MECHANISMS OF EFFECTS OF PLATINUM (II) AND (IV) COMPLEXES. COMPARISON OF CISPLATIN AND OXALIPLATIN WITH SATRAPLATIN AND LA-12, NEW PT(IV)-BASED DRUGS. A MINIREVIEW

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A b s t r a c t

Platinum-based complexes are important drugs for the treatment of cancer diseases. Compared to the commonly used Pt(II) compounds cisplatin and oxaliplatin, the recently reported complexes containing Pt(IV) seem to have several advantages; they are safer, can be used orally, have a higher scope of anticancer effect, and do not show cross-resistance to cisplatin.

In the first part, cisplatin and oxaliplatin, and satraplatin and LA-12, the Pt(II) and Pt(IV) complexes, respectively, are characterised. Their structures, range of action and side effects are described. In the following part, the mechanisms of their effects are briefly explained, i.e., transport of the active agents to cells, adduct formation, biotransformation pathways, etc. The last part deals with protective mechanisms of the cell, differences in DNA repair mechanisms, and ideas concerning the development of resistance to these drugs.

A b b r e v i a t i o n s   u s e d

CDDP, Cisplatin [cis–diamminedichloroplatinum(II)]; L-OHP, oxaliplatin [oxalato-1,2-diaminocyclohexaneplatinum(II)]; DACH, (diaminocyclohexane); LA-12 [(OC-6-43)-bis(acetato)(1-adamantylamine)amminedichloroplatinum(IV)]; JM216, satraplatin [(OC-6-43)-bis(acetato(amine-dichloro)cyclohexylamine)platinum(IV)]

In 2003, 653.2 patients per 100 000 citizens were newly diagnosed with cancer in the Czech Republic, and cancer mortality per year amounted to 286.2 per 100 000. This was comparable with the situation in the EU, where incidence was 546.2 and mortality 234.2 new cases per 100 000 citizens (*1*). The statistical data also show that the number of patients diagnosed with cancer disease is growing every year; since 1975 cancer incidence has doubled. Patients with cancer undergo surgery, radiation treatment or anticancer drug therapy (chemotherapy) alone or in combination. Chemotherapy has recently achieved good outcomes in 6 % of newly diagnosed patients and in 10 % of all cancer survivors (*2*), but as a single therapeutic approach its efficiency is mostly limited to blood neoplasm; the treatment of solid tumours usually requires multispecialty and multimodality approaches.

In the management of cancer, anticancer therapy including surgical intervention, radiation therapy and chemotherapy, aims at killing all malignant cells or at least considerably reducing their numbers. Adjuvant radiation therapy or chemotherapy is used in patients after surgery, neoadjuvant therapy is given before primary treatment, such as surgery, to reduce tumour size or eliminate micrometastases. In some cases, anticancer therapy has only a palliative effect. Anticancer therapy is supplemented with supportive care for the alleviation of symptoms due to cancer disease itself (pain, dyspnoea) and/or due to its therapy (mycositis, infection).

Apart from killing cancer cells, anticancer therapy usually brings about also destruction or damage to healthy cells and tissues, and thus produces serious side effects.

Drug therapy in cancer patients includes chemotherapy, treatment with differentiating agents, biotherapy designed to repair, stimulate, or enhance the body's own immune responses, and therapy with monoclonal antibody against some cancer antigens.

Amongst the most frequently prescribed anticancer drugs are those based on platinum, such as cisplatin, carboplatin and oxaliplatin. In this paper, cisplatin will be dealt with in detail and also compared with another platinum (II) compound, oxaliplatin, and with two recently prepared platinum (IV) complexes, satraplatin and LA-12.

The platinum-based compound known for the longest time (since 1864) is Peyron's chloride (*3*), today used under the name of cisplatin or CDDP (cis-diamminedichloroplatinum (II)) *(Fig. 1)*. As a chemotherapeutic drug it has been used for cancer treatment since 1978 (4). However, its use is limited due to two drawbacks, namely side effects (nephrotoxicity, ototoxicity, vomiting) and resistance, which is either primary (intrinsic) or secondary (acquired). Cisplatin is administered for a broad range of malignancies, such as testicular, ovarian, bladder,
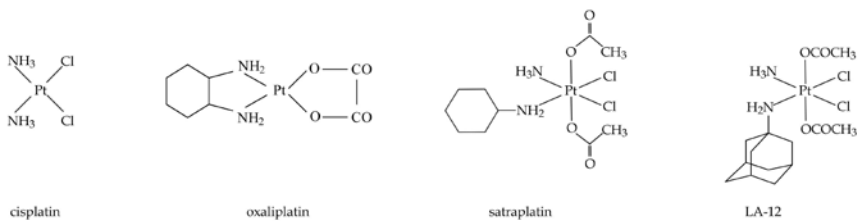
Fig. 1
Chemical structures of platinum compounds
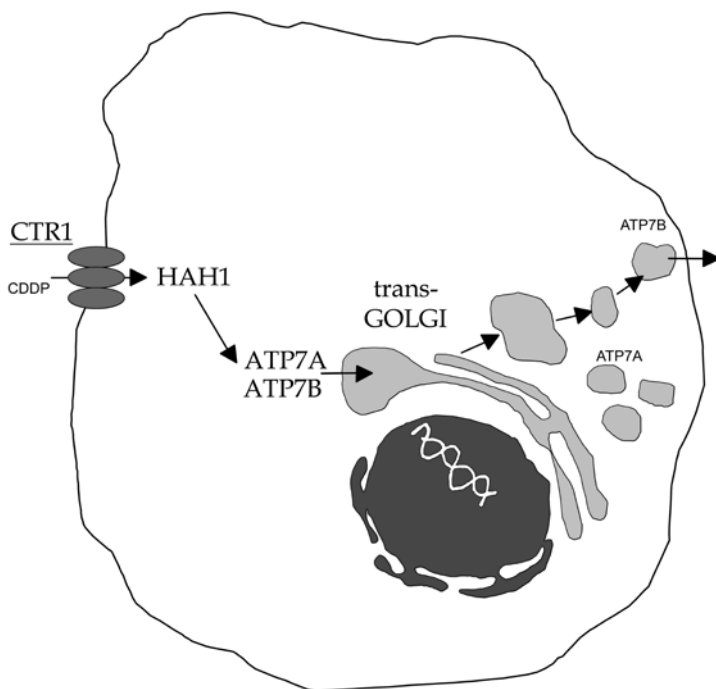
Fig. 2
Schematic drawing of CDDP uptake and efflux processes in the cell. Adapted from *Katano et al.* (*23*)

and head and neck carcinomas. Similar effects are also shown by a cisplatin analogue, carboplatin (cis-diamine(1,1-cyclobutanedicarboxylato) platinum(II)), which has a cross-resistance with cisplatin and exerts lower cytostatic effects on healthy cells.

Recently, a second-generation cisplatin analogue, oxaliplatin (L-OHP; oxalato-1,2-diaminocyclohexane platinum(II)), has been introduced into clinical practice (5) *(Fig. 1)*. It was synthesised around 1970 (6) and was first described in a clinical study in 1986 (7). Since 1999 it has been used as anticancer medication, together with 5-fluorouracil or leucovorin, for the treatment of colorectal cancer in the European Union (5, 8). It shows no cross-resistance with cisplatin or carboplatin, but is associated with other side effects such as peripheral sensory neuropathy or haematological suppression. Since no effective and safe anticancer therapy has so far been available, current research is aimed at developing new drugs or improving those used at present.

The early studies by Rosenberg et al. indicated that both bivalent (Pt (II)) and tetravalent (Pt (IV)) platinum complexes possess antitumour activity (9). Their effects are further improved when a lipophilic group, as a non-leaving ligand, is introduced in the molecule. This facilitates entry of the drug into the cell, allows for drug accumulation and, consequently, for its higher efficacy, thus helping to overcome resistance to other Pt (II) and Pt (IV) complexes (10, 11). Because some tetravalent agents are taken orally, patients' compliance and their comfort should be better.

Satraplatin (JM216) [(OC-6-43)-bis(acetato(amine-dichloro)cyclohexylamine) platinum] is another Pt (IV) compound with the characteristics mentioned above *(Fig. 1)*. It was first described in a clinical study in 1992 (12, 13) and is currently at the third stage of clinical studies. Their results have raised further interest in Pt (IV) compounds and resulted in developing more cisplatin analogues derived from this group. One of these is LA-12 [(OC-6-43)-bis(acetato)(1-adamantylamine)am minedichloroplatinum(IV)], prepared by *Žák et al.* (14) *(Fig. 1)*. In the first trails involving A2780, A2780cis and SK-OV-3 cell lines, it was shown that its efficiency was higher than those of JM216 and CDDP (11, 15, 16). Subsequently, more detailed studies confirmed that blood toxicity, such as leukocytopenia, thrombocytopenia or neuropenia, were milder, hepatotoxicity and nephrotoxicity was absent, and there were no adverse effects on the respiratory and cardiovascular systems or on motor functions (17, 18).

Mechanism of action

The anticancer action of Pt-containing drugs is best described for cisplatin (CDDP). At first, it was believed that it entered the cell by passive diffusion. However, recent studies have shown that there is a relationship between copper transport and CDDP concentration in the cells and that a copper transporter (CTR1) is involved

(*19, 20*). Other proteins participating in cisplatin regulation in the cell include ATP7A and ATP7B (two kinds of copper-efflux-transporting P-type adenosine triphosphate). CTR1 plays a role in uptake and ATP7B regulates efflux processes (*21, 22, 23*). ATP7A is involved in copper transport from the cytoplasm to secretory vesicles via the Golgi complex, and then out of the cell. In cells treated with cisplatin, ATP7A mediates its inclusion in vesicles and, in some cell lines, it brings about cell detoxication (*24*) *(Fig. 2)*. Other active transporters that have been described, e.g., human organic cation transporter (hOCT) or human multidrug and toxin extrusion (hMATE) are found only in certain types of human cells, and therefore it has been observed that tissues can vary in their preference for CDDP entry (*25*).

In the cell CDDP acts as a bifunctional alkylating agent on DNA. Due to a low intracellular concentration of Cl^- ions, CDDP reacts with H_2O or OH-groups, giving rise to hydrated forms of this compound *(Fig. 3)*. Because of their nucleophilic properties, these forms can bind to DNA with a covalent bond to create DNA-Pt adducts, as well as to other cellular compounds with reduction potential, such as thiols. The DNA-Pt adducts are most frequently produced with guanine residues (monoadducts); second chloride ligands react with one of the other bases in the same strand, giving rise to major intrastrand cross-links, or with purine residues of the covalent chain, resulting in interstrand cross-links. DNA-Pt adducts are considered to be the major cytotoxic lesions (*26, 27*). Cisplatin forms approximately 60–65 % intrastrand GG, 25–30 % intrastrand AG, 5–10 % intrastrand GNG, and 1 %-3 % interstrand GG diadducts; it also creates DNA-Pt adducts between DNA and proteins (*28, 29*) *(Fig. 4)*. The bifunctional adducts, which can take the form of an intra- or interstrand cross-link, may cause a major local distortion of DNA structure, involving both bending and unwinding of the double helix. Intrastrand cross-links are the most abundant products of the interaction with DNA. Although interstrand cross-links are associated with lower numbers of cisplatin lesions, several studies have suggested that they can be responsible for cytotoxicity of the drug (*4, 30*). CDDP also readily reacts with other cellular molecules like proteins, RNA, and others. The resulting inactive forms, involving small thiol molecules such as glutathione, cysteine or methionine, then participate in CDDP detoxication. This is the reason why only about 1 % CDDP reacts with nuclear DNA. In intermolecular adducts, i.e., CDDP-DNA-proteins, the major lesions involve cross-links that are believed to be responsible for blockage of replication and cell division, and for activation of apoptosis (*27, 31*).

However, not all damage to DNA always leads to the effects as described above. Cells possess protective mechanisms which can regulate drug accumulation or can lead to its detoxication, as well as repair mechanisms for DNA lesions.

Oxaliplatin (L-OHP) acts in a way similar to cisplatin. The hydrophobic properties of L-OHP play a role in its uptake by the cell (32). L-OHP biotransformation is accelerated in the presence of HCO_3^- and $H_2PO_4^-$ ions, resulting in monochloro-, dichloro- and hydrated forms, which are nucleophilic and can subsequently react
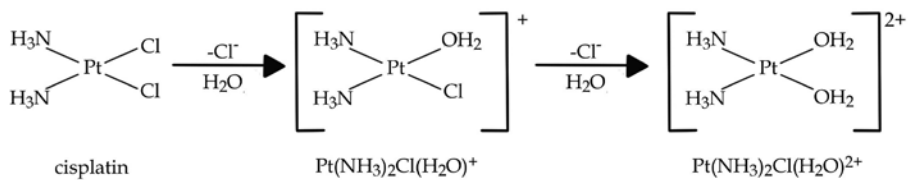
Fig. 3
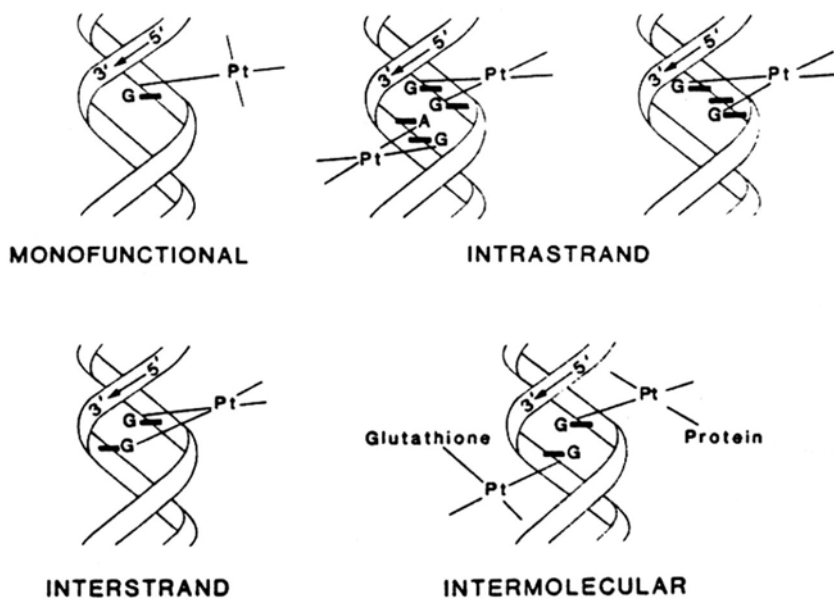Biotransformation products of cisplatin

Fig. 4
Pt-DNA adducts. Adopted from *Eastman* (*3*)

with DNA, proteins and other macromolecules (*33, 34, 35*) *(Fig. 5)*. Inactive forms, resulting from reactions with molecules with reducing properties (cysteine, methionine or glutathione) are involved in L-OHP detoxication (*5*).

Although oxaliplatin is also covalently bound to DNA, the total number of adducts, even at their equitoxic concentrations, is significantly lower in comparison with CDDP (*37*); the proportion of adducts, however, is similar (*5*). Since DACH-Pt-DNA adducts have biological properties slightly different from DNA-CDDP adducts, L-OHP does not show full cross-resistance with CDDP and is more efficient in, for instance, inhibiting DNA synthesis (*37–41*). This is due to the fact that DACH-Pt-DNA adducts are more bulky and cause different damage to DNA by changing the conformation of its molecule. Also, differences have been described in intracellular cascades induced by DNA damage; these may lead to apoptosis or cell cycle arrest (*42, 43*).

Tetravalent platinum compounds exhibit a slightly different mechanism of action, because they exist primarily in a "non-effective" form (*44*) but react well with proteins in the bloodstream, which is comparable with Pt(II) complexes (*45*). They are also believed to enter cells by passive diffusion (*46*). A study on the relationship of copper transporters (CTR1, ATP7A and ATP7B) and cellular concentrations of Pt complexes has shown that the absence of CTR1 is not related to lower uptake of JM118, which is the major satraplatin biotransformation product. A higher expression of ATP7A and ATP7B results in an increased Pt accumulation in the cell and its sequestration to vesicles; as a result, cytotoxicity is reduced (*47*). On satraplatin entry into the cell, Pt(IV) is activated through two metabolic pathways: first, the platinum (IV) complex is reduced to its bivalent form, the active metabolite JM118, by glutathione, ascorbic acid or other reducing agents *(Fig. 6)*; second, the active tetravalent metabolite JM383 is involved (*44, 48–51*). Further analyses of the effects of Pt (IV) compounds and their metabolites on DNA show that, for instance, JM216 can produce Pt-DNA adducts similar to CDDP and L-OHP (*53*), but at lower amounts than, for instance, JM118 or CDDP (*52*). These adducts affect DNA replication, as do Pt(II) compounds; the Pt (IV) complexes, however, show a higher efficacy than CDDP. Kaludjerovic et al. have reported that the anticancer effect of JM216 is not only more effective, but also faster. They also describe induction of the necrotic death of cancer cells and formation of reactive oxygen radicals (54). Other studies deal with the effects of Pt(IV) complexes on the cell cycle and induction of apoptosis (*11, 15, 16*) and also describe other mechanisms leading to cell death.

CELL PROTECTIVE MECHANISMS AND RESISTANCE TO PT COMPOUNDS

Any modification in the formation or destruction of Pt-DNA adducts may interfere with a good outcome of anticancer treatment with this group of drugs and may be manifested as the resistance of cancer cells to Pt compounds.
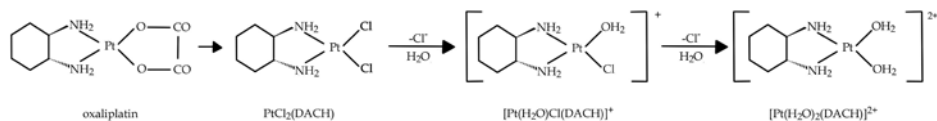
Fig. 5
Biotransformation products of oxaliplatin. Taken from *Raymond et al*. (*36*)
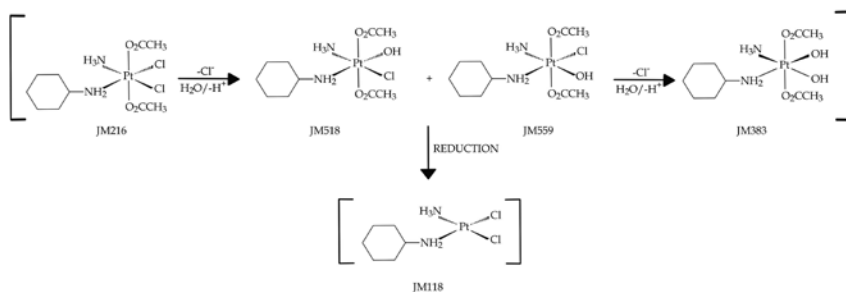

Fig. 6
Biotransformation pathway for satraplatin. Taken from *Raynaud et al* (*51*)

The ability to influence both platinum influx and efflux can be regarded as a protective mechanism by which the cell can regulate the amount of a toxic substance. In the cell, some molecules with reducing potential, such as glutathione, methionine, etc., can react with Pt compounds to give non-functional metabolites, and thus decrease their toxicity. Other mechanisms include reactions of macromolecules (various proteins) with Pt-DNA adducts or cell tolerance to damage caused to DNA; both are associated with repair processes. When Pt complexes (CDDP, L-OHP and JM216) are used, all Pt-DNA adducts are, as a rule, corrected by nucleotide excision repair (NER) (*34, 53, 55, 56*). After the damaged site is identified by these proteins, the defect is cut out at the 3'- and 5'-ends, a short sequence ranging from 22 to 32 nucleotides with damaged DNA is removed, and DNA is resynthesised along the template. Because this pathway is very active in cancer cells, NER activation leads to an increase in the cell's resistance to Pt compounds. The repair process can be inefficient or absent due to mutations in the NER-coding genes or by the activity of other proteins. These include non-histone chromosomal proteins from a family of the high mobility group which, by binding to Pt-DNA adducts, may block the repair process and thus preserve sensitivity of the cell to Pt compounds (*57*).

On the other hand, differences are found in the DNA mismatch repair system (MMR). The variations are ascribed to different chemical and biological

characteristics of DNA-Pt adducts derived from the three agents reviewed here (*58*). MMR proteins have a much higher affinity for CDDP than for L-OHP or JM216 and produce an increased number of spontaneous mutations that give rise to microsatellite instability (*34, 59*). By binding with MMR complexes, the cytotoxicity of a cisplatin-DNA adduct is increased and mechanisms inducing cell death are triggered (*60, 61*). It has been reported that a defective MMR activity results in an increased resistance of cell lines to CDDP, but not to L-OHP or JM216 (*62*).

Cancer treatment can therefore fail due to low sensitivity of malignant cells to commonly used anticancer drugs (intrinsic resistance) or because of "adaptation" of the cell to a drug arising in the course of treatment. The factors of resistance involved in the processes mentioned above can be distinguished as follows:

decreased accumulation of Pt compounds in the cell due to either lower uptake, enhanced efflux or inclusion of Pt into compartments; proteins such as CRP, ATP7A or ATP7B are involved;

detoxication of Pt compounds by reductants such as glutathione or methionine;

higher rate of DNA repairs or higher tolerance to DNA-Pt adducts; NER, MMR and other processes are involved.

CONCLUSION

The results of studies on satraplatin and LA-12 show these Pt(IV) compounds are more efficient in their action on cancer cells than cisplatin or oxaliplatin, and that they could act on malignant cells resistant to cisplatin. Their different effects are related to their chemical structure and, for instance, involve production of bulky non-leaving ligands or Pt-DNA adducts. This probably results in activation of different repair mechanisms in the cell (MMR, HMG proteins, etc.) and, consequently, activation of different transcription pathways leading to apoptotic death, etc. The data reviewed here warrant further investigations into these compounds and their action at the cellular as well as the whole organism level, with a prospect of their eventual clinical use.

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