How cisplatin created the start of a revolution in cancer treatment

Each year, thousands of people who are successfully treated with platinum-based chemotherapy have inquisitive Michigan physicist Barnett Rosenberg to thank for their improved health. In 1964, he electrocuted a batch of *Escherichia coli* using platinum electrodes and discovered that the electric current stopped the cells from dividing, although they continued to grow. The fact the cells failed to divide even when the current was switched off made Rosenberg think that a chemical reaction had been set up between the usually non-reactive platinum electrodes and something in the bacterial culture medium. He was right, and the antimitotic chemical that had been produced was cis-diamminedichloroplatinum (II) — cisplatin — a chemical first made in 1845.

Subsequent animal studies showed that, after administration, cisplatin reached high concentrations in kidney, liver, ovary, testis and uterus, and the first promising clinical results were in testicular and ovarian cancers.

"In the mid to late 70s, cisplatin was the single most important advance for testicular cancer, and there's no doubt that many young men were cured who wouldn't otherwise have been cured. For ovarian cancer, we weren't able to cure women but cisplatin certainly shrank the tumours, so that patients lived longer," says Stan Kaye, Cancer Research UK professor of medical oncology and chairman of the Section of Medicine at the Institute of Cancer Research, Sutton, Surrey.

Start of a revolution

Cisplatin (Neoplatin) was first marketed in the UK in 1979 by Mead Johnson, which later became part of Bristol-Myers Squibb (BMS). The precise way in which cisplatin and other platinum drugs prevents cells from multiplying is the subject of continuing research — not least because tumours generally become resistant to treatment at some stage.

Cisplatin binds to purine bases in DNA to form cross links within and between strands. This damage disrupts DNA replication and transcription and activates cellular signalling pathways, which lead to cell death. It appears to be the attenuation of these apoptotic signals that contributes to tumour resistance to platinum treatment.

It was not long after cisplatin was first used to treat testicular and ovarian cancers that clinicians realised they could get even better results by combining the drug with chemotherapy cocktails already in use.

Combining cisplatin with high-dose vinblastine and bleomycin soon produced a complete remission rate in over 70 per cent in testicular cancer, and adding cisplatin to doxorubicin and cyclophosphamide boosted responses in ovarian cancer.

The high concentrations of cisplatin that accumulated in the kidney proved a challenge for cancer specialists because of the risk of renal toxicity, and deafness and damage to the nervous system were additional hazards.

"Patients had to come in for intensive hydration with intravenous fluids, but people got used to this, and cisplatin became part of standard treatment for much of the 1980s," recalls Professor Kaye.

Carboplatin — a less toxic rival

A second platinum compound, carboplatin, developed at the Institute for Cancer Research proved a major advance because it lacked both renal and ototoxicity. It was launched by BMS in 1989.

"Carboplatin was much easier to use and could be given as outpatient treatment, and trials showed it to be as effective when combined with cyclophosphamide as cisplatin with cyclophosphamide," Professor Kaye explains.

The introduction of paclitaxel in 1991 further improved the outlook for women with ovarian cancer. The combination of paclitaxel and cisplatin was shown to prolong survival.
by 14 months compared with cyclophosphamide and cisplatin in women with advanced ovarian cancer.7

A few years later, another comparative study sealed cisplatin’s fate in ovarian cancer, when the combination of carboplatin and paclitaxel was shown to be less toxic, easier to administer and no less effective than cisplatin and paclitaxel.1

The need to overcome resistance

Since platinum-based chemotherapy is rarely curative for women with ovarian cancer, subsequent research has focused on optimising second-line chemotherapy in those with recurrent disease, and in understanding more about the mechanisms that lead to platinum resistance.2

The National Institute for Health and Clinical Excellence defines women with so-called platinum-sensitive disease as those who do not relapse for 12 months or more after platinum-based treatment, as can 25 to 30 per cent of those with partially platinum-sensitive disease.3

“The majority of patients, we can give platinum treatment more than once, and some can have it two to three times, but eventually the tumour will become resistant, and apoptosis signalling pathways are no longer activated. So we are now looking at drugs that will turn the clock back and restimulate apoptosis,” says Professor Kaye.

He adds that another option is to juggle treatment regimens for platinum-based treatment, for example, using a lower dose weekly regimen for paclitaxel after surgery, instead of the current standard dose, three-weekly cycle, or administering chemotherapy to shrink tumours before debulking surgery. Also under investigation is intraperitoneal administration of chemotherapy, which allows higher concentrations of drug to reach ovarian tumours than intravenous treatment. Initial studies have suggested improved responses but this is at the price of increased adverse and catheter-related events.

Cisplatin — down but not out

Although carboplatin is the basis for current and experimental approaches to treatment of ovarian cancer, cisplatin has retained a role in the treatment of lung, cervix, head and neck, bladder and upper gastrointestinal cancers.4

Professor Kaye explains that cisplatin has less impact on bone marrow than carboplatin so it is the preferred partner in treatment of tumours, such as head and neck cancer, which require bone marrow-damaging radiotherapy.

“The platinum compounds have come to be the most widely used class of drugs for treating cancer,” he concludes, “and that’s especially fortuitous given that the anti-cancer effects of cisplatin were discovered by accident.”

References