ejpmr, 2024, 11(6), 197-203

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

CISPLATIN: A BEACON OF HOPE IN CANCER TREATMENT - UNVEILING THE POTENT ALKYLATING ANTINEOPLASTIC AGENT

Ankur Vashi[1]* and Akhilesh Kumar Kuril[2]

[1]Flamma USA LLC, Malvern, PA, USA.
[2]Bhagwant University, Sikar Road, Ajmer, Rajasthan, India.

***Corresponding Author: Ankur Vashi**

Flamma USA LLC, Malvern, PA, USA.

Article Received on 09/04/2024 **Article Revised on 30/04/2024** **Article Accepted on 21/05/2024**

ABSTRACT

Over the past 60 years, alkylating compounds have been utilized to treat cancer, and their uses are still growing. At every step of the cell cycle, these substances directly affect DNA by crosslinking the N-7-guanine residues, which results in DNA strand breakage, aberrant base pairing, the suppression of cell division, and, in the end, cell death. An alkylating agent is an alkylating antineoplastic agent if it attaches an alkyl group (CnH2n+1) to DNA. It is applied to cancer patients. Cisplatin, also known as (SP-4-2)-diamminedichloridoplatinum (II), is one of the most promising and widely used drugs for the treatment of a number of solid tumors, including testicular, ovarian, head and neck, bladder, lung, cervical, melanoma, lymphomas, and numerous others. Although there are several methods that cisplatin exerts its anticancer effects, the most likely one involves interacting with purine bases on DNA to cause DNA lesions, which then trigger several signal transduction pathways and, in the end, apoptosis.

KEYWORDS: Cancer, Cisplatin, Platinum resistance, Toxicity, Alkylating agent, etc.

1. INTRODUCTION

Cancer is the second largest cause of mortality worldwide and one of the most serious health problems. Cancer is the uncontrollable growth of abnormal cells anywhere in the body. It is recognized that abnormalities in the body's regular functions might lead to cancer. Old cells multiply uncontrolled to produce new, abnormal cells rather than dying. These extra cells may group together to become a tumor. Two other pathways via which cancer cells might metastasize to different parts of the body are the lymphatic and vascular systems. Clinical outcomes are used by translational cancer medicine to apply important scientific discoveries to medical practice and provide feedback to fundamental research. According to the World Health Organization (WHO), three different kinds of external agents can interact with an individual's genetic makeup to cause cancer: chemical carcinogens, which include asbestos, tobacco smoke components, aflatoxin, and arsenic; physical carcinogens, which include ionizing radiation and ultraviolet light; and biological carcinogens, which include infections from specific bacteria, viruses, or parasites.[1,2] In order to stop tumor cells from growing, anticancer drugs alter cellular growth factors and interact with DNA. When released into waterbodies including urban and hospital effluents, these pharmaceutical chemicals may provide a risk to aquatic creatures that are not intended targets due to their mechanism of action, which includes cytotoxicity, genotoxicity, mutagenicity, and teratogenicity.[3]

Cisplatin is one efficient chemotherapy medication for a variety of tumor forms. The most common side effect of cisplatin is ototoxicity. This high frequency, long-lasting, bilateral hearing loss is dose-related. Unfortunately, there is no prophylactic procedure in place, and in clinical practice today, ototoxicity is the reason for stopping cisplatin-assisted cancer therapy, or the resulting hearing loss is recognized as an inevitable side effect of cancer treatment. In clinical therapy, cisplatin, a potent antitumor alkylating drug, is frequently used to treat a variety of malignancies, such as small cell lung, testicular, ovarian, head and neck, bladder, and esophageal cancers. Cisplatin exhibits its anticancer activities by forming 1,2-intrastrand cross-links with DNA.[4] A combined treatment modality Platin-Cbl is a prodrug of the FDA-approved chemotherapeutic drugs chlorambucil (Cbl) and cisplatin. In order to explore the compound's potential to initiate a chemowar on cancer cells, it was synthesized and characterized. This involved delivering the active medicines, cisplatin and Cbl, to the cellular powerhouse, the mitochondrion, using a targeted nanoparticle designed to connect with this organelle. Plentine-Cbl had notably more cytotoxic activity in many tumor cell lines and in a cisplatin-resistant cancer cell line when compared to cisplatin or its combination with

Cbl, suggesting its unique effectiveness in cisplatin-resistant tumors. Platin-Cbl's medication formulation that was specifically aimed at the mitochondria allowed for efficient mitochondrial delivery.[5] Cisplatin, or cis-diammine-dichloro-platinum II, was discovered to inhibit the growth of Escherichia coli and to has cytotoxic and anti-neoplastic effects on cancer cells. Intravenous cisplatin is used as first-line chemotherapy for human patients with a range of cancer diagnoses, such as lymphomas, leukemia, breast, testicular, ovarian, head and neck, cervical, and sarcomas. In order to produce cytotoxicity, cisplatin enters the cell, binds to DNA to create intra-strand DNA adducts, loses one chloride ligand, and inhibits DNA synthesis and cell growth. The DNA repair reaction is started by the NER (nuclear excision repair system) in response to the DNA lesions caused by cisplatin-induced DNA damage. Through the activation of the ATM (ataxia telangiectasia mutated) pathway, this action halts the cell death produced by cisplatin.[6]

The coordination chemical cisplatin has a square planar shape. It looks like a crystalline powder that might be white, bright yellow, or orange when it's room temperature. Cisplatin is reported to be stable at room temperature and pressure, with a water solubility of 2.53g/L at 25°C.[7]

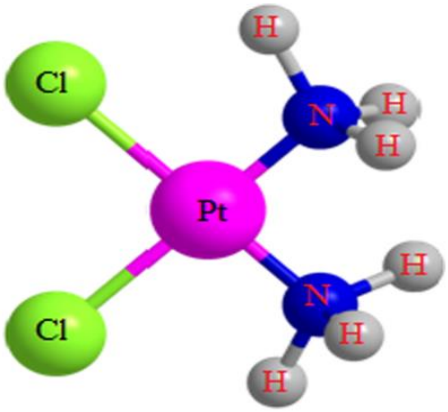

Fig. 1: 3D Structure of the Cisplatin.

2. Molecular bases of action

Through DNA binding, single-stranded DNA breaks have been linked to cisplatin's cytotoxicity. As cisplatin reaches the cytoplasm, it replaces chloride atoms with water molecules, creating an electrophile that binds to sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids. Apoptosis and the inhibition of cell division are caused by the specific binding of cisplatin to 1, 2-intrastrand cross-links of purine bases.[8] The locations of most common formation of cisplatin-DNA adduct produced by covalent binding have been identified as the N7 positions of the imidazole ring on two neighboring guanines. According to reports, cisplatin's toxicity is increased by nonfunctional adducts, inter- intra strand crosslinks, and other factors.[9] An electron probe micro analyzer revealed that the matrix contained the majority of the cisplatin molecules. The in vitro release profile of CDDP from microspheres showed that the remaining CDDP was released progressively over a period of 14 days, following an initial burst of 21.2%. Because cisplatin is less toxic, it was administered in large quantities to mice with peritoneal carcinomatosis in a therapeutic trial; nevertheless, when compared to the same dosage of an aqueous cisplatin solution, CDDP-MS did not enhance the therapeutic effect.[10]

Anticancer treatment has problems with toxicity and resistance. Because of their toxicity, most of the 3000 variants of cisplatin that were evaluated as anticancer medicines were discarded. Data from the literature indicate that the strategies for generating platinum anticancer medicines and preventing resistance to Cisplatin derivatives and their toxicity include combination treatment, Pt IV prodrugs, and targeted nanocarriers. One important tactic for lowering the toxicity and medication resistance of cisplatin derivatives is the use of nanocarriers, such as polymers and liposomes. greater targeted administration, higher intracellular penetration, greater therapeutic effectiveness, and selective accumulation in tumor tissue are all provided by these carriers. The following are some advantages of combination therapy: it reduces toxicity, stops resistance, stops tumor cell adaptability and mutation, and eliminates the maximum number of tumor cells in each phase.[11]

DNA cross-links and adducts have anticancer effects in addition to generating superoxide radicals. Nephrotoxicity is the most well-known toxicity and may also be the most significant toxicity in terms of clinical importance. Despite the development of several ideas, the mechanism responsible for cisplatin nephrotoxicity is still not fully known. Among the additional hazards include ototoxic, neurotoxic, myelosuppressive, and gastrointestinal. Cisplatin has shown effective in treating a variety of cancers in dogs, including squamous cell carcinoma (SCC), mesothelioma, osteosarcoma, and

germinal cell tumors. It is not possible to use cisplatin since typical dosages in cats produce fulminant pulmonary oedema. Intralesional cisplatin has been used as a treatment for sarcoids and SCC in horses.[12]

3. Mechanisms of action

By covalently binding to DNA-forming adducts, cisplatin induces apoptosis, which results in the death of the tumor. Cisplatin has a great attraction for sulfhydryl groups (found in proteins) and nitrogen donor atoms (found in nucleic acids) when it enters the circulation. Strong electrophiles are created as a result of aquation, which creates adducts.[13] Purine bases and the drug create 1,2-intrastrand cross-links, which are responsible for 90% of the adduct formation and consequent cytotoxicity of cisplatin. Damage to DNA, RNA, and proteins often results in apoptosis or non-apoptosis in cells, even in the presence of DNA repair systems. The initial stage in the toxicity process is the modulation of calcium signaling by copper transporters, which culminates in the production of oxidative stress. Following then, the mitochondria disintegrate and vital membrane proteins seep out.[14]

After entering the circulation, cisplatin becomes amphoteric and binds strongly to the sulfhydryl group of glutathione-S-transferase (GST) and metallothionein. Cisplatin has a limited bioavailability as a result. Several studies have been conducted to investigate the role of metallothionein and GST in cisplatin resistance. The transfer of metallothionein from the cytoplasm to the nucleus appears to minimize DNA damage by lessening the cytotoxic action of cisplatin.[15] Merely 1% of cisplatin that enters the cell interacts with DNA to form so-called DNA-cisplatin interactions. Both necrosis and apoptosis can occur in the same population of exposed cells to cisplatin; the kind of cell death that takes place is determined on the metabolic state of the target cell and the dose of cisplatin. A significant fraction of cisplatin also attaches to glutathione and other biomolecules rich in cysteines. The platinum component of the drug interacts to blood proteins in the circulation.

The disruption of cells' and mitochondria's antioxidant defense mechanism by cisplatin leads to oxidative stress. Three primary mechanisms underlie cell resistance to cisplatin: (1) enhanced repair of cisplatin-induced DNA damages; (2) reduced uptake and/or greater efflux; and (3) intracellular cisplatin inactivation.[16]

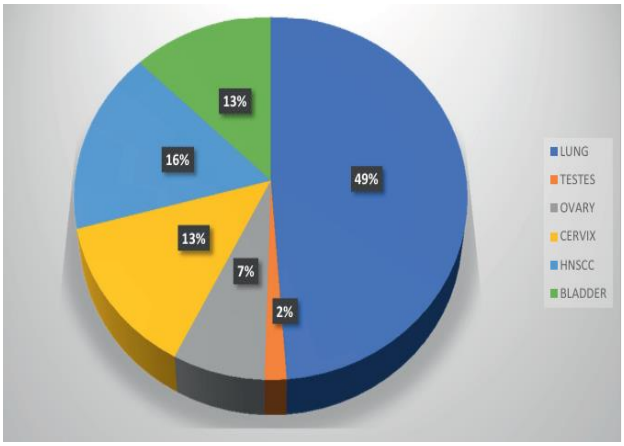

Fig. 2: The incidence of major cisplatin-treated cancers worldwide in 2020.[17]

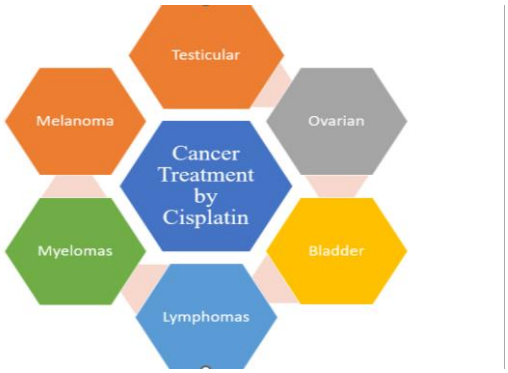

Fig. 3: Type of cancer treated by cisplatin in world wide.

4. Synthesis of cisplatin

4.1 Method – I

The synthesis of transplatin in modern times usually takes two steps. Using excess ammonia treatment, K2[PtCl4] is first changed to [Pt(NH3)4]Cl2 (colorless). The required transplatin product is then precipitated by evaporating the volume and adding HCl. On the one hand, transplatin is neutral and precipitates out of

solution, while the intermediate [Pt(NH3)3Cl]+ is charged and soluble. Transplatin can be formed because the chloride group has a greater trans action than the ammine group. The synthesis of transplatin in modern times usually takes two steps. Using excess ammonia treatment, K2[PtCl4] is first changed to [Pt(NH3)4]Cl2 (colorless). The required transplatin product is then precipitated by evaporating the volume and adding HCl. On the one hand, transplatin is neutral and precipitates out of solution, while the intermediate [Pt(NH3)3Cl]+ is charged and soluble. Transplatin can be formed because the chloride group has a greater trans action than the ammine group. Because of their greater trans action, chloride ligands are more susceptible to trans ammine groups. Transplatin is produced when the trans position is substituted by a second chloride. The transplatin synthesis technique is shown in Figure 4.

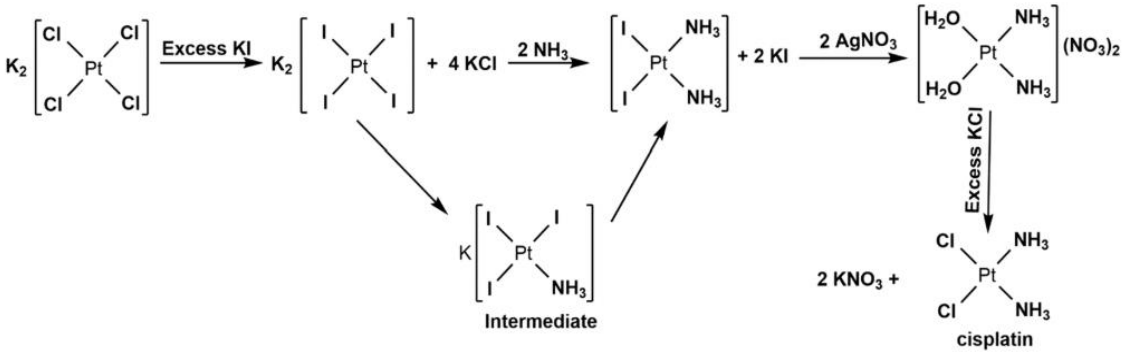

Fig. 4: Step-1 Cisplatin Synthetic Scheme (Dhara method).

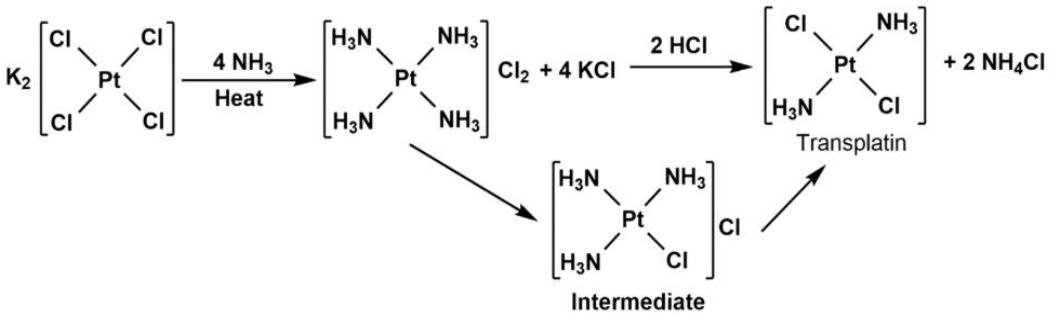

Fig. 5: Step-2 Synthetic transplatin scheme.

4.2 Cisplatin analysis

Total platinum levels in plasma ultrafiltrate are tested in order to calculate the free fraction of cancerostatic platinum compounds (CPC). A lot of work has gone into improving the medicinal qualities of platinum compounds while reducing their unfavorable side effects. Compared to cisplatin, carboplatin has a smaller therapeutic window and is mostly used to treat ovarian cancer. The goal of therapeutic drug monitoring is to ascertain the patient's bloodstream's free and intact drug concentration.[18] There are several ways to analyse cisplatin, such as direct or indirect via derivation using UV spectroscopy with HPLC as a validated technique. While other methods may occasionally be nonselective, HPLC provides a more selective potential for the separation of compounds related to cisplatin based on their surface functional groups. The molar UV absorption of cisplatin is low. Nevertheless, spectrophotometric UV detection of cisplatin in USP at 301 nm wavelengths. Cisplatin's instability and poor solubility in a wide range of common solvents limit the use of chromatographic analytical methods. The ion pairing agents sodium dodecyl sulphate, hexansulfonic acid, and methanesulfunic acid are non-reactive, and the methanol reaction is substantially lower. Research indicates that mono-aqua species of Cisplatin exhibit a shorter retention time at higher pH values in contrast to Cisplatin. Studies reveal that, in contrast to Cisplatin, mono-aqua forms of Cisplatin have a lower retention duration at higher pH levels.

5. Mode of action

It is possible to identify one nuclear and one cytoplasmic module in the intricate signaling route that cisplatin employs to exert its anticancer effects. Cisplatin must be intracellularly activated since it is inactive and requires the replacement of one or both cis-chloro groups with water molecules through a sequence of aqueous processes. This reaction occurs spontaneously in the cytoplasm due to the comparatively low concentration of chloride ions, and it results in exceptionally reactive forms of mono- and biaquated cisplatin. These compounds are most likely to interact with a wide range of endogenous nucleophiles, including reduced glutathione (GSH), methionine, metallothioneins, and proteins, among other cytoplasmic substrates.

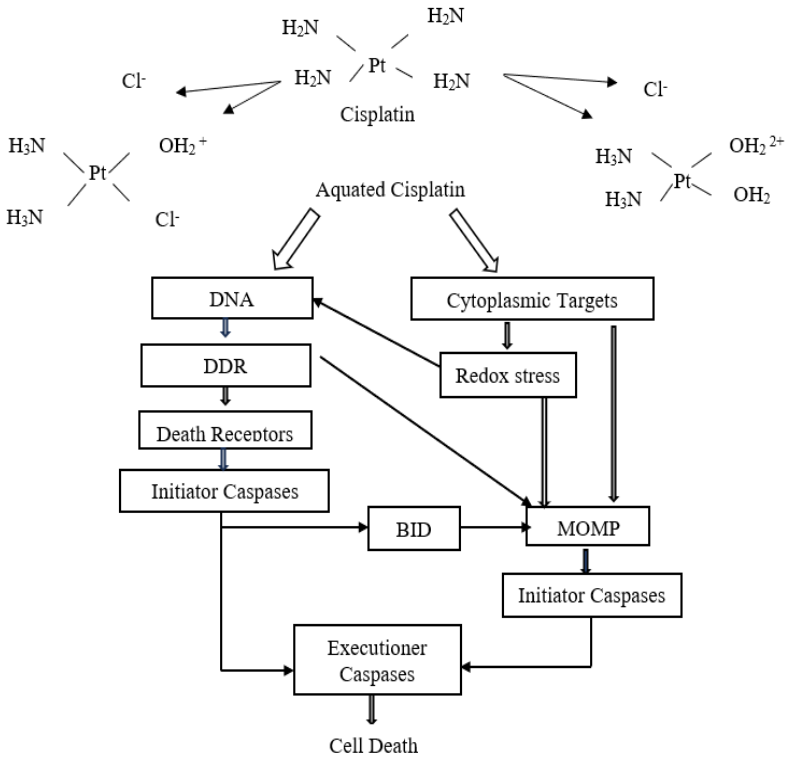

Fig. 6: Mode of action.

5.1 Cisplatin nephrotoxicity

Cisplatin remains a crucial anti-tumor drug for the treatment of solid tumors. The primary adverse effect that is dose-limiting is nephrotoxicity, which manifests gradually and steadily after both first and recurrent exposure. The kidney collects cisplatin more than other organs, presumably through facilitated transport. The primary problem preventing it from being more effective is its nephrotoxicity, which calls for a decrease in dose and patient hydration. The kidney's sensitivity to cisplatin is most likely caused by its major role in excreting cisplatin. Regular oxygen consumption is necessary for the method by which cisplatin reaches renal cells, and organic bases specifically block this action. A significant portion of cell platinum is biotransformed into a potentially benign and nonmutagenic material, even though the majority of intracellular platinum is linked to macromolecules like DNA and protein. The primary effects of cisplatin biotransformation could be the generation of reactive metabolites and a decrease in sulphydryl groups in the kidney. Patients who are well hydrated have been reported to have a decreased risk of cisplatin nephrotoxicity, and a new idea suggests that a calcium blocker may help mitigate the nephrotoxic effects of cisplatin.

6. Future perspective of cisplatin in drug delivery

Anticancer medications based on platinum have been used extensively as first-line therapies for a range of solid tumors for many years. For instance, cisplatin is still a part of conventional chemotherapy treatments. Anticancer medications are mostly injected directly into the tumor parenchyma or distributed systemically to tumor cells. Since anticancer medications are easier to deliver and better tolerated by patients when given systemically, this is the optimal route for administration. The anticancer substance enters the blood arteries of the tumor, passes through the vascular wall into the interstitium, and then diffuses or convenes throughout the tissue. In tumors of various sizes and forms, the diffusion route predominates. Metal nanoparticles are useful for both cancer diagnosis and treatment because they may efficiently transport medications to tumor cells. They may also be precisely controlled in terms of size and form through synthesis. After systemic or local injection, the stability, biocompatibility, and capacity to specifically target tumor cells of metal nanoparticles are major factors influencing their efficacy in cancer therapy.[19] The US Food and Drug Administration (FDA) has authorized cisplatin cis-(diammine) dichloridoplatinum (II) (CDDP), the first platinum-based compound. The first-line chemotherapeutic treatment for many malignancies, such as head, neck, and lung cancer, is cisplatin. It can be used either on its own or in conjunction with other anti-cancer drugs or radiation treatment.[20] Furthermore, cisplatin is an effective treatment for two pediatric cancers: osteogenic sarcoma and medulloblastoma. Most contemporary treatment regimens combine the medicine with additional cytotoxic agents such as otoposide, doxorubicine, paclitaxel, 5-fluorouracil, gemcitabine, vinblastine, bleomycin, and others. The World Health Organization's List of Essential Medicines,[21] which includes it, states that it is among the safest and most effective drugs that are needed in the healthcare system. Because chemotherapy can have

harmful side effects on healthy cells, it is a painful and controversial cancer treatment. One of the first and most effective chemotherapy drugs, cisplatin, is now a mainstay of many cancer treatment plans.

Even the other platinum-based drugs that came out in the following years were unable to fully take the place of cisplatin. Furthermore, it is demonstrated that the needs of the patient ought to direct the choice of platinum compounds. Innovative liposomal cisplatin formulations have demonstrated potential in mitigating adverse effects, presenting fewer therapeutic obstacles, and preventing avoidable bio interactions.

7. CONCLUSION

The most widely used platinum-based chemotherapy drug that has been clinically shown to treat a variety of malignancies and sarcomas is cisplatin. Cisplatin, which is mostly used to treat malignancies of the ovaries, testicles, head and neck, and bladder, is one of the most often used anticancer drugs. This medication acts by causing oxidative stress, harming the mitochondria of cancer cells, and causing damage to the cells' genetic material (via the creation of cisplatin-DNA adducts), all of which help to trigger apoptotic processes in cells. The prevalence of severe side effects, which include gastrointestinal toxicity, cardiotoxicity, and nephrotoxicity as well as ototoxicity, is one of the biggest barriers to the widespread use of cisplatin in cancer therapy. The emergence of drug resistance, which affects a great deal of patients receiving cisplatin treatment, is another important problem associated with its usage. It is known that cancer cells have evolved a variety of defence mechanisms to fend against the cytotoxic effects of cisplatin.

REFERENCE

1. A. “Cancer” World Health Organization. 12 September 2018. https://www.who. int/en/news-room/fact-sheets/detail/cancer (accessed 06/01/2019).
2. Blackadar, C. B. Historical review of the causes of cancer. World journal of clinical oncology, 2016; 7(1): 54-86.
3. Fonseca, T. G., Morais, M. B., Rocha, T., Abessa, D. M. S., Aureliano, M., & Bebianno, M. J. Ecotoxicological assessment of the anticancer drug cisplatin in the polychaete Nereis diversicolor. Science of the total environment, 2017; 575: 162-172.
4. Mantri, Y., Lippard, S. J., & Baik, M. H. Bifunctional binding of cisplatin to DNA: why does cisplatin form 1, 2-intrastrand cross-links with AG but not with GA?. Journal of the American Chemical Society, 2007; 129(16): 5023-5030.
5. Pathak, R. K., Wen, R., Kolishetti, N., & Dhar, S. A prodrug of two approved drugs, cisplatin and chlorambucil, for chemo war against cancer. Molecular cancer therapeutics, 2017; 16(4): 625-636.
6. Brown, A., Kumar, S., & Tchounwou, P. B. Cisplatin-based chemotherapy of human cancers. Journal of cancer science & therapy, 2019; 11(4).
7. Smoke, T., & Smoking, I. IARC monographs on the evaluation of carcinogenic risks to humans. IARC, Lyon, 2004; 1: 1-1452.
8. Ishida, S., Lee, J., Thiele, D. J., & Herskowitz, I Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. Proceedings of the National Academy of Sciences, 2002; 99(22): 14298-14302.
9. Beck, D. J., & Brubaker, R. R. Effect of cis-platinum (II) diamminodichloride on wild type and deoxyribonucleic acid repair-deficient mutants of Escherichia coli. Journal of bacteriology, 1973; 116(3): 1247-1252.
10. Fujiyama, J., Nakase, Y., Osaki, K., Sakakura, C., Yamagishi, H., & Hagiwara, A. Cisplatin incorporated in microspheres: development and fundamental studies for its clinical application. Journal of controlled release, 2003; 89(3): 397-408.
11. Tsvetkova, D., & Ivanova, S. Application of approved cisplatin derivatives in combination therapy against different cancer diseases. Molecules, 2022; 27(8): 2466.
12. Barabas, K., Milner, R., Lurie, D., & Adin, C. Cisplatin: a review of toxicities and therapeutic applications. Veterinary and comparative oncology, 2008; 6(1): 1-18.
13. Dasari, S., & Tchounwou, P. B. Cisplatin in cancer therapy: molecular mechanisms of action. European journal of pharmacology, 2014; 740: 364-378.
14. Djordjević, M., Ilić, J., & Stojanovic, N. M. CISPLATIN-AN OVERVIEW OF ITS EFFICIENCY AND TOXICITY. Facta Universitatis, Series: Medicine and Biology, 2023; 025-035.
15. Salvesen, G. S., & Abrams, J. M. Caspase activation–stepping on the gas or releasing the brakes? Lessons from humans and flies. Oncogene, 2004; 23(16): 2774-2784.
16. Lee, J. H., Chae, J. W., Kim, J. K., Kim, H. J., Chung, J. Y., & Kim, Y. H. Inhibition of cisplatin-resistance by RNA interference targeting metallothionein using reducible oligo-peptoplex. Journal of controlled release, 2015; 215: 82-90.
17. ME, J. F., Siegel, R. L., Isabelle Soerjomataram, M. D., & Ahmedin Jemal, D. V. M. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, 2024.
18. Falta, T., Koellensperger, G., Standler, A., Buchberger, W., Mader, R. M., & Hann, S. Quantification of cisplatin, carboplatin and oxaliplatin in spiked human plasma samples by ICP-SFMS and hydrophilic interaction liquid chromatography (HILIC) combined with ICP-MS

detection. Journal of Analytical Atomic Spectrometry, 2009; 24(10): 1336-1342.
19. Paresishvili, T., & Kakabadze, Z. Challenges and Opportunities Associated With Drug Delivery for the Treatment of Solid Tumors. Oncology Reviews, 2023; 17: 10577.
20. Farooq, M. A., Aquib, M., Farooq, A., Haleem Khan, D., Joelle Maviah, M. B., Sied Filli, M., & Wang, B. Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: an overview. Artificial cells, nanomedicine, and biotechnology, 2019; 47(1): 1674-1692.
21. Jadon, A. S., Bhadauriya, P., & Sharma, M. An integrative review of Cisplatin: the first metal anti-tumor drug. Journal of Drug Delivery and Therapeutics, 2019; 9(3): 673-677.