Chemotherapy: Renewed Interest in Platinum Compounds

Early clinical trials of the platinum coordination compound PDD [*cis*-dichlorodiammineplatinum(II)] for cancer chemotherapy must have proved frustrating for oncologists. The results were encouraging because regressions did occur in the tumors of some cancer patients—all of whom had very advanced disease and many of whom were resistant to chemotherapy with other drugs or to radiotherapy. In such patients, who are usually near death, any therapeutic benefits, even brief ones, are considered encouraging. Moreover, a wide variety of tumors, including carcinomas of the head and neck, ovaries, and testes, in addition to some sarcomas and lymphomas, were among those responding. However, the high toxicity of the drug, especially to the kidney, limited the size of the dose that could be given and was a major impediment to its routine use for humans.

The results were promising nonetheless, and investigators have been looking for a way to reduce the kidney toxicity of platinum coordination compounds without decreasing the antitumor activity. Recently, a group of investigators at Memorial Sloan-Kettering Cancer Center found that they could achieve this goal simply by increasing the flow of urine through the patient's kidneys at the time the PDD is administered. Irwin Krakoff, Estaban Cvitkovic, and their colleagues first administer 1 to 2 liters of fluid to the patient by intravenous injection. Then they give PDD intravenously together with a diuretic.

Increasing the urine flow in this manner helps to prevent kidney damage so that the patients can receive the therapeutic benefits of larger PDD doses. According to the investigators, the technique permits the administration of doses of PDD up to three times greater than those that can be given by conventional methods. Moreover, approximately 40 percent of 60 patients with advanced disseminated cancers had measurable tumor regressions. Krakoff says that this response rate is greater than that seen in previous studies.

Claude Merrin of Roswell Park Memorial Institute has also found that increasing urine flow permits the administration of high doses of PDD without damaging the kidneys. He infuses the platinum drug together with diuretics in 2 liters of fluid. With this technique, Merrin has obtained complete remissions, lasting an average of 1½ months with no recurrences, in five of nine patients with advanced testicular cancer. Three patients had incomplete tumor regressions.

Another way to minimize toxicity without sacrificing therapeutic effectiveness is to use combinations of two or more drugs that have different side effects. The idea is that each drug can be administered in doses low enough to avoid irreversibly damaging a particular organ or system. Frequently, however, the therapeutic effects are at least additive and the combination proves even more effective than either agent alone.

Chemotherapy combining PDD with other drugs is already being tried for some human cancers and with some success. Krakoff, for example, has found that PDD given as described previously, in combination with bleomycin caused brief, but complete regressions of far advanced testicular cancer in 9 of 16 patients. Recently, Krakoff has added the drugs actinomycin, cyclophosphamide, and vinblastine to the combination and has observed regressions—two-thirds of them complete remissions—in 95 percent of 30 patients with cancer of the testis. These were all patients with metastatic disease that was not as far advanced as that of the patients in the previous studies. In the 10 months since the current study began, only four of those experiencing regressions have relapsed.

Ovarian cancer is difficult to treat successfully because it has usually spread before it is detected. James F. Holland, Howard Bruckner, and their colleagues at Mount Sinai School of Medicine compared the efficacy of three chemotherapeutic regimes for treating advanced metastatic cancer of the ovary. These were PDD alone, PDD plus adriamycin, and thio-TEPA with methotrexate. Each treatment group consisted of 12 patients. Two-thirds of those getting both PDD and adriamycin responded with partial remissions, whereas 40 percent responded to PDD alone, and 50 percent responded to the remaining combination. The investigators concluded, perhaps somewhat conservatively, that the combination of PDD with adriamycin is at least equal in effectiveness to standard treatments for ovarian cancer.

Although kidney damage is the factor that has been limiting the size of the doses of PDD that can be given to human patients, the drug, like other cancer chemotherapeutic agents, also causes gastrointestinal problems such as nausea and vomiting and depresses the function of the bone marrow so that it produces fewer than normal white blood cells and platelets.

Many investigators think that PDD exerts its antitumor effects by inhibiting cell division. This would be consistent with its effects on bone marrow, for example. Glen Gale and his colleagues at the Medical University of South Carolina and the Veterans Administration Hospital in Charleston, have evidence that platinum coordination compounds bind to DNA and also to RNA, and that they inhibit DNA synthesis. Cells must duplicate their DNA before they can divide. The compounds inhibit RNA and protein synthesis to a lesser extent.

Barnett Rosenberg and Harold Harder of Michigan State University have observed similar inhibitory effects, but Rosenberg thinks that the drugs do not necessarily act by directly killing tumor cells. He has evidence that a mouse tumor can continue to grow for 4 to 5 days after drug administration before beginning to regress. Rosenberg hypothesizes that platinum coordination compounds may act by enhancing the antigenicity of tumors so that they become more susceptible to destruction by the immune system.

In one experiment, he exposed tumor cells to a PDD concentration that was two orders of magnitude lower than that killing cells. A high proportion of the cells appeared to remain viable after the treatment. When he transplanted the treated cells into a host animal in which they would normally produce tumors, no tumors grew. But the hosts did develop an immunity that prevented the growth of subsequently administered untreated tumor cells. Killed tumor cells did not grow or induce immunity in the animals.

With Philip Conran, also of Michigan State, Rosenberg has shown that hydrocortisone, a known depressor of immune responses, decreases the number of PDD-induced cures of a tumor in one strain of mice. Normally PDD is almost 100 percent effective against the tumor in this mouse strain. On the other hand, zymosan, an immunostimulant, increased to 50 percent the number of PDD-induced cures of the same tumor in a different type of mouse; the drug alone has little activity in this system.

Although these results indicate that the immune system may work in conjunction with platinum drugs in evoking tumor regressions, several investigators, including Joseph M. Hill and his colleagues at the Wadley Institutes of Molecular Medicine in Dallas, have evidence that platinum coordination compounds suppress both humoral and cell-mediated immunity. For example, these investigators showed that PDD decreases the capacity of mice to produce anti-

body-forming cells in response to antigen and suppresses antibody production by cells that had been sensitized to antigen. The compound also prolongs the survival of skin grafts in mice.

Rosenberg hypothesizes, however, that platinum drugs increase the cells' antigenicity sufficiently so that even a depressed immune system can destroy them. How the drugs do this is unclear, but a recent serendipitous discovery by Rosenberg with Surinder Aggarwal, also of Michigan State, may provide an explanation. Platinum coordination compounds are known to bind to DNA and RNA. The Michigan investigators wanted to make use of this property to develop platinum stains for electron microscopy. They found that "platinum blues," certain complexes of platinum with pyrimidine derivatives, could stain the DNA- and RNA-containing structures of cells. While examining a number of cell types, they noted that tumor cells appeared to carry surface DNA.

According to Rosenberg and Aggarwal, only cells that can produce tumors when transplanted into suitable hosts have the surface material that binds platinum blues; normal cells do not. They think that the material is probably nucleic acid because platinum blues do not appear to bind to cell membranes or other components. They think that it is DNA and not RNA because treatment of tumor cells with deoxyribonuclease, an enzyme that breaks down only DNA, abolishes the binding whereas treatment with ribonuclease has no effect on it.

Investigators, including Richard Lerner of the Scripps Clinic and Research Foundation, have found DNA on the surfaces of other cells, principally on lymphocytes. The function of this DNA is unknown. Lerner has expressed reservations about whether or not tumor cell surfaces really do carry DNA. He says that he has had trouble duplicating some of Rosenberg and Aggarwal's experiments.

Nevertheless, Rosenberg hypothesizes that DNA, which is known to be only a very weak stimulator of the immune system, may help protect tumor cells against immune attack by masking tumor antigens. Combination of the platinum compounds with the DNA might then eliminate the masking effect and make the cells more antigenic and susceptible to destruction. If the presence of DNA on tumor cell surfaces is confirmed and if this turns out to be a general characteristic of tumor cells, then it may provide a basis for designing drugs that can bind specifically to these cells and trigger their destruction by the immune system without harming normal cells.

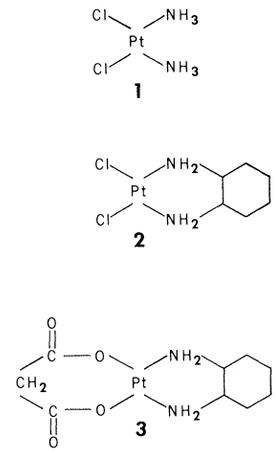

Fig. 1. Structures of some platinum coordination compounds: (**1**) the parent compound *cis*-dichlorodiammineplatinum(II); (**2**) dichloro(1,2-diaminocyclohexane)platinum(II); (**3**) malonato(1,2-diaminocyclohexane)platinum(II).

Synthesis of different platinum coordination compounds (Fig. 1) with less renal toxicity and, ideally, greater antitumor activity is another goal actively sought by investigators. One compound that has been recently tested is *cis*-dichlorobiscyclopentylamineplatinum(II). The compound, which was synthesized and tested for antitumor activity by Martin Tobe of University College in London and T. A. Connors at the Chester Beatty Institute in London, was found to be active, at least against certain animal tumors, much less toxic than PDD, and, unlike most drugs used for cancer chemotherapy, not an immunodepressant.

However, preliminary trials with human cancer patients that were carried out by Hill and his colleagues illustrate another problem that must be solved if platinum compounds are to be widely used. That is their insolubility in the solvents normally used for dissolving drugs. The Wadley investigators found that virtually all of this platinum derivative remained at the injection site and no clinical benefits ensued for the patients.

The platinum blues, whatever their composition, are soluble in water. Hill began testing these complexes in 13 patients with far advanced cancers and observed no therapeutic benefits. He stopped the trial because one patient had a fatal adverse reaction that may have been due to an atypical cardiac toxicity or to an allergic reaction.

Investigators hope that some of the organoplatinum compounds that are now being synthesized prove more effective against human tumors than did *cis*-dichlorobiscyclopentylamineplatinum(II) and the platinum blues. Gale and his colleagues have recently tested a series of 46 compounds against L1210 mouse leukemia. This leukemia is one of the standard cancers that the National Cancer Institute uses to screen for chemotherapeutic drugs; the results are considered highly predictive of the efficacy of an agent in humans.

Several materials screened by Gale did prolong the lives of leukemic mice. The most effective was dichloro(1,2-diaminocyclohexane)platinum(II). The toxicity of this compound is about the same as that of PDD, but is more effective than PDD against L1210 leukemia.

This compound is still not very soluble, so the South Carolina investigators have synthesized derivatives of it in which the chlorides were replaced with various anions. The substitutions did increase the solubility of the products while either enhancing or at least not diminishing their effectiveness against L1210 leukemia. One of these derivatives is malonato(1,2-diaminocyclohexane)platinum(II). Hill and his coworkers have shown that this compound is effective against a number of animal tumors in addition to L1210 leukemia. Their early data suggest that it may be less toxic than PDD and consequently less difficult to use for cancer chemotherapy in humans. The investigators are now carrying out clinical trials to determine its toxicity and the doses tolerated by human patients. In these early trials on patients with far advanced disease, the drug produced a complete remission of acute myelogenous leukemia, that lasted 45 days, in one patient and partial remissions in four others.

Gale has tested the platinum compounds he found to be active against L1210 leukemia, including dichloro(1,2-diaminocyclohexane)platinum(II) and its malonate derivative, in combination with other drugs. He found that they act synergistically with cyclophosphamide in prolonging the lives of leukemic mice. Untreated controls survive only for 6 to 7 days after inoculation with leukemia cells. Although neither the platinum compounds nor cyclophosphamide cured the animals, as judged by survival for more than 60 days, the average cure rate when the two were given in various combinations, was about 50 percent. Addition of a third drug, such as cytosine arabinoside, 5-fluorouracil, or methotrexate, to the combination increased the overall cure rate to about 70 percent. Investigators hope that this kind of tinkering with the structures of the complexes and with different drug combinations will one day enable them to make chemotherapy with platinum compounds as good as gold.—JEAN L. MARX