Cisplatin: an overview of clinical research focus since its approval

While at the National Cancer Institute (NCI), we shepherded cisplatin clinical development under the aegis of the Investigational Drug Branch and the NCI Cooperative Group Program (1-3). Its unprecedented activity against testicular and ovarian cancers ensured its use in the treatment of these cancers as initially described by Einhorn (4) and clinical investigators in UK and US (5, 6). Table 1 highlights developments as documented in the symposia listed in the table below (copied from reference with number referring to original article, unless referenced in text below):

Year	Site	Chairs	Selected Highlights
1971	Prague, Czech Republic	Barnett Rosenberg	Discovery and preclinical activity of cisplatin (unpublished; based on Rosenberg et al[11])
1973	Oxford, United Kingdom	Tom Connors and John Roberts	Interactions with DNA, excision repair, and analogue development[12]
1976	Dallas, TX	Joseph Hill	Preclinical and clinical studies in solid tumors and leukemias by Wadley Institute and NCI[13,14]
1978	Washington, DC	Franco Muggia, Marcel Rozencweig, Vincent Bono, and Edwin Jacobs	Cures for most germ cell cancers and imminent FDA approval for ovarian and bladder cancers[20]
1983	Burlington, VT	Irving Krakoff	Carboplatin introduced (unpublished)
1987	Padua, Italy	Mario Nicolini	Biochemistry and toxicology, kidney protection by chloruresis, and expanding clinical indications[15]
1991	San Diego, CA	Stephen Howell	Chemistry, molecular effects, toxicity protection, and Calvert formula for carboplatin dosing[16]
1995	Amsterdam, the Netherlands	Herbert Pinedo and Jan Schornagel	Preclinical and clinical comparisons of cisplatin, carboplatin, and other analogs in clinical study[17]
1999	Oxford, United Kingdom	Lloyd Kelland	New useful platinums, such as oxaliplatin (1,2-diaminocyclohexane platinum), in phase III trials[18]
2003	New York, NY	Nicholas Farrell and Franco Muggia	Copper transporters and mature clinical results in gynecologic and colorectal cancers (unpublished)[18a,18b]
2007	Verona, Italy	Andrea Bonetti and Roberto Leone	Modulation of DNA repair, detection of platinum cellular damage in normal tissues, and overview of radiosensitization[19]
2012	Verona, Italy	Andrea **Bonetti** and Roberto Leone	Neuro-, nephro-, and ototoxicity protection by organic cation transporter inhibitors[20]

Cisplatin highlights since 1978 are the following areas: 1) **Analogue development -**toxicity modification led to 1988 approval of *carboplatin*, and further extending cisplatin's therapeutic spectrum with *oxaliplatin's* unique activity against gastrointestinal cancers. 2) **Toxicity modification -**preclinical studies helped introduce hydration, mannitol and chloruresis; more recently, organic transporter inhibitors and use of sodium thiosulfate are convincingly protecting against nephron- and oto-toxicities. A major landmark was introducing effective **antiemetics** during the past two decades. 3) **Radiosensitization -** clinical trials initially in head & neck cancers and eventually most convincingly in locally advanced squamous cancers of uterine cervix, cisplatin + radiation led to improvements in survival and universally adoption as standard treatment. 4) **Intraperitoneal (IP) therapy -**cisplatin administered via IP route has consistently led to superior results in low-volume residual disease ovarian cancer after surgery versus intravenous administration. The latest phase III studies give contrary results: one including bevacizumab and weekly paclitaxel in IP and IV arms fails to favor IP cisplatin, while the other study yielded superior survival after IP cisplatin consolidation plus heat plus kidney protection by sodium thiosulfate (8). 5) **Deeper understanding of DNA repair** in animal models (9) and the clinic has identified additional cancers such as BRCA mutation-related triple negative breast cancer to be highly sensitive to cisplatin, and, lastly, 6) **Immunogenic cell death -**cisplatin and oxaliplatin enhance localization of tumor infiltrating lymphocytes (TILs) and have effects on immune-surveillance (10) and enhancement by anti-PD1, heralding new areas of clinical investigation (11).

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