New Cisplatin Analogues in Development
A Review

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Summary

Cisplatin was discovered to have cytotoxic properties in the 1960s, and by the end of the 1970s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers. Since the early seminal work in the preclinical and clinical development of this drug, several thousand analogues have been synthesised and tested for properties that would enhance the therapeutic index of cisplatin. About 13 of these analogues have been evaluated in clinical trials, but only one (carboplatin) has provided definite advantage over cisplatin and achieved worldwide approval. However, carboplatin has afforded benefit only in reducing some cisplatin toxicities; it has not enlarged the spectrum of platinum-sensitive cancers, nor has it proved active in cisplatin-resistant cancers.

The major obstacle to the efficacy of cisplatin or carboplatin is platinum resistance, either innate or acquired. The mechanisms of this resistance have been under intense study, and many of the cisplatin analogues synthesised in the past decade have been designed specifically with the hope of overcoming platinum resistance. The mechanism of the cytotoxic activity of platinum complexes has also been studied intensely. Recently synthesised analogues have been designed
to interact with DNA in a manner different from cisplatin and carboplatin, with the desire of finding new structures with a superior or wider spectrum of antitumour efficacy. Most recently, water soluble platinum complexes that retain antitumour activity, but that can be effectively absorbed after oral administration, have been synthesised with the goal of improving patient quality of life.

Nine platinum analogues are currently in clinical trials around the world (ormaplatin [tetraplatin], oxaliplatin, DWA2114R, enloplatin, lobaplatin, CI-973 [NK-121], 254-S, JM-216 and liposome-entrapped cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) [L-NDDP]). Some of these analogues only represent attempts to reduce cisplatin toxicity and/or allow administration without forced hydration and diuresis, which carboplatin already does. Others are 'third generation' complexes shown to have limited or no cross-resistance with cisplatin in preclinical studies. They are being tested clinically with particular attention to this highly desirable property. Some of these complexes will undoubtedly disappear into oblivion as have most of their predecessors. It is hoped that the 1990s will see the development (and worldwide registration) of another platinum complex that represents a step forward in cancer therapy, perhaps one active in cisplatin-refractory cancers and/or capable of being administered orally.

There are three drugs that have a broad spectrum of antitumour activity and are the most widely used agents for the treatment of human cancers. One of these is the platinum coordination complex cisplatin (the others are doxorubicin and cyclophosphamide). Cisplatin (fig. 1) has been a known chemical since 1845 when it was first named Peyrone's chloride, but its potential cytotoxic properties were unknown until the serendipitous work of Barnett Rosenberg. Rosenberg was studying the effects of an electric field on bacterial cell cultures in 1962. *Escherichia coli* colonies were incubated in a chamber containing ammonium chloride and two platinum electrodes because this metal is a good conductor of electricity and is inert. When a current was applied across the electrodes, bacterial cell division ceased. Instead of dividing, the bacterial cells grew into filaments up to 300 times their normal length. After interruption of the electrical current, bacterial proliferation remained inhibited. This finding meant that it was not an effect of the current but the production of a long-lasting chemical through electrolysis of the platinum electrode that was inhibiting bacterial growth. With two more years of work Rosenberg isolated cisplatin as one of the soluble platinum salts causing the bacterial growth inhibition (Rosenberg et al. 1965, 1967).

Rosenberg reasoned that if these platinum compounds could inhibit bacterial cell division, they might also inhibit cancer cell replication. Testing of relatively nontoxic doses of cisplatin in murine sarcoma 180 produced remarkable tumour regressions and even cures (Rosenberg et al. 1969, 1970). Cisplatin proved to have the most antitumour activity of the evaluated platinum compounds. It also proved active against L1210 leukaemia and other murine cancers (Kociba et al. 1970).

Preclinical toxicological evaluation indicated that cisplatin produced testicular degeneration in monkeys, prostatic atrophy in dogs and acute renal tubular necrosis in dogs (Schaeppi et al. 1973). Therefore, when phase I trials were begun, patients with advanced genitourinary cancers (especially testicular cancer) were particularly sought. A phase I study demonstrated significant tumour regressions in 6 of 11 patients with metastatic testicular carcinoma, including 3 patients with complete remissions (Higby et al. 1974). Such an achievement of a 55% response rate and complete remissions (of any carcinoma) in a phase I study has never been equalled by any other drug.

During this same period in the early 1970s, the combination of bleomycin and vinblastine was proven effective for the treatment of metastatic testicular cancer (Samuels et al. 1975). Cisplatin was added to the bleomycin and vinblastine combination by Lawrence Einhorn. By 1977, 50 patients were reported to have received the 3-drug combination, with 85% achieving durable complete re-