Drugs Against Cancer: Stories of Discovery and the Quest for a Cure

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CHAPTER 3

The Platinum Story: From Imagination to a New Anticancer Drug.

The previous 2 chapters were about alkylating agents: anticancer drugs that damage DNA by binding tightly (covalently) to DNA bases, especially to guanine. Surprisingly, it turned out that certain molecules centered on a platinum atom can bind and damage DNA in a manner that is rather similar to that of alkylating agents, again especially by attacking DNA at guanines. The anticancer activity of platinum complexes was one of the most surprising and far-reaching discoveries in all of anti-cancer drug research. Particularly remarkable is how that landmark discovery was made.

The first and structurally simplest of the platinum complexes to be discovered was cisplatin, which, with its modified forms, became a mainstay of cancer chemotherapy. Cisplatin would not have been discovered in the drug screening programs, because it is an inorganic chemical, while all cancer drug research had been in the realm of organic chemistry, which is based on carbon atoms. Cisplatin is made up entirely of an atom of the heavy metal, platinum, 2 chlorine atoms, 2 nitrogen atoms, and a few hydrogens; there is not a single carbon atom in it (Figure 3.1). Nor would it have been discovered by searching natural products made by animals, plants, fungi, or microorganisms, because platinum has not been found in any natural biological system.

Even if heavy metal complexes had been screened for anti-cancer activity, cisplatin could easily have been missed, because the atoms and their configuration have to be just right. For example, cisplatin and transplatin consist of the same atoms and bonds, differing only in whether the 2 chlorines are next to each other (*cis*) or across

from each other (*trans*), yet only the *cis* configuration has anti-cancer activity (Figure 3.1).

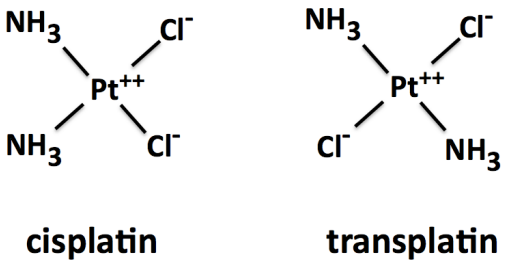


Figure 3.1. Chemical structures of cisplatin and transplatin. The 2 chlorides (Cl^-) and 2 ammonias (NH3) are arranged in a plane around the platinum (Pt^{++}) atom. The chlorides are next to each other (*cis*) in cisplatin and across from each other (*trans*) in transplatin. The platinum atom has 2 positive charges, while the chlorides have one negative charge each; therefore. these platinum complexes are electrically neutral, which allows them to enter cells easily. Both cisplatin and transplatin bind to DNA at guanine-N7 positions. But only cisplatin has the geometry to form DNA crosslinks, and only cisplatin was effective as an anticancer drug.

Discovery by imagination

The clue to the discovery of cisplatin came from an accidental and seemingly bizarre observation by an imaginative and persistent investigator. As noted by Pestko (Petsko, 2002): “cisplatin came from outside the box - so far outside that the box wasn't even visible; it came from a place no one would have dreamt of looking in for an anticancer drug”.

Also relevant to the story is a remark by Albert Einstein: "Imagination can be even more important than knowledge."

Barnett Rosenberg -- his friends called him "Barney") (Figure 3.2) -- was a biophysicist, working in a small laboratory at Michigan State University with just one assistant. He had graduated from Brooklyn College in 1948 and obtained a PhD in physics from New York University in 1956.

As a biophysicist, a natural way to combine biology and physics in those early days was to examine the effects of electric current on the growth of bacteria; the techniques for such a study were straight forward and easily set up in a modest laboratory. There was little reason to expect any interesting findings.

Figure 3.2. Barnett ("Barney") Rosenberg (1926-2009), discoverer of cisplatin. (Picture from Wikipedia. Source: General Motors Cancer Research Foundation.)

Here is what happened ((Rosenberg et al., 1965), and from what he told me). Barney had a culture of E. coli bacteria growing in a growth medium in which he had inserted 2 electrodes connected to pass an electric current through the medium while the bacteria were in there growing and dividing. The electrodes were made of platinum, which was considered to be an inert metal that would not react chemically with anything in the culture. One day, according to Barney, the culture didn't grow. He thought his technician must have forgotten to inoculate the bacteria into the broth. The technician may have known that he did indeed inoculate it, but thought that, well, he'd inoculate it again in the morning. But the broth was perfectly good, he thought, so why bother preparing it again in the morning, so he just put it into the refrigerator. Next day, despite a fresh inoculum of bacteria, still nothing seemed to be growing in that old medium. Now, under similar circumstance, many a researcher would have just dumped the old medium and started fresh. But Rosenberg was curious, so he took a bit of the medium, which was still perfectly clear, as if nothing was growing -- and looked at it under the microscope. What he saw was astonishing.

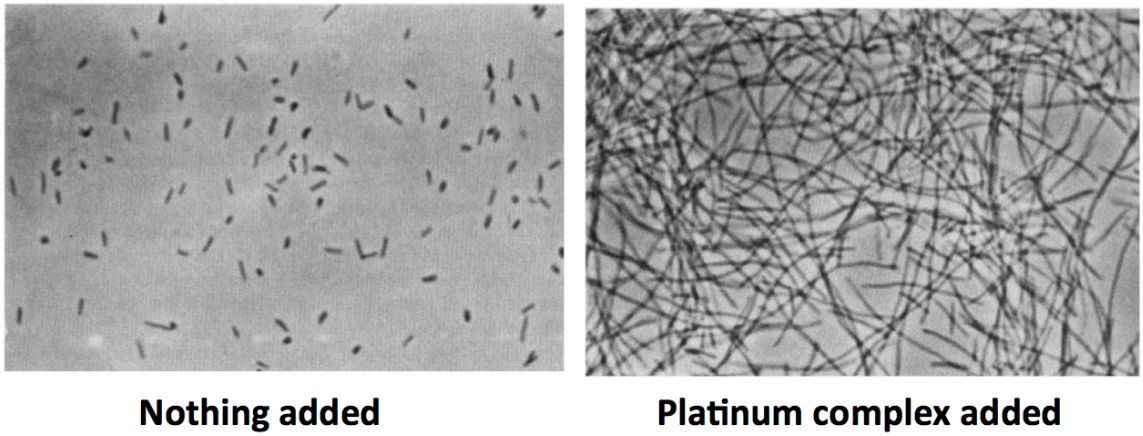


Figure 3.3. The platinum complex prevented the bacteria from dividing but allowed them to grow into long filaments. E. coli grown without (left) or with (right) an active platinum complex (X600) (Rosenberg et al., 1967a). The image on the right may have been concentrated by centrifugation, because what Rosenberg saw would have been a much sparser number of filaments in the microscope field.

E. coli bacteria are normally short rods. But what Rosenberg saw under the microscope were long filaments (Figure 3.3). It seemed that the E. coli were growing in length but not dividing. It is impossible to know exactly what was going through his mind when he saw that, but it might have been something like this: There is something in this medium that is preventing the bacteria from dividing, even though it is allowing them to grow in substance, thereby producing those long threads. It has recently been reported, he might have reasoned, that x-rays and agents like nitrogen mustard do exactly that: they let the bacteria grow but inhibit their ability to divide: they were reported to grow into long threads just like what is here now in this medium. Furthermore, x rays and nitrogen mustard have anticancer activity. So, maybe an anti-cancer substance might somehow have gotten into the medium. But how? The only thing different from the original medium in which the bacteria were growing normally is that there were thin platinum bars (the electrodes) immersed in it and I had passed an electric current through them. But platinum is chemically inert. Or is it? What about the electricity that was going through those platinum electrodes? It might have caused some platinum atoms to come off and bind to the ammonia or chloride in the medium.

So that was it! Following up on those ideas, Rosenberg ordered several platinum complexes that were available from a chemical supply company. He soon discovered the active material that prevented the bacteria from dividing while allowing them to grow into long threads: it was indeed a complex of platinum with ammonia and chloride (Rosenberg et al., 1967b); it was in fact the drug that we now call cisplatin (Figure 3.1). In short order, it was tested at the National Cancer Institute and at the Chester Beatty in England for anti-cancer activity in mice. And the results were spectacular! The anticancer activity of the platinum complex was astounding.

Moreover, when cisplatin was combined with other drugs, such as cyclophosphamide, the anti-cancer effects were even more impressive (Rosenberg and VanCamp, 1970) (Woodman et al., 1973).

Cisplatin and nitrogen mustard are chemical cousins.

The chemical structures of cisplatin and nitrogen mustard may look different (Figure 3.4); nevertheless they both work by crosslinking DNA (Zwelling et al., 1981). The favored site of attack on DNA was found to be the same for cisplatin and nitrogen mustard: the nitrogen at position 7 of guanine.

The only similarity between the two structures is that each has 2 chlorine atoms -- which indeed is the key to the similarity in their chemical actions. In both drugs, each chlorine can come off, leaving behind a reactive site capable of forming a covalent bond with DNA or proteins. Both drugs have 2 reactive sites whereby DNA can become crosslinked. Although cisplatin, like nitrogen mustard, can produce interstrand crosslinks (Zwelling et al., 1981), cisplatin differs in that it more frequently produces DNA-disabling intra-strand crosslinks (Figure 3.5).

Crosslink repair is paramount to the drug-treated cell's survival. The cell has highly effective DNA repair mechanisms, which however are not foolproof. Sometimes it leaves the repaired DNA with missing bases, thus producing mutations.

However, there was a puzzle about cisplatin: the powerful antitumor action of cisplatin was completely abolished if the 2 chlorine atoms were across from each other (*trans* configuration) rather than next to each other as in cisplatin (*cis* configuration). (Figure 3.4). Leonard Zwelling, who was then a Clinical Associate in my laboratory, decided to investigate this puzzle using the DNA filter elution methods we had been developing at that time to measure both DNA interstrand and DNA-protein crosslinks (Kohn, 1996) (see Chapter 9). Len's results were quite remarkable: he showed that the *trans* compound produced almost exclusively DNA-protein crosslinks, and lacked the potent cell-killing and mutation-producing actions of cisplatin (Zwelling et al., 1979a; Zwelling et al., 1979b). Evidently, having the active chlorines across from each other (*trans* geometry) was unsuited for DNA crosslinking, whereas it easily crosslinked between DNA and proteins. We were then able to measure the rates of formation and repair of both types of crosslinks. The t*rans*-platinum compound was also useful in our developing a method to quantify DNA-protein crosslinks (Kohn and Ewig, 1979), a method that proved key to our discovery of topoisomerase-targeted anti-cancer drugs, as related in Chapters 9 and 10.

We found that the interstrand crosslinks produced by cisplatin in cells did not form right away. The number of crosslinks increased for 12 hours before reaching its peak and then declined as they were repaired (left panel in Figure 3.6). DNA-protein

crosslinks produced by transplatin, on the other hand, formed rapidly and then were repaired (center panel in Figure 3.6).

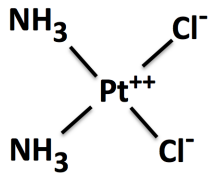
We were astonished by the remarkable difference between the two isomers in that the *trans* isomer (transplatin) produced many DNA-protein crosslinks, but virtually no interstrand crosslinks, a finding that was substantiated by more precise quantitative measurements (Kohn and Ewig, 1979).

That difference went along with cisplatin being tremendously more effective than transplatin in killing cells (right panel of Figure 3.6). We concluded that, at least in the cells we studied, cisplatin-induced DNA inter-strand crosslinks (or the intra-strand crosslinks that correlated with them) were highly toxic, but DNA-protein crosslinks were effectively repaired and were toxic only at very high drug concentrations.

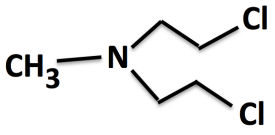
Cisplatin's platinum atom (Pt) binds to the same nitrogen atom on guanines (GN7) as nitrogen mustard does, although nitrogen mustard more often forms *inter*-strand crosslinks than cisplatin does (Figure 3.5).

Although it may seem surprising, the 2 DNA crosslinking drugs, cisplatin and cyclophosphamide (a derivative of nitrogen mustard, see chapter 1), often are more effective when used together (synergistic) than either of them used separately (Woodman et al., 1973). The reason may be that the crosslinks produced by the two drugs produce different alterations in DNA structure, such as *intra*-strand versus *inter*-strand crosslinks, which are repaired by different molecular systems. Some tumor cells may have a high ability to repair one or the other type of crosslink, while relatively few could repair both types well.

Another remarkable finding was in a cell line that was selected for resistance to cisplatin but that remained sensitive to L-phenylalanine mustard (melphalan). The cisplatin-resistant line had completely lost its interstrand crosslinking response to cisplatin, as might be expected for a cell line selected for resistance to this drug. That same cisplatin-resistant cell line however produced just as many interstrand crosslinks to melphalan as the original sensitive line cell line (Figure 3.7). This result supported the idea that the sensitivity or resistance of these cell lines depended on whether interstrand crosslinks were produced.



cisplatin



nitrogen mustard

Figure 3.4. The chemical structures of cisplatin and nitrogen mustard look different, but their key chemical reactions are similar. Nitrogen mustard has 2 carbons separating the Cl from the N; that arrangement facilitates the loss of the Cl, leaving behind a reactive group on the molecule (see Chapter 1). Cisplatin too is made reactive by the loss of a chloride, which is facilitated by an abundance of water molecules that replace the Cl^-. An H_2O molecule bound to the Pt^{++} constitutes the reactive site in cisplatin (as well as in transplatin). In both cisplatin and nitrogen mustard, two chlorines are essential, because the departure of each one leaves behind an active center, thus allowing 2 reactions to form a crosslink; the 2 chlorines in cisplatin have to be next to each other for the geometry to allow crosslink formation in DNA.

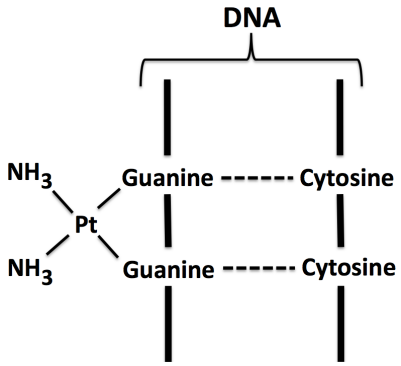


Figure 3.5. After its 2 chlorine ions have come off (and replaced by 2 water molecules), cisplatin can bind to 2 guanines on the same DNA strand. The resulting intra-strand crosslink distorts the DNA, which has to be repaired before the DNA can continue to function; but if the repair fails, the crosslink has lethal potential.

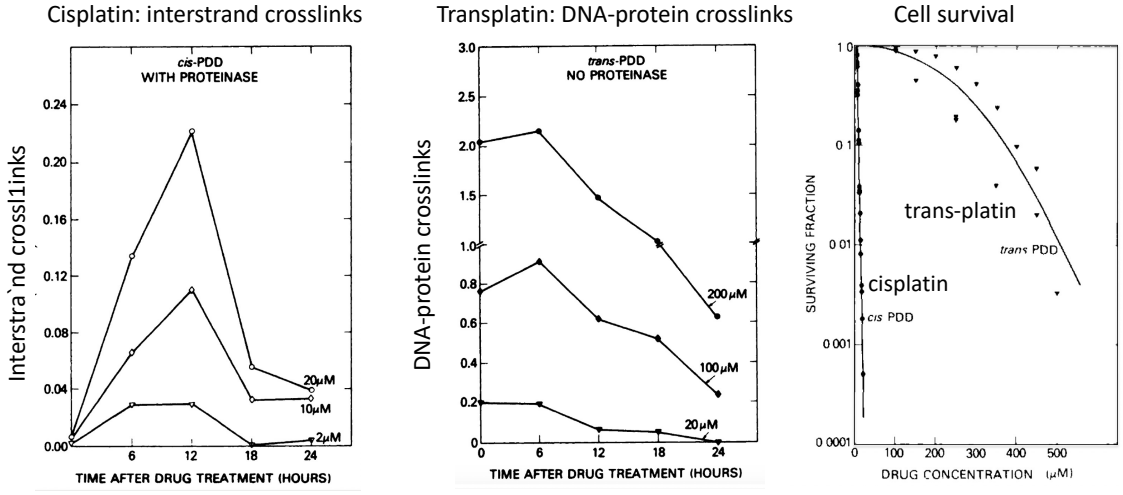


Figure 3.6. *Left:* formation and repair of cisplatin-induced DNA interstrand crosslinks. *Center:* formation and repair of transplatin-induced DNA-proteins crosslinks. *Right:* survival after treatment of cells with cisplatin or transplatin. Interstrand crosslinks and DNA-protein crosslinks in mouse leukemia L1210 cells were measured by filter elution (Zwelling et al., 1978) (see Chapter 9). Cell survival was measured by survival of colony-forming ability of

human V79 cells (Zwelling et al., 1979b). (The production of inter-strand crosslinks may be an approximately proportional measure of the production of intra-strand crosslinks.)

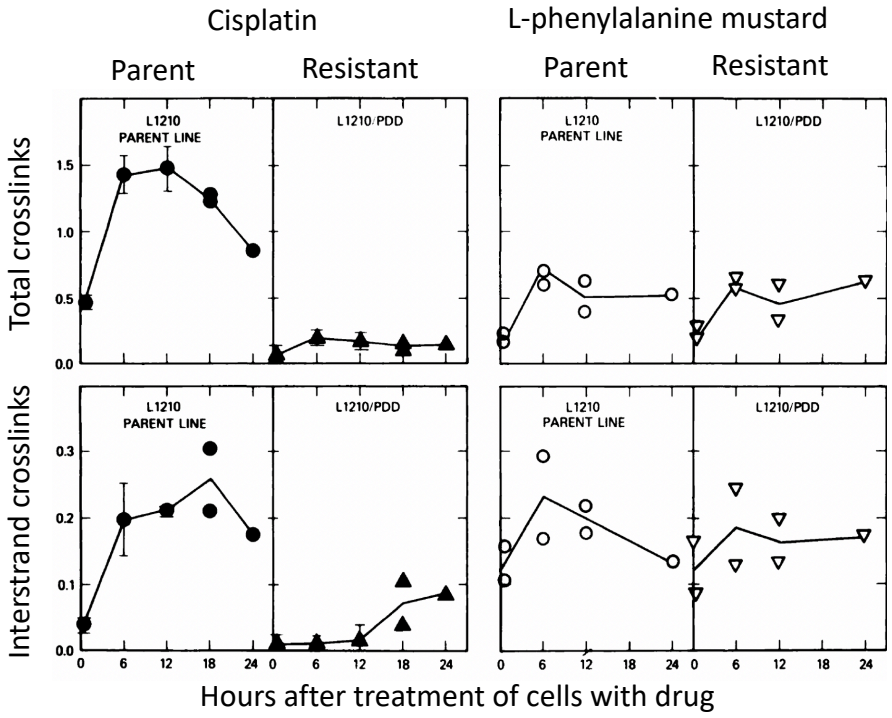


Figure 3.7. A cell line that had been made resistant to cisplatin did not form DNA crosslinks after being treated with cisplatin (*left*). However, the cisplatin-resistant cells retained their sensitivity to L-phenylalanine mustard (melphalan) and melphalan produced crosslinks despite the cell's resistance to cisplatin (*right*) (Zwelling et al., 1981).

From cisplatin treatment to cancer cell death.

There is joy when a patient's cancer responds to chemotherapy. The factors that determine whether the cancer will respond however were complicated and not very well understood. Much attention was paid on identifying factors that gave some degree of predictability of response. Some of them were empirical clinical factors and some were physiology- or molecular-based and all were given much attention as chemical and molecular details were elucidated. A general idea of what was involved is shown in Figure 3.8, which is an overview of some of the main factors that were thought to determine whether a cisplatin-treated cell will live or die.

As the steps governing cancer cell killing were elucidated, that information was used to help improve the clinical effectiveness of the platinum drugs (Galluzzi et al., 2014; Kelland, 2007; O'Grady et al., 2014). The main reaction steps that were found to affect the death or survival of cisplatin-treated cells are diagrammed in Figure 3.8:

first, cisplatin must pass through the cell's plasma membrane to get into the cell, which occurs in part by way of specific channels in the membrane that normally allow essential copper compounds to enter. Particularly important however are other channels, which actively pumped cisplatin (normally copper) out of the cell. The intake and export channels affect how much cisplatin is inside the cell (*a* and *b* in Figure 3.8).

When those particular export pumps were defective, copper was known to accumulate in cells and cause Wilson's disease. One might expect that cisplatin would also accumulate in the cells of Wilson's disease patients, thereby making those cells, whether normal or cancerous more sensitive to the drug. However, Wilson's disease cells express a copper-binding protein that can bind and detoxify cisplatin. The protein binds cisplatin tightly at a pair of cysteines separated by two amino acids (CxxC) and affects the sensitivity of the cells to cisplatin despite the higher concentrations of the sulfur-containing cisplatin binders glutathione and metallothionine (Dolgova et al., 2013).

Once inside the cell, cisplatin is activated by its platinum-bound chlorides being replaced by water molecules (*c* in Figure 3.8). The reason that this replacement activated cisplatin is that the platinum-water bond is weak, and the platinum atom would much rather bind to a nitrogen atom, such as, for example, the one at position 7 of guanine in DNA. That would be the first bond in a prospective DNA crosslink. The main reason that this chloride-water replacement would occur inside the cell, but not outside, is that the concentration of free chloride is much lower inside the cell than outside in the blood.

When cisplatin is water-activated (seems odd to put it that way, so scientists instead say "aquated"), what happens next? Sometimes the aquated cisplatin will bind to N7 of DNA guanine, as mentioned above; that toxic reaction however was relatively rare overall, but its impact overrode its rarity. More often, the aquated cisplatin would have been inactivated by binding tightly to one of the many sulfur compounds in the cell (such as glutathione, a common sulfhydryl compound, or to metallothionein, a metal-binding protein that has a large number of exposed sulfhydryl groups) -- platinum loves sulfur (*d* in Figure 3.8).

The aquated site on the second arm of cisplatin could then proceed to form a DNA crosslink (*e* in Figure 3.8). The resulting DNA damage would be detected by surveillance systems, which signal to the cell's molecular response systems that danger is afoot (*f* in Figure 3.8). The signals activate a remarkable network of logically integrated components that cause the cell to delay DNA replication and cell division to give more time for the cell to adapt and to repair the damage before the replication machinery boggles by trying to replicate through a crosslink, or the chromosomes scramble if the cell tries to mitose while its genome was unrepaired. It also put the cell's DNA repair machinery on high alert (*g* and *h* in Figure 3.8).

After all that, if DNA crosslinks still remained as the cell tried to move forward in the cell division cycle, a lethal event would happen when the DNA replication machinery encountered a crosslink (*i* in Figure 3.8).

Another process that determined life or death for the cell came as an output from the damage detection and response network. If the damage persisted too long, the system took no chances and actively suicided the cell -- aficionados call it "apoptosis" (from Greek "falling off," as in falling off of leaves) (*j* in Figure 3.8). This helped avoid the production of mutated cells that could lead to cancer. However, apoptosis of cancer cells obviously was desirable and was a positive factor for chemotherapeutic response.

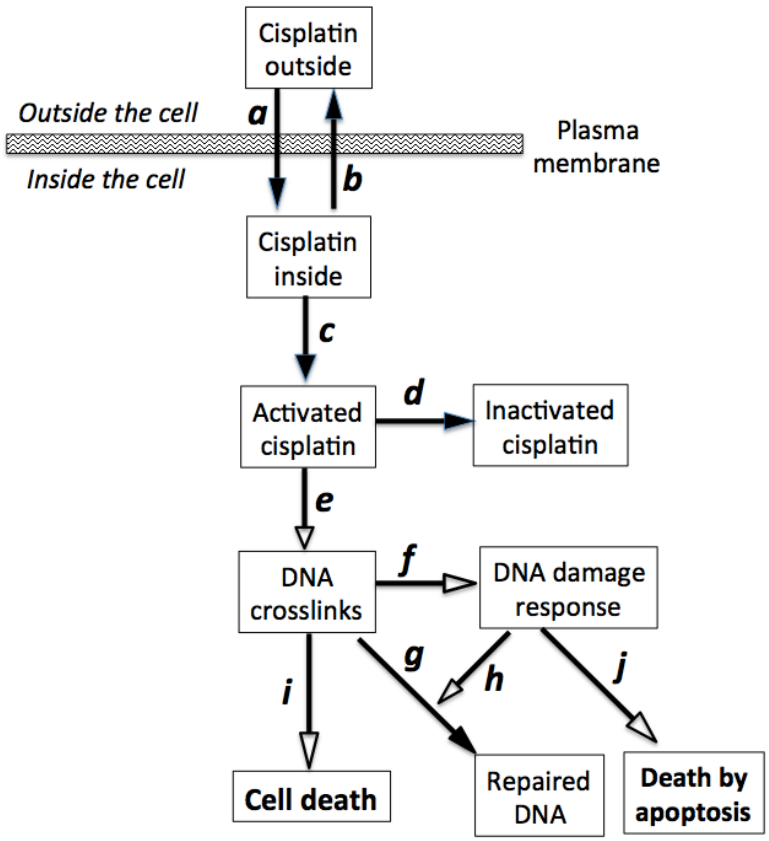


Figure 3.8. Simplified scheme showing factors that were thought to govern the effects of cisplatin on cells. ***a*** Channels allow cisplatin to enter the cell. ***b*** Channels that pump cisplatin out of the cell. ***c*** Cisplatin becomes activated inside the cell by its chlorides being replaced by water molecules (favored inside the cell, where chloride concentration is low). ***d*** Cisplatin can react with sulfur-containing molecules inside the cell to form inactive products. ***e*** Cisplatin produces DNA crosslinks. ***f*** DNA crosslinks stimulate the cell's DNA damage detection and response systems. ***g*** DNA repair machinery of the cell repairs the crosslinks. ***h*** DNA damage response system stimulates the cell's DNA repair machinery. ***i*** Unrepaired DNA crosslinks lead to death of the cell. ***j*** If the DNA damage repair system fails, it induces the cell to suicide by apoptosis (Galluzzi et al., 2014) (O'Grady et al., 2014).

A problem: Cisplatin damages the kidney.

The main toxicity that limited how much cisplatin could safely be given was damage to the kidneys (Figure 3.9). Cisplatin is actively taken up by cells of the kidney tubules, resulting in deleterious drug concentrations in the cells (Yao et al., 2007). Although the problem was not fully solved, the kidney toxicity was reduced by giving patients lots of fluid and diuretics to increase urine flow that would reduce the concentration of the drug in the urine as it flows through the kidney.

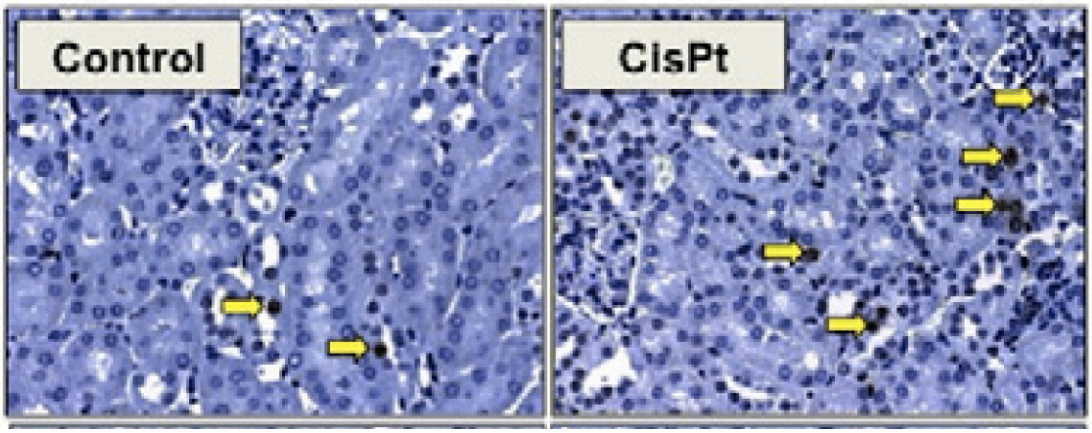


Figure 3.9. Damage to cells of the kidney tubules after a course of cisplatin treatment in mice (Kruger et al., 2016). The yellow arrows point to some of the cell nuclei that have sustained extensive DNA damage (as revealed by staining with antibody to gamma-H2AX; see Chapter 28). After cisplatin treatment (*right*), the number of DNA damaged cells increased 6-fold compared with untreated cells (*left*).

Why some patients refused to take cisplatin.

Cisplatin-containing therapy made most patients so nauseous that many could not stand it. Even entering the hospital where the drug was given was sometimes sufficient to trigger nausea. Many chemotherapeutic drugs can cause nausea, but cisplatin stood out as an extreme case, and the vomiting it induced was sometimes alarming. The cause might be a direct action on certain centers in the brain, but drugs to interfere with that direct action were not yet available. Ordinary available medications would control nausea shortly after the drug was administered. However, extreme nausea occurred later (perhaps after the drug had entered and affected certain neurons in the vomiting center in the brainstem), at which time it was not easily controlled (De Jonghe et al., 2016; Ishido et al., 2016; Shi et al., 2016).

Treatment of cancer patients with Cisplatin and related drugs.

The testing of cisplatin in tumor-bearing mice, which began in 1968, produced results that were so encouraging that only 3 years later the first clinical trial was begun. That was a remarkably short time between finding anti-tumor activity in mice and approval for clinical trial. Not only was there strong evidence of antitumor activity, but the toxicity and dose-levels were well enough understood to try the drug on human patients. Substantial antitumor effect was first reported in 1974 for testicular and ovarian cancer, and several subsequent clinical trials reported increased survival also in lung cancer patients (Lebwohl and Canetta, 1998). Moreover, cisplatin was unusual because it was not toxic to the blood-forming cells in the bone marrow. By 1978, the benefit to cancer patients was promising enough to make cisplatin available for general oncology practice.

The chemical structure of cisplatin is modified in search for better drugs.

Many variations on the cisplatin structure were tested in search for compounds with increased effectiveness against a greater variety of tumors, with less toxicity, or with lack of cross-resistance to cisplatin (Lebwohl and Canetta, 1998). Two structural relatives became widely used: carboplatin and oxaliplatin (Figure 3.10).

In carboplatin, the two chlorine atoms are replaced by a chemical group that has two carboxyl (COO-) groups attached to the platinum atom (Figure 3.10). The carboxyl groups activated the platinum in the same way that the chlorides did, that is, by being replaced by water molecules; however, carboplatin was activated more slowly than cisplatin. Another feature was that the two carboxyl groups were part of a structural unit that might favor both carboxyls coming off at nearly the same time; thus, the two platinum sites would be aquated together, setting the stage for efficient crosslink production. Carboplatin formed the same kinds of DNA crosslinks as cisplatin, but formed them 10-times more slowly, and 30-times higher drug concentrations were needed. The clinical benefit in terms of increased survival time however was not very different from cisplatin; the main benefit of carboplatin was that it was less toxic: it did not damage the kidneys, and spared the gastrointestinal tract and central nervous system; its dose-limiting toxicity, instead, was suppression of platelet and white blood cell production in the bone marrow (Kelland, 2007; Lebwohl and Canetta, 1998).

In oxaliplatin, like carboplatin, the chlorides were replaced by carboxyl groups in a structural unit. Unlike cisplatin and carboplatin, however, the two amino groups were linked together via a 6-membered ring, a cyclohexyl group (Figure 3.10). Oxaliplatin-mediated DNA crosslinks therefore retained this cyclohexyl structure, which might impair the binding of some DNA repair proteins to the damage site. A notable finding in the clinical experience with oxaliplatin was that, unlike

carboplatin, it sometimes was effective in patients whose tumors had stopped responding to cisplatin (Kelland, 2007).

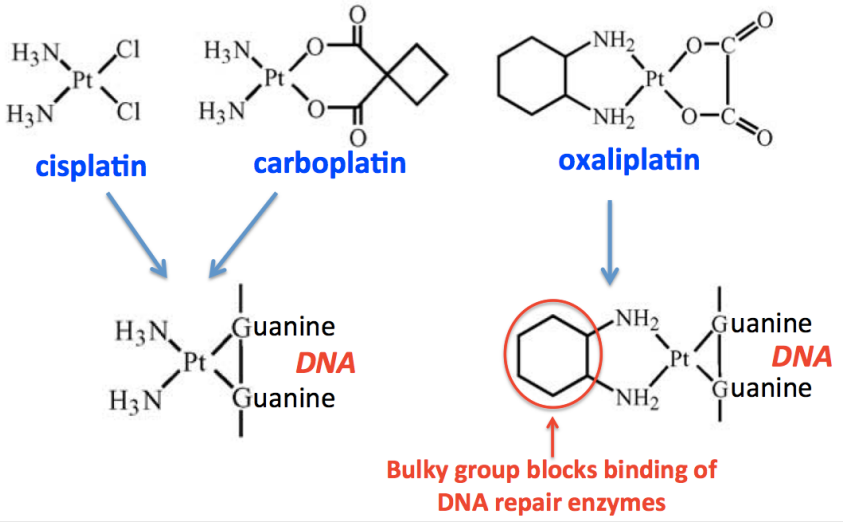


Figure 3.10. The upper row shows the chemical structures of cisplatin and its two relatives that were most commonly used: carboplatin and oxaliplatin. The bottom row shows the structures of the DNA crosslinks formed by each of the drugs. The DNA crosslink produced by oxaliplatin differed from the kind produced by cisplatin or carboplatin in that it had an additional 6-membered ring (cyclohexyl group) sticking out from the DNA; this may block the binding of some DNA repair proteins, and may be why oxaliplatin sometimes worked against tumors that were resistant to cisplatin or carboplatin (Chaney et al., 2005; Kelland, 2007).

Cisplatin cures advanced testicular cancer.

The greatest benefit of cisplatin was for patients with testicular cancer: cisplatin produced lasting remissions in nearly 80% of the cases, and most of the patients who had the common germ cell type of testicular cancer were cured with a drug combination based on cisplatin (Figure 3.11).

Germ cell cancer of the testis, although relatively rare compared to some other types of cancer, was one of the very few types of cancers that could be cured by chemotherapy after the cancer has spread (metastasized). What made cure possible was the addition of cisplatin to previously established drug combinations that by themselves were much less effective (Einhorn, 1997; Einhorn, 1981; Hinton et al., 2003). The susceptibility of testicular cancer to chemotherapy was in part due to a relatively rapid cell proliferation rate compared to other cancers, and to the fact that testicular cancers rarely become dormant. Tumors with active cell division tended to be susceptible to chemotherapy, as was the case for acute leukemias and choriocarcinoma, and those tumors were often curable. Also contributing to their

being curable, may be that testicular cancers were nearly unable to repair the DNA damage caused by the drug. (Kelland, 2007).

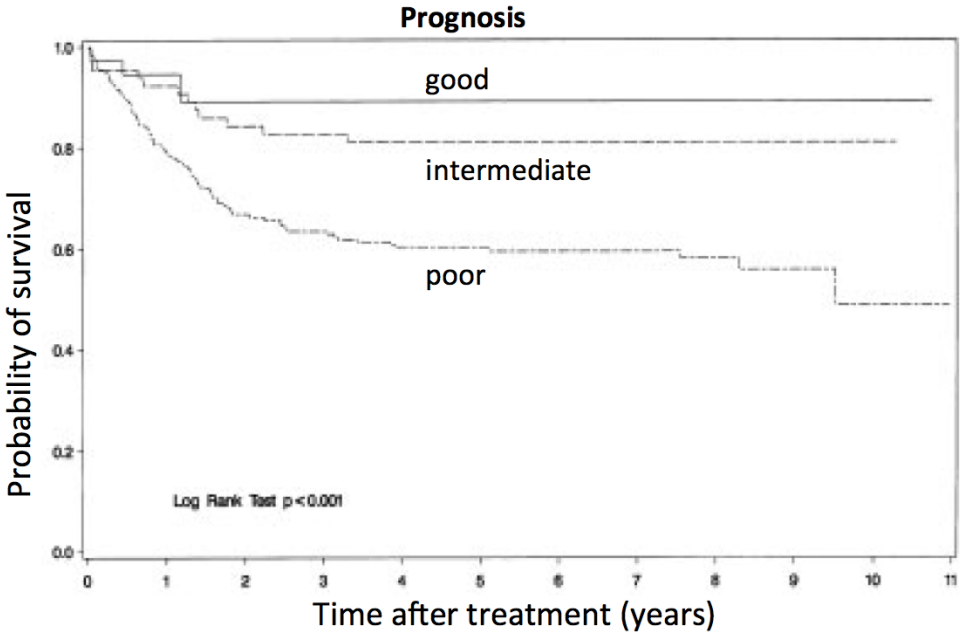


Figure 3.11. A cancer cure. Patients with testicular cancer that had already spread were treated with a cisplatin-based drug combination. The three curves are for patients who were judged at the beginning of treatment to have a good, intermediate, or poor prognosis, based on how advanced their disease was at the time. The results showed that patients whose disease was not highly advanced had greater than 80% chance of remaining alive after 10 years; even highly advanced cases had a 50% chance (Hinton et al., 2003). The curves leveled off with time, showing that patients who survived the first few years were unlikely to die of the disease in the years to come.

Summary

Cisplatin, which became one of the most useful anticancer drugs, was discovered as the result of an accidental event in a very modest laboratory. Its discovery was due to bold thinking by Barnett Rosenberg. The story is remarkable, because there had been no clue that a heavy metal compound, such as cisplatin, could have anticancer activity, and the major drug discovery programs had never considered testing such compounds.

Cisplatin therapy was so promising that great effort was made to overcome the drug's toxicities, and those efforts had significant success. Cisplatin was highly effective and enabled the cure of testicular cancer. The aim then was to modify cisplatin-type therapy so as to find treatments that would be as effective for the common cancers as cisplatin was for testicular cancer. One possibility was that

higher drug doses could be used if toxicity were controlled. Another possibility was to develop better platinum drugs or better drug combinations.

The major toxicity of cisplatin was kidney damage, which however was largely overcome by increased hydration of the patient. Many variations of the cisplatin structure were put in clinical trial, but nothing was found better than the old standbys: cisplatin, carboplatin, and oxaliplatin. Unfortunately, many cancer patients were not helped by any platinum regimens or other available chemotherapy. When tumor regression did occur, it was often brief and survival was extended for but a few months. But complete durable remission did sometimes occur, which gave reason for hope, especially if the exact reasons for the effectiveness against testicular cancer could eventually be worked out.

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