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REVIEW ARTICLE

Platinum derivatives: a multidisciplinary approach

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Summary

Cancer is one of the most difficult diseases to be treated. The particularities regarding the tumors' occurrence mechanism, their evolution under chemotherapy, disease-free interval, but also the increasing number of patients make cancer an intensively studied health domain. Although introduced in therapy since the early 80s, platinum derivatives play an essential role in anticancer therapy. Their use in therapy resulted in improving the patient quality of life and prolonging disease-free interval, which makes them still a benchmark for other anticancer compounds. However, adverse reactions and allergic reactions are a major impediment in therapy with platinum derivatives.

This paper summarizes data about platinum derivatives through a multidisciplinary approach, starting from a chemical point of view and on to their mechanism of action, mechanism of cellular resistance, predictive factors for the outcome of chemotherapy such as micro RNAs (miRNAs), tumor suppressor protein p53, and the excision repair cross-complementing 1 protein (ERCC1).

Key words: *cancer, ERCC1, miRNA, p53, platinum derivatives*

Introduction

Introduced in therapy since the early 80s, platinum derivatives still represent a reference class of anticancer compounds. In 1845, Michele Peyrone discovered cisplatin, lately known as Peyrone's salt, whose antitumor properties have been highlighted serendipitously in 1965 by Barnett Rosenberg et al. [1].

Until the present date, there are three compounds that are being used on a large scale as anticancer agents: Cisplatin – the first generation, Carboplatin – the second generation, and Oxaliplatin – the third generation. On a smaller scale, other platinum derivatives that are being used are Nedaplatin – approved in Japan, Lobaplatin – approved in China, and Heptaplatin – approved in the Republic of Korea. Cisplatin is being used in various types of cancer treatment, with remarkable results in ovarian and testicular cancer. These results pushed researchers to concentrate on synthesizing new compounds with an activity at least as good as cisplatin, but with a much lower toxicity [2].

Chemical structure and stability

In terms of chemical structure, cisplatin, carboplatin and oxaliplatin are complex combination

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of Pt (II). Cisplatin shows a structure of two ammine groups and two Cl^- in the *cis* position. Carboplatin shows a structure of two ammine groups in the *cis* position and the Cl^- ligands are replaced by 1,1-cyclobutanedicarboxylato bidentate ligand. Oxaliplatin has a more complex structure by replacing the ammine monodentate ligands with the 1,2-diaminocyclohexane (dach) bidentate ligand and the Cl^- ligands with the oxalato bidentate ligand (Figure 1).

These molecules are prodrugs, and the active metabolites are the same for cisplatin and carboplatin, Cl^- anions and 1,1-cyclobutanedicarboxylato are being replaced with water molecules, while for oxaliplatin the water molecules are replacing the oxalate leaving groups. Due to the bidentate ligands, both carboplatin and oxaliplatin have a higher stability compared to cisplatin in terms of aquation [3,4]. Biotransformation to active metabolites of platinum derivatives takes places inside the cell due to low Cl^- ions concentrations at this level (16 mM comparing to 160mM in extracellular environment) [5]. Some researchers consider that the active metabolite of platinum derivatives is the monoaqua-platinum form: *cis*-$[Pt(NH_3)_2Cl(H_2O)]^+$ is the active metabolite of cisplatin and carboplatin and $[Pt(dach)Cl(H_2O)]^+$ is the active metabolite of oxaliplatin. While others think that the diaqua-platinum form is responsible for the anti-tumor effect, *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ is the active metabolite of cisplatin and carboplatin and $[Pt(dach)(H_2O)_2]^{2+}$ is the active metabolite of oxaliplatin [6-8]. It is certain that, due to the positive charge, both compounds would be more likely to approach and coordinate to the negatively charged DNA. A schematic representation of the metabolism of cisplatin is given in Figure 2.

Mechanism of action

Concerning the mechanism of action, platinum derivatives belong to alkylating agents category. Forming intrastrand or interstrands adducts with the cancer cell's DNA is characteristic for this class of drugs, having an affinity for guanine's 7th position nitrogen atom (Figure 3). The

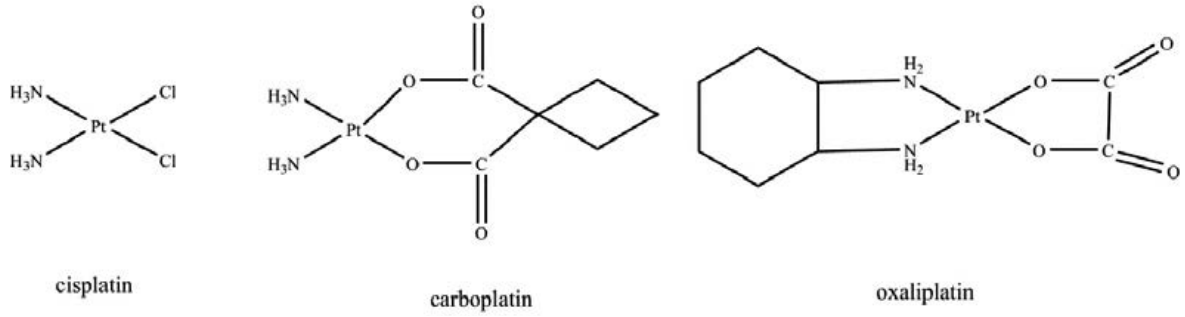

Figure 1. Chemical structure of platinum derivatives.

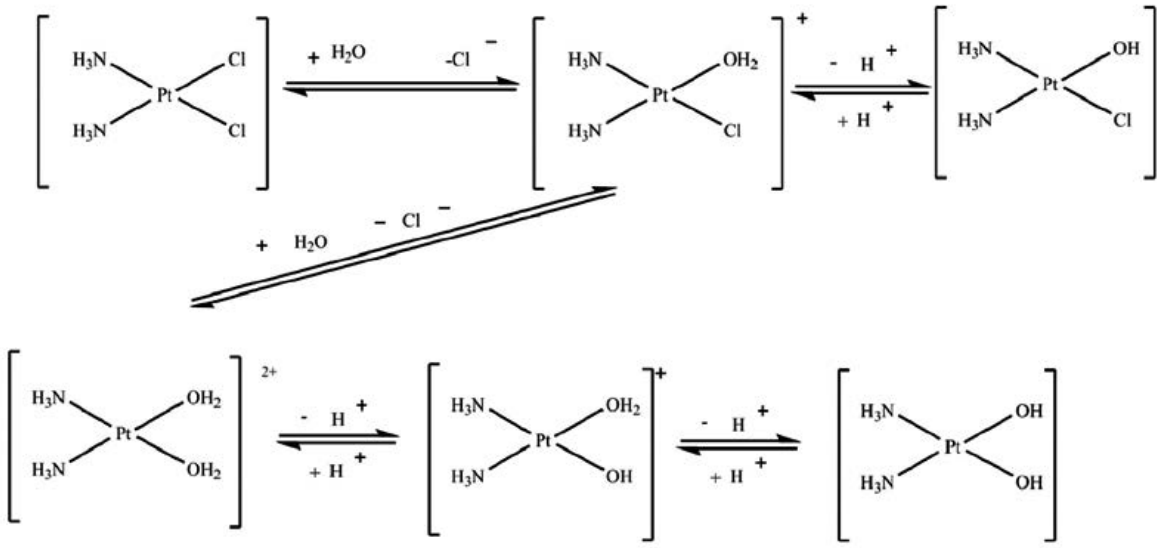

Figure 2. Schematic representation of cisplatin metabolism.

Figure 3. Intrastrand and interstrand adducts of cisplatin.

forming of these adducts induces modifications in DNA structure, which inhibits cellular replication [9]. The *cis* position of the ligands offers a greater stability to the drug than the *trans* position [10].

Due to cisplatin`s affinity for thiol groups, the aquation is limited by its interaction with glutathione, methionine, metallothionein and protein [11]. Hence only 5-10% of the intracellular concentration of cisplatin binds with DNA, while 75-85% of the intracellular quantity binds to thiol groups. Binding to other targets different than DNA explains installing cellular resistance to cisplatin and its high toxicity [12,13].

Carboplatin`s protein binding is reduced and it's excreted in high quantities through urine. It shows a lower toxicity on kidneys and the central nervous system. Another advantage of this molecule is that it passes easier through the blood-brain barrier and doesn't remain stored at erythrocytes level.

Oxaliplatin's mechanism of action is similar to cisplatin and carboplatin. Due to dach ligand's bulky size, the adducts formed by oxaliplatin are more hydrophobic, which makes them more efficient in DNA synthesis inhibition and more cytotoxic than the ones formed by cisplatin and carboplatin [14]. Although its metabolites can form covalent bonds to the thiol groups in glutathione, cysteine, methionine, albumin and gamma globulin structures, it does not accumulate in plasma as cisplatin does. This could explain the lack of nephrotoxicity and delayed emergence of a reversible neurotoxicity. Oxaliplatin covalently binds to erythrocytes globin, and the occurrence of anemia in patients may be explained by this affinity of oxaliplatin [15].

Mechanism of nephrotoxicity, neurotoxicity, ototoxicity and myelosuppression

Although highly effective in the treatment of cancers of various origins, platinum derivatives are also noticeable for their various toxicities that may require cessation of therapy. These include nephrotoxicity, neurotoxicity, ototoxicity and myelosuppression.

Nephrotoxicity

Nephrotoxicity is one of the main adverse reactions of cisplatin therapy, less seen in carboplatin and oxaliplatin. This is because the elimination of cisplatin is mostly through the kidney, which leads to a significant accumulation of the derivatives at the kidney level, prefferentially at the proximal and distal tubules level and in the loop of Henle [16]. Exposure for a long period of time at low doses of cisplatin may induce apoptosis of renal cells, or in case of exposure to high doses over a short period of time, necrosis of renal cells [17]. This reaction can be controlled by intravenous administration of saline solutions, mannitol, by diuresis or by the administration of antioxidants such as L-arginine, amifostine, bismuth subnitrate, and salicylates [18].

Neurotoxicity

Due to the low lipophilicity, cisplatin can't cross the blood–brain barrier and does not affect the central nervous system, but it mainly produces primary sensory neuropathy, as a result of affecting the dorsal root ganglia of the spinal cord. This effect has been investigated in a study on animal model, which showed accumulation of intrastrand adducts in neuronal cells of mice (especially dorsal root ganglia) and cells' incapacity to repair these adducts which leads to instalation of peripheral polyneuropathy [19]. Carboplatin-induced neurotoxicity is extremely lower comparing to cisplatin, and occurs at high doses or when combined to other neurotoxic cytotoxics.

Oxaliplatin is the compound noticeable for the high neurotoxicity that it produces, and peripheral neuropathy is the most known and dose-limiting toxicity. Acute sensorial neuropathy can occur during administration or after the first infusions, and the apparition mechanism can be represented by damage of voltage-gated sodium channels. Chronic peripheral neuropathy occurs due to accumulation of oxaliplatin. The symptoms consist of paresthesias and dysesthesias in the extremities and the perioral region, and are exacerbated by cold exposure [20]. *In vivo* and *in vitro* studies revealed that the common mechanism for neurological disorder of the three platinum compounds is forming DNA adducts in the dorsal root ganglia cells. The degree of damage is proportional to the number of the formed adducts. There are many potential agents that could protect from neuropathy: erythropoietin, amifostine, carbamazepine, vitamin E, intravenous calcium or magnesium. Their use is debatable because they can interfere between the platinum derivatives antitumor mechanism of action, so until now, there does not exist a consensus standard treatment recommended [21].

Ototoxicity

Cisplatin has the highest ototoxicity comparing to carboplatin and oxaliplatin. This effect depends on the period of exposure to chemotherapy and the dosage. Hearing loss is generally bilateral and starts by affecting high frequencies towards low frequencies, and the degree of damage is correlated with the accumulated dosage. Besides hearing loss, tinnitus and ear pain may appear. Some of the risk factors for ototoxicity are patient's age (children are more susceptible), noise exposure, other ototoxic drugs exposure (aminoglycosides), low serum albumin, anemia and cranial irradiation [22]. Cisplatin is cochleotoxic and the mechanism of damage to the inner ear correlates with its accumulation in the inner ear, affecting DNA, producing of reactive oxygen species (ROS) and decreasing the antioxidant system, all leading to apoptosis [22] of auditory sensory cells [23].

Myelosuppression

Myelosuppression is dose-limiting side effect of carboplatin, while cisplatin and oxaliplatin are not frequently incriminated for this effect. The incidence of myelosuppression for cisplatin is 5%, very rare for oxaliplatin, while for carboplatin, using conventional doses, the incidence is 20-40%, and up to 90% for higher doses [24]. The mechanism for this adverse effect hasn't yet been elucidated, but forming DNA adducts in the blood cells is incriminated, and the amount of adducts may be related to the severity of leukopenia and thrombocytopenia [25-28].

Studies show that responsibles for platinum derivatives uptake are enhanced permeability and retention effect (a structural modification of the cancer tissues), organic cation transport proteins and the copper transporter protein (CTR1).

Micro RNA and platinum derivatives

miRNAs are a family of short non-coding RNAs, about 22 nucleotide long, that serve as gene expression modulators by inhibiting mRNA translation or by mRNA degradation [29,30]. The first miRNA discovered was *lin*-4, in 1993 by Ambros` and Ruvkun`s research teams. Lin-4 is a gene which controls the transition from L1 to L2 larval stage in the nematode *Caenorhabditis elegans*. Their research concluded that at a postranscriptional level lin-4 regulates lin-14 genes through its 3`untranslated regions (UTR) [31]. miRNAs were found in flowering plants, worms, flies, fish, frogs and mammals.

They play an important role in stem cell differentiation, hematopoiesis, cardiac and skeletal muscle development, neurogenesis, insulin secretion, cholesterol metabolism and the immune response. Likewise, aberrant expressions of miRNAs are involved in some human diseases such as cardiac disease, cancer, skeletal and growth defects, hereditary progressive hearing loss, familial severe keratoconus combined with early-onset anterior polar cataract [29,32-34]. In a study published in 2005, the authors tested 217 miRNAs from 334 samples including human cancers. Their findings showed that miRNAs profiles could play an important role in cancer diagnosis, including cancer staging [35]. Over the years the scientific community became very interested in their potential as therapeutic targets or biomarkers. We summarized some of the existing data regarding miRNAs and their therapeutic relevance in platinum-based chemotherapy in Figure 4.

Cellular resistance

A major obstacle in platinum derivatives therapy is the appearance of resistance. This can have multiple causes: decreased amount of DNA adducts, the repair of flaws created by DNA adducts, and increased drug efflux.

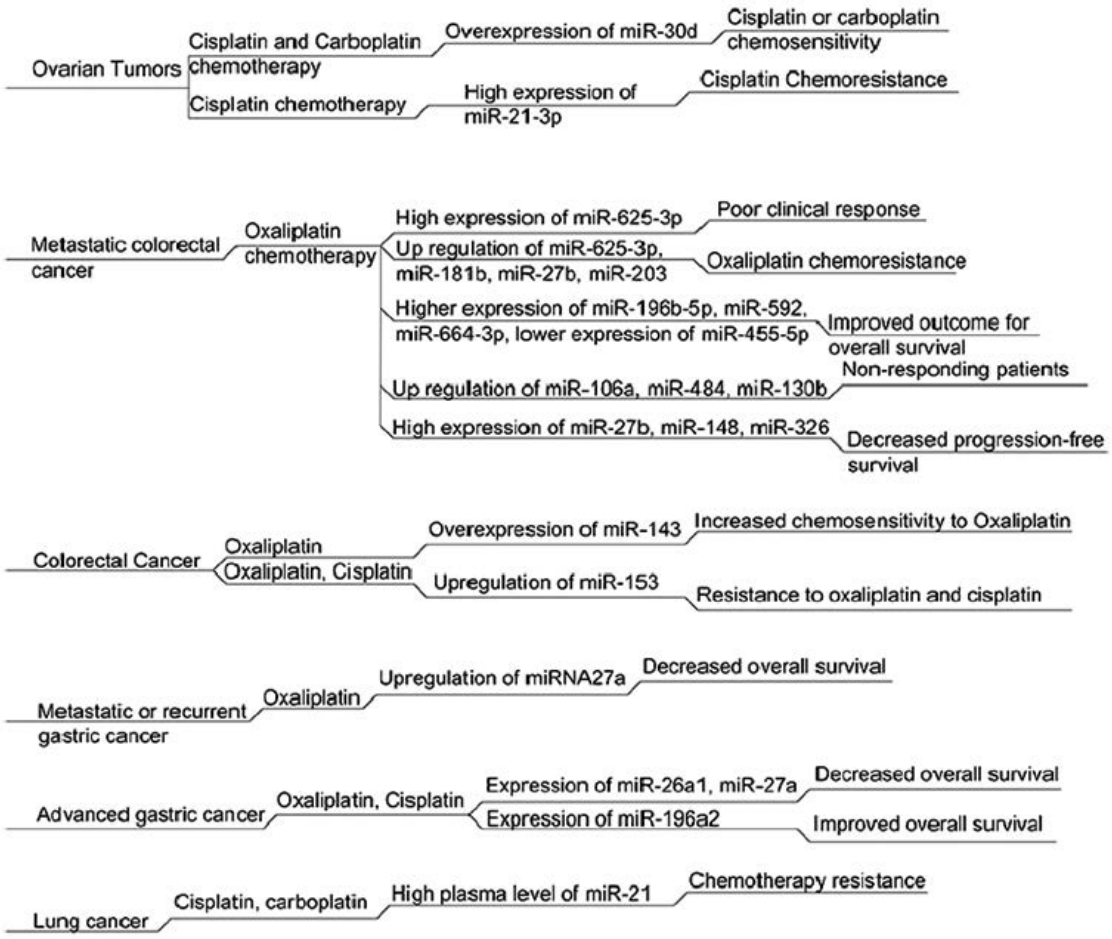

Figure 4. miRs therapeutic relevance in platinum-based chemotherapy [Refs 64-74].

Disturbing factors of intracellular uptake or efflux of platinum derivatives

Cisplatin interaction with thiol groups

As mentioned above, cisplatin has a high affinity to thiol groups in amino acids, peptides, proteins and glutathione (GSH) structures, as these molecules are involved in cisplatin metabolism [36]. Cancer cells contain important quantities of GSH and metallothionein that interact with platinum compounds through their thiol groups, forming new bonds that will prevent platinum binding to DNA [10]. Gamma-glutamyl transpeptidase (GGT) is an plasma membrane enzyme that plays an important role in cellular handlings of thiols (including GSH). It's been observed that this enzyme is often expressed in malignant tumors, including melanoma. Researchers have shown that overexpression of GGT led to a decrease in the amount of intracellular GSH, while in the case of lower amounts of GGT an extracellular accumulation of GSH, glutathione disulfide (GSSG) and glutathione-cysteine disulfide (GCD) has been observed. This resulted in a higher sensitivity of tumor cells to platinum compounds in the presence of overexpressed GGT [37].

Metallothioneins are low molecular mass proteins that contain about 30% thiol groups in their structure. They are located at the Golgi apparatus and have the capacity of forming covalent bonds both with metals that are usually physiologically found in the body and xenobiotics. They play a dual role regarding the behavior to cisplatin because they can contribute at both its removal from the cell and prevention of nephrotoxicity [38].

Copper carriers

In vitro studies showed that cancer cell lines resistant to cisplatin are also copper cross-resistant. Further researches observed that cisplatin and copper are competitive inhibitors of copper transporting proteins CTR1 and ATP7A/ATP7B. CTR1 insures intracellular influx of copper in the cell through three chaperones COX17, CCS1 and HAH1 which transport intracelular copper to cytochrome C oxidase, superoxide dismutase and

P-type ATPase transporter (ATP7A or ATP7B). A 20-70% decrease of cisplatin concentration has been observed in cisplatin resistant cell lines. This drop was attributed to downregulation of CTR1 carrier. ATP7A and ATP7B are responsible for copper extracellular transport and are located in the trans-Golgi network [39]. While ATP7B mediates cisplatin efflux, ATP7A is responsible for storing it to the intracellular compartments. Overexpression of those two transporters was corelated with the development of resistance to platinum derivatives therapy [40]. Another interesting fact is the location of these carriers. Studies on human cell lines highlighted that in platinum II compounds sensitive cells, ATP7A and ATP7B are located at trans-Golgi network level, while on platinum II compounds resistant lines they are located at cytosol vesicles level [41].

DNA platination impairements

Forming platinum adducts with DNA does not necessarily mean apparition of cell death. These adducts can be detected by a series of factors that determine the repair of these flaws, thus, the surviving of the cancer cell, among them nucleotide excision repair (NER), mistmatch repair (MMR), B-cell lymphoma 2 (bcl-2), tumor supressor protein p53, epidermal growth factor (EGF) receptor [9,42,43].

Nucleotide excision repair (NER)

Nucleotide excision repair pathway is the main way of repairing the platinum formed adducts [24]. This mechanism has a broad specificity that allows it to recognize both the cisplatin formed adducts and the ones formed with other platinum derivatives [11]. This pathway implies DNA damage recognition, demarcation of the affected area, formation of complexes that will help the affected portion excision and reconstruction of damaged DNA [44,45]. For NER to function the presence of the ERCC1 protein [46,47] is vital because it dimerizes with xeroderma pigmentosum complementation group F, and this newly formed compound helps the excision of DNA damage [48,49].

Low expression of ERCC1 is associated with a favorable response with platinum derivatives, while ERCC1 overexpression is associated with chemotherapy resistance. ERCC1 can therefore be considered a predictive and prognostic marker of tumor response to therapy [50-52].

Mistmatch repair (MMR)

MMR is a DNA mistmatch repair pathway which corrects base mispairs and small strands. *In vitro* studies showed that MMR plays an important role in detecting and repairing adducts formed

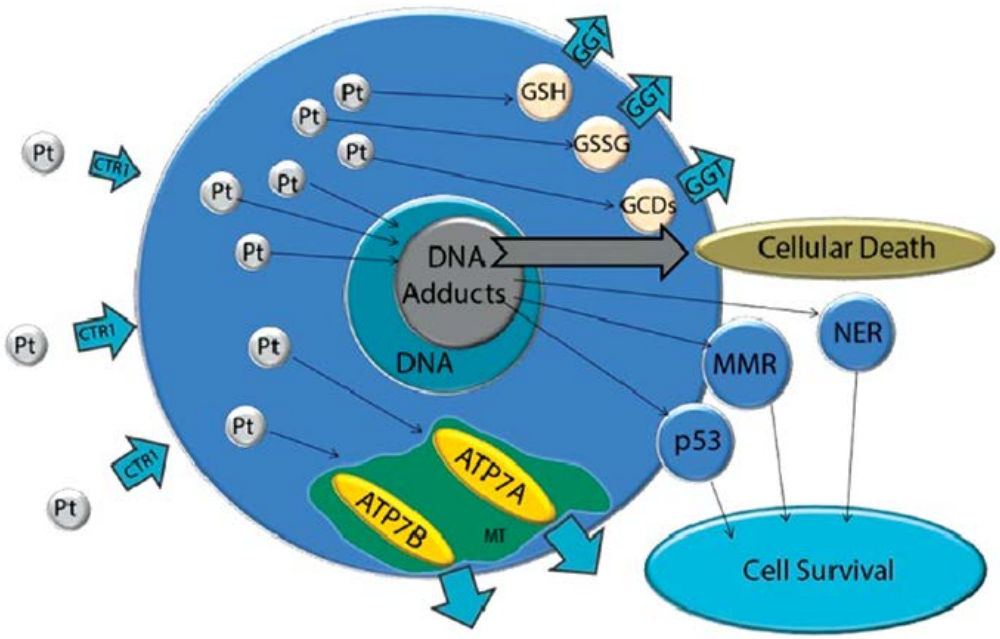

Figure 5. Factors involved in platinum derivatives cellular uptake and efflux. Pt=Platinum derivatives; CTR1=Copper transporter; GSH=Glutathione; GSSG= Glutathione disulfide;GCDs=Glutathione-cysteine disulfide; p53=Tumor suppressor protein 53 cytoplasmic mislocalization or mutant form; MMR=Mistmach repair; NER=nucleotide excision repair;ATP7A/ATP7B=P-type ATPase transporter; MT=Metallothioneins.

by cisplatin and carboplatin, while oxaliplatin had no such effect. This can be due to the different type of distorsion that DNA–oxaliplatin interaction produces and also to the presence of dach ligand [53]. MMR regulates post-replicative defects made by DNA polymerase and acts in three stages: identifies errors, removes the affected portion and re-synthesizes DNA. There are 5 proteins involved: MLH1, MSH2, MSH3, MSH6, and PMS2 [54]. Damaging this system may increase cellular tolerability of cisplatin and carboplatin [55-57].

The role of p53 protein

The tumor suppressor protein 53 (p53) is a protein that in humans is encoded by TP53gene. The tumor suppressor p53 plays an essential role in cellular growth, acting through various mechanisms in order to eliminate DNA damage [53]. Expressing a functional p53 protein is important to increase cell sensitivity to chemotherapy [58,59]. p53 is related to the antineoplastic activity of cisplatin and is considered, in some studies, essential for the manifestation of the cytotoxic effect [60]. The mutations occurring at p53 gene most frequently appear in human cancer cells and the inhibition of the mutant form can affect the cells' survival by interfering with the cell cycle and cellular death [61]. In almost half of the human cancers loss or mutation of p53 has been observed [62]. p53 protein interacts with p35 fragment of caspase-9, producing caspase-9 inhibition. p53's incapacity to activate certain genes involved in cell cycle arrest and apoptosis is due to mutations or cytoplasmic mislocalization. These findings suggest that in tumors that have p53 protein expressed in their cytoplasm, the mechanism of resistance to cisplatin is inhibition of caspase-9 [63]. Another very interesting fact is the link between p53 and metastasis. Loss of p53 contributes to the development of metastasis through some conformational modifications of the tumor enviroment (loosening of cell-cell junction and disruption of epithelial cell integrity) whereas the mutant form induces the metastatic phenotype. p53 may play the role of a therapeutic target, as the study by Powell et al. has revealed tumor regression once the p53 function was restored [62].

A schematic representation of influential factors on cell resistance to platinum derivatives therapy is shown in Figure 5.

Conclusions

Platinum derivatives play an important role in the treatment of cancers of various origins. Although they have been used for more than 30 years, they remain a benchmark in cancer therapy due to their therapeutic effectiveness. Drug resistance and adverse reactions is a challenge of cancer therapy. The ideal chemotherapy should only damage tumor cells, with a minimum effect on healthy cells and minor adverse reactions. Choosing the right type of platin derivative should take into account the kind of cancer, stage, overall prognosis and survival, patient comorbidities, and overall and specific platin compound toxicities. All these aspects represent an important issue for patient quality of life.

Notice

The Figures in this article are original, made by the authors, drawn with programs ChemDraw (Figures 1,2) and AutoCad (Figures 3,4,5).

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Conflict of interests

The authors declare no confict of interests.

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