-fluorouracil and its eventual potential in the treatment of breast and gastrointestinal cancers (9).

Clinical Investigators

It was important to link such therapeutic drug discovery efforts with physicians skilled in diagnosis, and eventually with experience in dealing with supportive care and management of complications of malignancies and drug treatments. It is not a coincidence that early pioneers in cancer treatment focused either on hematologic diseases (following their training in internal medicine), or on certain solid tumors (following their training in surgery and its specialties). In either case, these physicians considered clinical investigation the final common pathway for anticancer drug development and, in the course of patient care, began to apply them systematically in situations that, until that time, had been considered hopeless. Documentation of their success in clinical trials became a major important step in these efforts (reviewed by DeVita and Chu) (10).

Often unrecognized is one such pioneer: Ezra Greenspan (1919–2004), best known for developing the foundations of combination chemotherapy against advanced breast and ovarian cancers (11, 12). His optimistic outlook – as stated

in the autobiographical notes he left to his colleagues – derived from having survived pneumonia while attending college at Cornell, because his physician opted to treat him with the recently obtained Prontosyl (a classmate who had preceded him in the hospital died without such intervention). Subsequently, upon finishing his medical studies at NYU, he was exposed to his first clinical trial under the mentorship of Isidore Snapper: the use of urethane (ethyl carbamate) in multiple myeloma (5) that included attempts to correlate clinical benefit with serial bone marrow examinations. When recruited into the Army in 1947, he became a physician at the Tumor Service at Walter Reed, where he describes adding the first available drugs (nitrogen mustard, triethylene melamine, and methotrexate) to radiation therapy for the treatment of testicular cancers and Hodgkin's disease. As the NCI opened its first clinical unit, Greenspan became the first clinical investigator in this fledgling program, and teamed up with the preclinical scientist, Abraham Goldin, who was to develop many of the principles of chemotherapy based on optimizing dose-scheduling of a drug in mouse leukemia models (13, 14). This experience with new therapeutic agents provided Greenspan with the unwavering optimism he demonstrated in facing the challenges of his long career as a clinical oncologist at Mount Sinai Hospital in New York.

Greenspan was the first to exploit the antitumor effects of methotrexate for the treatment of solid tumors, and document positive results in combination with alkylating agents (11, 12). In the 1950s and 1960s, a number of other physicians in academic centers began to develop clinical units devoted to the treatment of cancer, but met with resistance and disdain, particularly from Departments of Medicine that were skeptical of investing human resources in coupling the semi-empirical identification of anticancer drugs with the science of clinical trials (10). Despite this, clinical oncology began to flourish in the 1950s under the leadership of Alfred Gellhorn at Columbia and David Karnofsky at Memorial Sloan-Kettering, to be followed in the 1960s by a number of prominent specialists in hematology, general internal medicine, and surgery that were to become the key developers of Medical Oncology, followed by other oncologic specialties (10).

In the meantime, the NCI with its Chemotherapy Program led by C. Gordon Zubrod (himself a product of pharmacology research first devoted to antituberculous drugs), and its Medicine Branch staffed with clinical investigators such as Emil Frei and Emil (Jay) Freireich, concentrated its efforts on finding therapeutic regimens useful against leukemias (15). These efforts were later expanded to the treatment of Hodgkin's and other lymphomas, and subsequently to breast and ovarian cancers, with investigators such as Vincent DeVita, Paul Carbone, George Canellos, Robert Young, Philip Schein, and Bruce Chabner (10, 16–19). The success of the NCI intramural programs, coupled with a dramatic extramural expansion via cooperative groups (initially under the leadership of James Holland, Bernard Fisher, and John Durant, among others) and its phase I/II working groups, led to widening of the clinical testing of anticancer drugs, thereby accelerating changes in cancer treatment worldwide. The investment of the pharmaceutical industries in this area, long considered a risky proposition, grew rapidly in the 1970s, with substantial

programs being developed in the U.S. by Bristol Myers, in Europe by Burroughs Welcome, Farmitalia, Rhone Poulenc, Roche, and Sandoz, and in Japan.

Curable Tumors as the "Stalking Horse" of Drug Discovery

Joseph Burchenal, who headed Developmental Therapeutics at Memorial Sloan-Kettering for approximately 40 years, starting from the 1950s (pairing up with David Karnofsky, who ran the Chemotherapy service), used the imagery of a "stalking horse" to describe Burkitt's lymphoma as an identifier of strategies applicable to leukemia in his 1966 presidential address to the American Association for Cancer Research. Early experience in testicular cancer has similarly served to validate treatment strategies: "prophylactic" radiation to the retroperitoneal space (20), and Greenspan's addition of alkylating agents to men he treated in 1947–1949 at Walter Reed's tumor service. Twenty-five years after the Walter Reed experience, complete responses to cisplatin in advanced testicular cancer were documented by Higby et al. (21) in Holland's group at Roswell Park, convincing initially skeptical investigators that it was worthy of further development. Shortly thereafter, trials performed at Memorial Sloan-Kettering (22) and at Indiana University with collaborators from the Southeastern Cancer Study Group (23) defined cisplatin-based treatments as curative. In the setting of recurrence, Einhorn and his group established the usefulness of certain anticancer drugs (e.g., etoposide and ifosfamide) (24), and also tested whether cisplatin dose-intensification would be a reasonable strategy. If such intensification did not prove useful in testicular cancer, it certainly would not be useful against cancers that are much less sensitive to platinums (25).

The impressive activity of cisplatin against germ-cell tumors, leading to cures in advanced disease conditions (exemplified by Lance Armstrong's extraordinary saga), should continue to influence our notions on how to succeed in drug development. Although it has been fashionable to speak about "personalized therapy," such a concept belies the fact that unparalleled successes can take place without individualized knowledge on the deranged pathways involved in tumorigenesis. Platinum contributions are not confined to this most impressive example; the extraordinary sensitivity of ovarian cancer to cisplatin and carboplatin is nothing short of remarkable, if one considers the very advanced presentations that are commonplace in this disease. In addition, the strides achieved during the past decade in the treatment of colorectal cancer owe as much to the introduction of oxaliplatin-based combinations as to the monoclonal antibodies against VEGF and EGFR (26). Emphasizing such contributions is not designed to shift the focus back to cytotoxic drug development, but to reiterate that research into mechanisms of platinum resistance and their manipulation may lead to therapeutic developments of the magnitude now preferentially expected from "targeted therapies." In fact, in an animal model of ovarian cancer from Dinulescu's laboratory (27), cisplatin is able to achieve cures that are beyond the reach of targeted agents directed against the targets that were

implicated in the model. Similar observations have been made in the engineered mouse model of triple negative breast cancer (28).

Platinums in the Era of "Targeted Agents"

One might ask: What is it that continues to bring together chemists, basic scientists, and oncologists to hold meetings on platinums? For those of us who have attended a number of these events, the answer appears to be that platinums represent the culmination of anticancer drug development to date, and their achievements have continued to expand over the years (see Table 1). As an example, the 2007 meeting showcased a new generation of "targeted" drugs, such as poly (ADP-ribose) polymerase-1 (PARP-1) inhibitors and the proteasome inhibitor bortezomib, which are reversing important mechanisms that mediate resistance to platinums, such as DNA-repair and intracellular transport, respectively. The involvement of chemists and experimental biologists gleaned from these publications stimulates clinical investigations, and vice versa.

For an oncologist, the overview of these meetings epitomizes the satisfaction of being part of scientific advances that have the potential of bringing about major improvements in outcomes where inexorable progression of a cancerous tumor was once the rule. The pioneers that led the field of cancer chemotherapy in the early days were undoubtedly similarly inspired. Learning more about platinum drugs continues to provide us with an expanding number of patients that can attain the most successful outcome: a cure.

Table 1 Highlights of the ten international symposia on platinum coordination compounds in cancer chemotherapy (ISPCC), from 1971 to 2007

Year	Site	Chair(s)	Highlights and/or (ref)
1971	Prague	Barnett Rosenberg	Cisplatin: discovery and preclinical activity (29)
1973	Oxford	Tom Connors and John Roberts	(30)
1976	Dallas	Joseph Hill	Phase II studies by NCI and the Wadley Institute (31, 32)
1983	Burlington	Irwin Krakoff	Carboplatin introduced (33)
1987	Padova	Mario Nicolini	(34)
1991	San Diego	Stephen Howell	(35)
1995	Amsterdam	Herbert Pinedo and Jan Schornagel	(36)
1999	Oxford	Lloyd Kelland and IR Judson	Oxaliplatin highlighted (37)
2003	New York	Nicholas Farrell and Franco Muggia	Copper transporters; clinical results in gynecologic and colorectal cancers
2007	Verona	Andrea Bonetti and Roberto Leone	Current publication

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Section A
Novel Platinum Analogues, Original Formulations and Other Heavy Metals