Transition Metal Based Anticancer Drug: A Review on Current Cancer Chemotherapy Drugs.

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Abstract: - Chemotherapy is one of the most common treatments for cancer. It uses certain drugs to kill cancer cells or to stop them from growing and spreading to other parts of your body. Your doctor might prescribe chemo by itself or with surgery or radiation therapy.More than 50 percent of cancer patients are treated with platinum complexes *viz* cisplatin, carboplatin and oxaliplatin. Cisplatin; cis-Diamminedichloroplatinum (II), the best chemotherapeutic agents is frequently used in the treatment of various types of cancers like sarcomas, carcinomas, lymphomas and germ cell tumors. Mode of action of cisplatin is related to its ability to form 1, 2 - intrastrand crosslink with DNA nucleotide. Clinically, the complexes of platinum are used as adjunct therapy in cancers that directly focuses to induce cell apoptosis. Platinum based drugs are like the backbone of metallo drugs as they can damage DNA by interfering with DNA repair mechanisms which induces apoptosis in cancer cells. This review mainly discuss about the chemotherapeutic properties of cisplatin and other platinum drugs in the treatment of various human cancers. Deep understanding of mechanisms of action of anticancer agents might lead to develop more efficient and well organized platinum antitumor drugs and therapeutically provide new opportunities in cancer treatment. Extensive research is underway to understand the role of metal complexes in cancer treatment.

Keywords: - Cancer, DNA, platinum, metal complexes, apoptosis, cisplatin.

Introduction: - Examples of cancer treatments from the early 19th century include radical, super-radical and ultra-radical surgery, as propagated by William S Halstedt . In particular, radical mastectomy was used to treat breast cancer for ~90 years, between 1891 and 1981. However, in 1981, Bernhard Fisher published a study that disproved radical surgery for the treatment of cancer. Cancer has become one of the biggest threats to humans globally. Recent WHO report on cancer reveals around 9.6 million deaths worldwide in 2018.[1] In India, cancer patients are increasing at the alarming rate and the latest report published in 2018 suggested that the total number of cancer cases reported are 1,157,294 (males: 5,70,045 and females: 5,87,249). Cancer is

defined as uncontrolled growth of normal cells which start destroying normal healthy body tissues at the later stage. Several chemotherapies are being used to prevent or slow down the spread of cancer.[2]

In medicinal chemistry, metal complexes have gained popularity as diagnostic tools as well as anticancer agents. In nature, biological system of metal ions plays crucial role in maintaining the normal life while deficiency of metal leads to several disorders.[3] Metal complexes affects the cellular processes in a dramatic way as they provide specific characteristics like variable coordination modes and their reactivity towards organic molecules which is useful to improve biochemical processes during cellular process. Hence, the existence of relationship between metals and cancer is broadly studied by the researchers and concluded that metal complexes are considered to be the potential candidates in cancer chemotherapy.

Work of metal complexes in cancer chemotherapy: -

Metal Complex: - A complex having metal ion present at its centre surrounded by various ligands is called metal complex. The ligands are believed to bind to the central ion *via* coordinate bond. Simple ligands can be water, chloride ions and ammonia. Usually, the bond between metal and ligand is much weaker than the covalent bond, hence it facilitates the biological media for the ligand substitution reaction. Metal complexes provide opportunities for building structures with defined properties. Therefore, from inorganic chemistry point of view, it can provide better opportunities for using metal complexes as therapeutic agents.[4]

The presence of positive charge on metal centres is favoured to bind biomolecules which are negatively charged. Proteins and nucleic acid are the moieties which can provide excellent ligands for binding with the metal ions. Therefore, metal complexes have outstanding potential in pharmaceutical field. The wide arrangement of pharmaceutical applications of these complexes has been studied.[5, 6] Many metal complexes and their mechanism of action of cytotoxicity have been analysed with the hope to develop new therapeutic agents.[7, 8]

However, to develop metal complexes as drugs is not an easy job because the insertion of metal in the body might lead to harmful effects. Therefore, development of metal complexes along with their medicinal specificity must be considered to overcome this issue. In this context, the favourable physiological responses of particular drug are required to be demonstrated by their *in vitro* and *in vivo* investigations along with targeted biomolecules and tissues before entering into clinical trials. The deep mechanistic knowledge of

metal complexes is very important to recognize the biological activities of metals which will be essential for the development of newer drugs with better efficacy.

Transition metals used in cancer treatment: -

Palladium(Pd)

Graham *et al* [9] have synthesized various palladium complexes and screened for its *in vitro* and *in vivo* anticancer properties which showed remarkable activities against various cancer cell lines *viz* lung and prostate cancer. Subsequently, Tusek-Bozic [10] in 1991 has reported that the Trans-Palladium complex (Figure 1(a) is effective against cancer while Cis-Palladium has no effect. The possible reason for high potency of Trans-Palladium is due to the easy dissociation of the chloride ions from the palladium centre which results free availability of Trans- Palladium that interacts with DNA. It could be the plausible reason for high anticancer activity though no experimental evidences are reported so far.

Ruthenium(Ru)

Recently, ruthenium complexes with oxidation states (II) and (III) have exhibited potent anticancer activity against tumor cell lines,[11] though no ruthenium based anti-cancer drug has been commercialized yet. Ruthenium based drugs known as New Anti-Tumor Metastasis Inhibitor (Figure 1a) was first to enter into clinical trial followed by another drug known as trans-[tetrachlorobis(1H-indazole) ruthenate (III)] (Figure 1b).[12] There is still further scope to discover newer ruthenium based drugs which can prevent cancer efficiently.

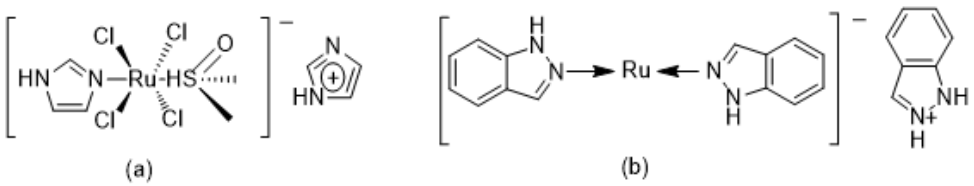

Figure 1. .

Gold(Au)

Gold complexes are known for their antimicrobial properties since ancient times.[13] Gold (III) compounds were amongst the first to be screened against anti-tumor activities. Gold in (III) and (II) oxidation state having d^8 electronic configuration has attracted considerable interest as they exhibited good to moderate anticancer activities. Some of the gold complexes with chelating N-donor ligands were investigated for anticancer applications and had shown promising cytotoxic as well as potential anticancer activity (Figure 2). A broad range of gold compounds was investigated, containing Gold (III) compounds which clearly indicated resurgence of interest in this area of medicinal chemistry.[14] Extensive research is on the way to find effective gold complexes with potential anticancer activities.

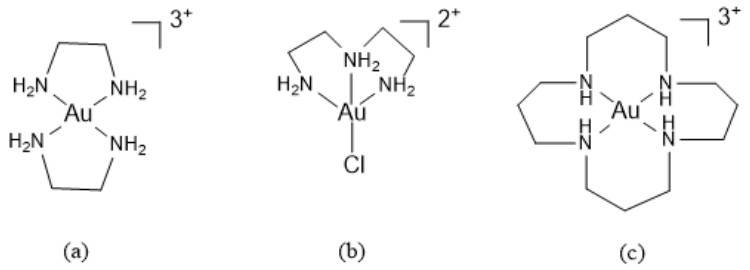

Figure 2. (a) Gold (III) ethylenediamine complex, (b) Gold (II) ethylenetriamine complex and (c) Gold (III) tetra azacyclotetradecane complex.

Platinum(Pt)

Platinum drugs got attention for the cancer treatment once antineoplastic activity of cisplatin was discovered by Barnett Rosenberg in the 1960s.[15] At present, 50% of cancer patients are receiving platinum based anticancer drugs to cure cancer.[16] Till date, nine complexes of platinum have been synthesized namely ormaplatin [tetraplatin], cisplatin, carboplatin, oxaliplatin, enloplatin, lobaplatin, heptaplatin, nedaplatin and liposome-entrapped *cis*-bis-neodecanoato-*trans*-*R*,*R*-1,2-diaminocyclohexane platinum (II) [L-NDDP] but only six of them namely cisplatin, oxaliplatin and carboplatin (as worldwide anticancer drugs) and heptaplatin, nedaplatin and lobaplatin (as regional anticancer drugs) have shown potent anticancer activity in various cell lines (Figure 3).[17-19] However, these drugs have severe side effects like nephrotoxicity, ototoxicity, nausea and hepatotoxicity due to high doses of platinum drugs hence, more safe and effective platinum based drugs are under investigation.[20-22]

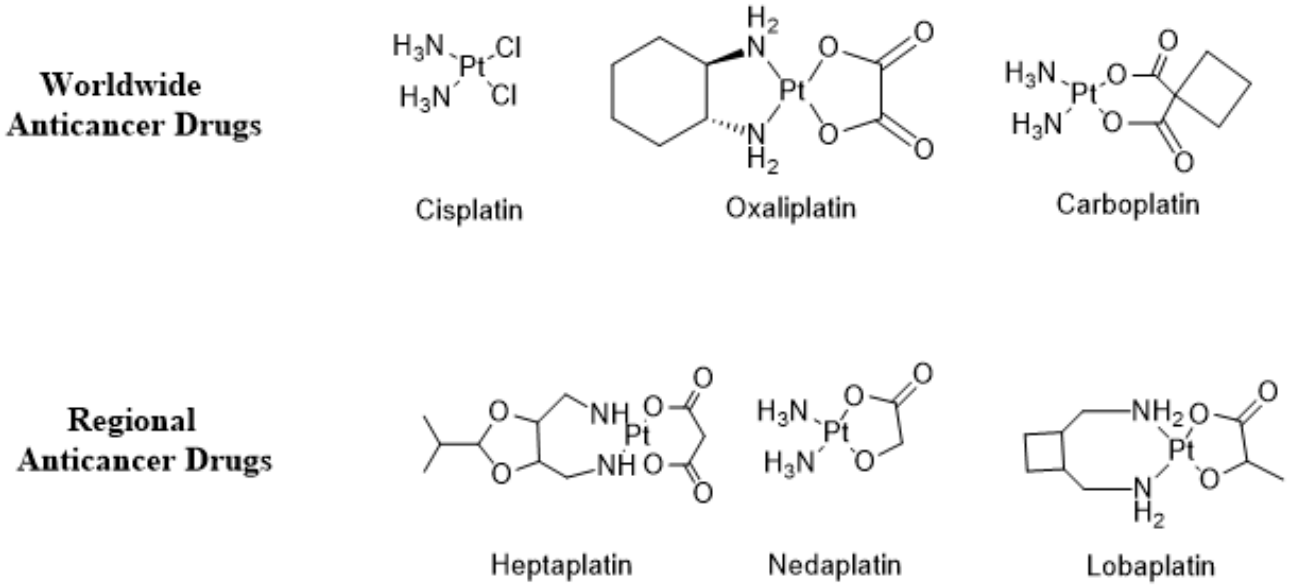

Figure 3. Platinum (II) drugs approved for the treatment of human cancer in worldwide and regional clinics.

Cisplatin

Cisplatin is generally a white to yellow crystalline powder which is soluble in dimethylpyrimidine and N, N-dimethylformamide (DMF). It is an inorganic molecule having molecular weight: 300.01 g/mol, melting point: 270 °C, and density: 3.75 g/cm^3. Structurally, it is an arrangement where platinum ion is bounded to two chloride ions and two amine groups aligned in a square (Figure 4). Amine groups act as the carrier ligands, while chlorides act as the leaving groups. The arrangement of chloride ion is next to each other in cisplatin which is biologically essential.

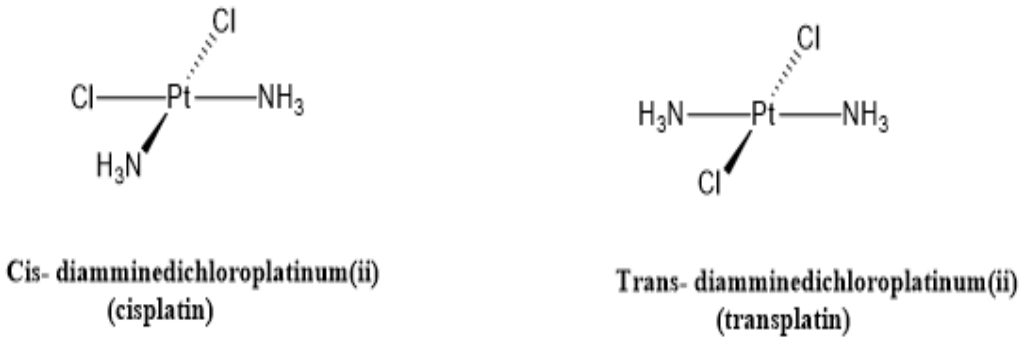

Figure 4. Structures of cisplatin and transplatin.

Interestingly, transplatin, the trans isomer of cisplatin, does not exhibit anticancer activity. The first reason for its reduced anticancer effect is the arrangement of trans-chloride ions. Because of the higher chemical reactivity of trans isomer, it becomes deactivated before reaching to the DNA nucleotide.[23] The second reasonable factor is that there is no formation of 1, 2-intrastrand adduct which can be formed in the case of

cisplatin. Hence, cisplatin is considered as one of the most powerful chemotherapeutic drugs used for the treatment for many types of cancer.

Synthesis of cisplatin: -

When potassium tetrachloroplatinate is treated with excess of potassium iodide, it gives potassium tetraiodoplatinate. Reaction of potassium tetraiodoplatinate with ammonia gives yellow compound, $K_2[PtI_2(NH_3)_2]$. After this, on adding aqueous solution of silver nitrate, silver iodide precipitates out and $K_2[Pt(OH_2)_2(NH_3)_2]$ left as residue in the solution. After adding potassium chloride, there is formation of the final product cisplatin. Overall synthesis is depicted in Figure 5.

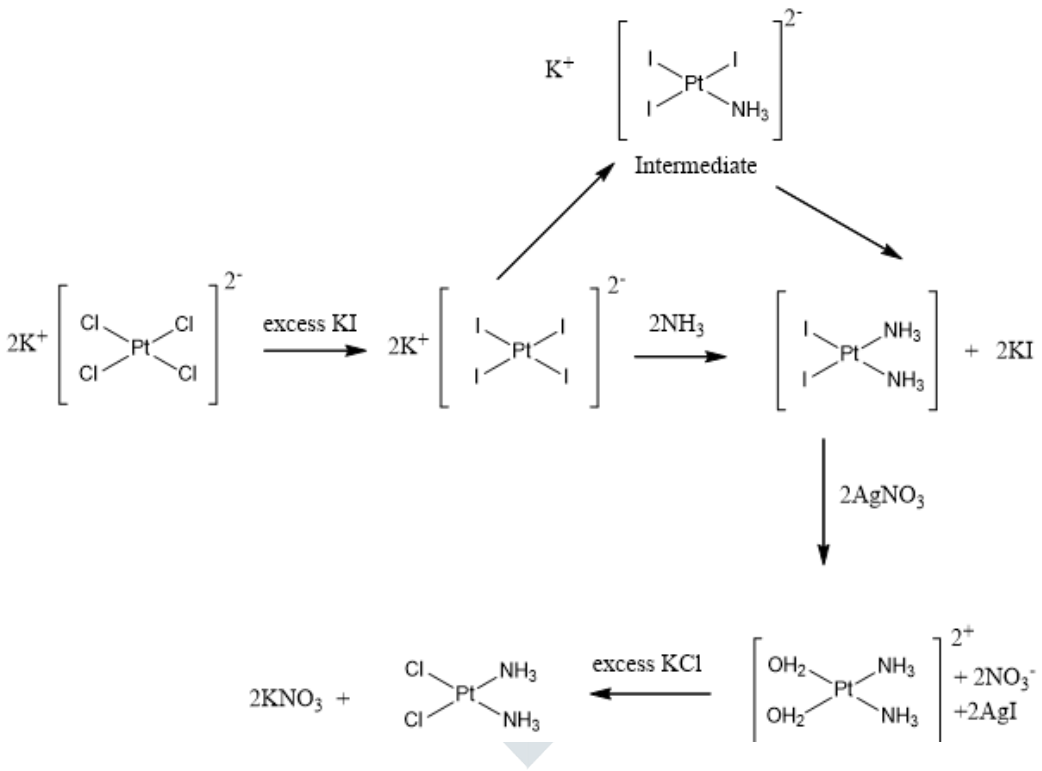

Figure 5. Stepwise synthesis of cisplatin

Oxaliplatin

Oxaliplatin, a well-known and effective drug for treatment of colorectal cancer is sold under the trade name, Eloxatin. A deep mechanistic understanding of tumor resistance to platinum drugs leads the discovery of oxaliplatin, a third generation drug. It is used in combination with folinic acid (leucovorin) and fluorouracil (FU) for advanced stage cancer treatment. Major side effects of drug oxaliplatin include nausea, numbness, low blood cell counts and diarrhea.[22] Preclinical studies have confirmed that oxaliplatin is found to be more toxic than cisplatin.[24] Unfortunately, oxaliplatin showed neurotoxicity. Other significant side effects of

oxaliplatin include allergic reactions, nausea and diarrhea. Oxaliplatin accumulates in body by blocking the duplication of DNA. The patient under oxaliplatin treatment must increase high intake of magnesium as the induction of hypomagneseia turned out to be one of the major side effects in oxaliplatin therapy.

Carboplatin

Carboplatin is generally used in the treatment of ovarian cancer. It is obtained by replacing two chloride ions of cisplatin with cyclobutanedicarboxylate ligand as a result it shows good aqueous solubility and high stability resulting minimal side effects. For the improved efficacy, carboplatin should be taken in higher doses.[25] Carboplatin is used in the treatment of cancers like ovarian, lung, brain, head and neck. Sometimes, carboplatin can also be used to treat testicular cancer though cisplatin is more effective. Relatively, the main advantage of carboplatin over cisplatin is its reduced side effects, especially eliminating the nephrotoxicity. Carboplatin shows the chelating effect in its mechanism of action which exhibits comparable stability to cisplatin. Nausea and vomiting are less severe side effects which can be controlled easily. Myelosuppressive effect is considered to be one of the major drawbacks associated with carboplatin. Use of cisplatin, oxaliplatin and carboplatin by the types of cancer is summarized in Table 1.[25]

Table 1 *Use of cisplatin, carboplatin and oxaliplatin by the type of cancer.*

Type of cancer	***Cisplatin***	***Carboplatin***	***Oxaliplatin***
Ovarian	*yes*	*yes*	***no***
Lung (particularly the small cell type)	*yes*	*yes*	*no*
Testicular	*yes*	***no***	***no***
Cervical	*yes*	***no***	***no***
Bladder	*yes*	***no***	***no***
Head and Neck	yes	**no**	**no**
Lung (particularly the small cell type)	yes	**no**	no
Colon (adjuvant)	**no**	**no**	yes

Nedaplatin

Nedaplatin or (cis-diammine-glycolatoplatinum), is the another derivative of cisplatin. It was synthesized in 1983 and used in the treatment of cancer having similar efficacy as that of cisplatin. Like cisplatin, nedaplatin has also two amines as the carrier ligands and a glycolate containing five-membered ring which is bounded to the platinum ion as depicted in Figure 3. It is used to treat cancers such as lung, testicles, and prostate. It interacts with the nucleophilic groups of DNA, causing cell apoptosis.

Lobaplatin

Lobaplatin or 1,2-diammino-l-methyl-cyclobutane-platinum (II)-lactate is one of the analogs of the platinum based drugs. Lobaplatin is useful in the treatment of human lung cancer, ovarian and gastric cancer xenografts. Lobaplatin was initially used to treat the patients suffering from chronic myelogenous leukemia, metastatic cancer and small-cell lung cancer. After getting positive outcomes from the clinical trial of phase I (when it recognized the human solid tumor), it provide chemists to recommend same dose for the clinical trial of phase II.

Heptaplatin

Heptaplatin is used in the treatment of gastric cancer. It consists of malonate as a chelating leaving group and 2-(1-methylethyl)-1, 3-dioxolane-4, 5-dimethanamine as a chelating group. As there is no separate anticancer mechanism of heptaplatin has been studied yet, it is considered to be similar as that of cisplatin. Heptaplatin interacts with DNA and forms different types of adducts which affects biological processes like DNA transcription and replication that eventually lead to cell apoptosis.

Mechanism of action of cisplatin: -

After the penetration of cisplatin molecule in the cell membrane, the first step is to replace the H_2O molecule by one of the chlorides. The resulting structure then binds to single nitrogen on a DNA nucleus. Then, the replacement of second chloride ion takes place by another water molecule and the platinum interacts with the second nitrogen on DNA nucleotide.[26-28] On the basis of binding studies, nitrogen 7 is most favoured for binding cisplatin with DNA on two adjacent guanines of the same strand (Figure 6). The binding can takes place with adenine also but to the lesser extent.The complex formed between cisplatin and DNA draws the

attention of DNA repair protein and HMG (high mobility group) that is irreversibly bounded. This creates distortion in the shape of DNA which prevents effective repair. Though, in transplatin, it is difficult to form 1,2-intrastrand adduct and hence, does not exhibit antineoplastic activity. In case of cisplatin, etoposide, which is one of the antineoplastic agents, contributes to the protein platinum-DNA complex which synergistically strengthens the cisplatin activity. In brief, it is considered that cisplatin kills the cancer cells by interacting with DNA nucleotide and interfering with its repair mechanism which eventually responsible for cell apoptosis.[29]

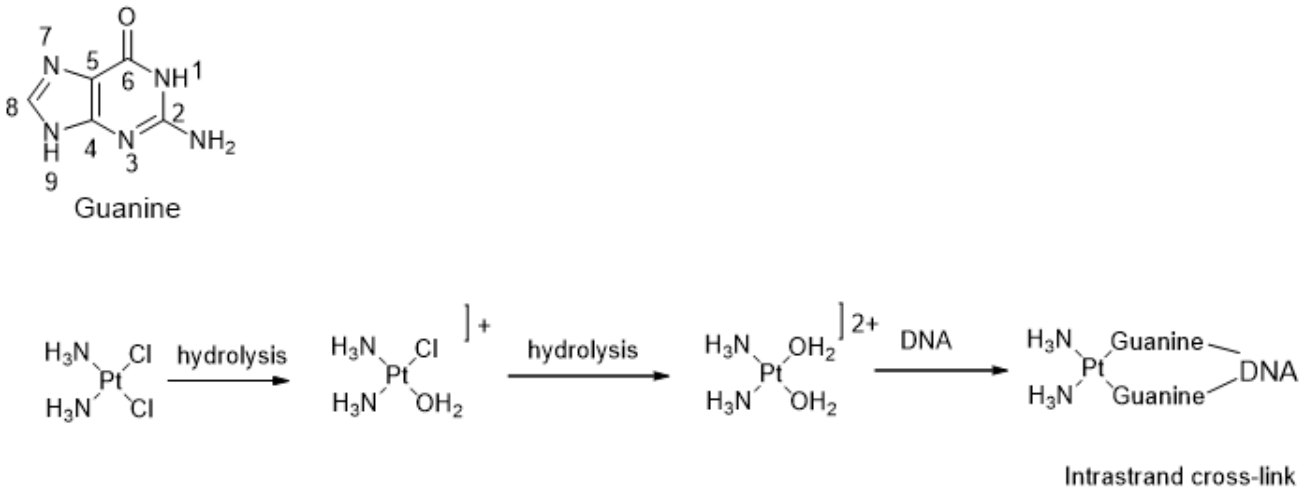

Figure 6. The pathway for GG intrastrand cross linking of DNA by cisplatin.

Toxicological effects of cisplatin:-

Though cisplatin is one of the best anticancer agents, it is associated with several toxicities. Toxicology of cisplatin depends upon its interaction with nucleotide DNA. Cisplatin interact with DNA and form covalent adducts with purine DNA bases. The resulting interaction of platinum complex is the major reason for the cytotoxicity in cisplatin.[30] Cisplatin treatment results several toxicities *viz* nephrotoxicity,[31] hepatotoxicity [32] and cardiotoxicity.[33]

Various cardiac events were also observed like electro-cardio graphic changes, arrhythmias, congestive heart failure and cardiomyopathy.[34]

Hepatotoxicity

Hepatotoxicity is the common problem associated with the use of high doses of cisplatin.[34] The main cause for toxicity in cisplatin is an oxidative stress which is mainly due to the depletion of reduced glutathione.[35] It is well documented that there was a remarkable increase in the hepatic malondehyde and depletion in the antioxidants found in the rats which were treated with cisplatin.[36] Cisplatin hepatotoxicity was found worsen on increasing the level of enzyme cytochrome P450-2E1.[37,38] Recently, studies have highlighted the methods for the prevention of hepatotoxicity induced by cisplatin by adopting the agents like selenium [39] and vitamin E.[40]

Cardiotoxicity

Cardiotoxicity is related to the damage of heart muscles. Leakage of creatinine kinase (CK) and lactate dehydrogenase (LDH) from cardiacmyocytes results cardiotoxicity. Myonecrosis and degeneration of cardiac muscle fibre cells with the fibrous tissue reaction are the histological changes for toxicology induced by cisplatin.[41] Cisplatin-induced cardiotoxicity is rare but if observed it is utmost important to stop cisplatin immediately.

Nephrotoxicity

Nephrotoxicity is related to the toxicity in kidneys. In comparison to other organs when the kidney collects cisplatin to a greater extent, it resulted as the main route cause for its excretion. Nephrotoxicity can be easily monitored through the blood sample. The depletion of creatinine shows poor renal functioning. Serum creatinine is another measure of renal function, which is useful for patients suffering from kidney diseases.[42] The unbalanced amount of cisplatin deposited in kidney tissues might lead to nephrotoxicity.[43]

Other organ toxicity

Several other cisplatin-induced toxicities are also very well reported *viz* gastrotoxicity, ototoxicity, allergic reactions, myelosuppression and some reproductive toxicities.[44]

Strategies to overcome cisplatin toxicity: -

STRATEGIES TO OVERCOME CISPLATIN RESISTANCE AND TOXICITY

1-ADMINISTERING CISPLATIN IN LIPOSOME AND POLYMER

2--INHIBITING GLUTATHIONE AND METALLOTHION SPECIES

3-USING ANTISENSE OLIGODEOXYNUCLEOTIDES(ODN) AND RIBOZYMES

4-COMBINATION THERAPY

Cisplatin-induced toxicities can be minimized by adopting several techniques depicted in above four points, for improved cisplatin delivery to the DNA nucleotide. There are ways to attain this by administering cisplatin in polymers and liposomes or by inhibiting species that is glutathione and metallothione which is used to inactivate cisplatin and eventually lessen its antitumor efficacy.[45] Cisplatin resistance can be also minimized in another way by using antisense oligodeoxynucleotides (ODN) targeting which is responsible oncogene for cisplatin resistance, where the antisense oligodeoxynucleotide hybridizes with the target m-RNA and prevents its translation.[46,47]

Cisplatin combination therapy: -

There are still various challenges for the improvement of cancer treatment. Recently, combination of one or more than one drug is very common which is being used to cure cancer in patients known as combination therapy. The combination therapy is more popular because two drugs exert two different mode of action.[48] In this way, one drug can reduce the ability of DNA replication and the other will attack on the cell's ability of making protein. Combination chemotherapy of cisplatin is one of the greatest advantages for treating number of cancers. In order to make the situation better, cisplatin are being used in combination with other drugs for treating various types of cancers *viz* ovarian, lung, biliary tract, breast, gastric, colorectal, melanoma, pancreatic, prostate, bladder and cervical cancer.[49] Success rate to cure patient becomes more than 90 percent when it is used as combination chemotherapeutic agents. In brief, cisplatin combination therapy exhibit tolerable toxicities and promising efficacies during cancer treatment. Some of the possible drugs which are used in combination with cisplatin very often *viz* Cisplatin and Paclitaxel, Cisplatin and Tegafur-uracil (UFT), Cisplatin and Doxorubicin, Cisplatin and Gemcitabine, Cisplatin and natural product (Osthole), Cisplatin and Everolimus, Cisplatin and (Fluorouracil, Doxorubicin and Cyclophosphamide), Cisplatin and Metformin, Cisplatin and (Oxaliplatin, Quercetin and Thymoquinone), Cisplatin and Tetraarsenic oxide.

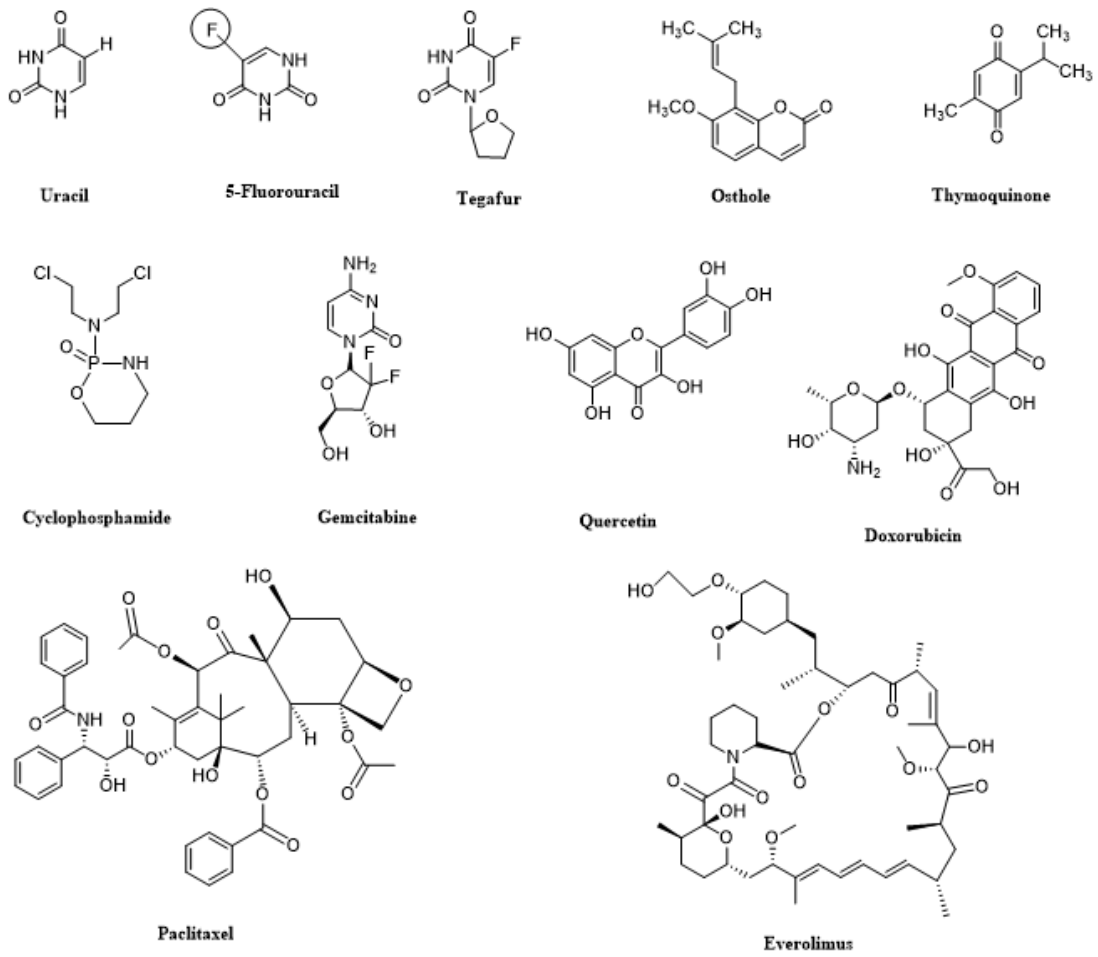

Figure 7. Structures of some combination drugs of cisplatin and other cancer drugs

Table 2 represents various cisplatin combination therapies with other cancer drugs and targeted cancers along with the corresponding references.

Table 2 Combination therapy of cisplatin and other cancer drugs

Combination Drug(s)*	**Cancer Types**	**References**
Paclitaxel	Ovarian carcinoma, Breast carcinoma, Lung carcinoma, Melanoma, Head and neck carcinoma.	Sarosy, Kohn *et al*, (1992) McGuire, Rowinsky *et al*, (1989) Einzig, Wiernik *et al*, (1992) Holmes, Walters *et al*, (1991) Murphy, Fossella *et al*, (1993) Legha, Ring *et al*, (1990) Einzig, Hochster *et al*, (1991) Forastiere *et al*,

		(1994)
Paclitaxel and 5-FU	Gastric and esophagogastric adenocarcinoma.	Kim *et al*, (1999)
UFT	Non small lung carcinoma.	Ichinose *et al*, (2000)
Doxorubicin	Diffuse malignant pleural mesothelioma.	Ardizzoni *et al*, (1991)
Gemcitabine	Biliary cancer.	Valle, Wasan *et al*, (2010)
Osthole	Lung cancer.	Xu, Zhang *et al*, (2013)
Everolimus	Urothelial bladder cancer.	Pinto-Leite, Arantes-Rodrigues *et al*, (2013)
Fluorouracil, doxorubicin and cyclophosphamide	Salivary gland carcinoma.	Dimery, Legha *et al*, (1990)
Metformin	Lung adenocarcinoma.	Lin, Yeh *et al*, (2013)
Oxaliplatin, quercetin and thymoquinone	Ovarian cancer.	Nessa, Beale *et al*, (2011)
Tetra arsenic oxide	Cervical cancer.	Byun, Jeong *et al*, (2013)

* Structures are provided in Figure 7

Conclusions: -

Cisplatin is considered to be the most effective anticancer agents widely used in the treatment of human solid tumors. It has been extensively used for the cure of different types of neoplasms including head and neck, lung, ovarian, leukaemia, breast, brain, kidney and testicular cancers. In general, cisplatin and other platinum-based compounds are considered as cytotoxic drugs which can kill cancer cells by distorting DNA, inhibiting DNA synthesis and mitosis which reinforces cell apoptosis. Cisplatin treatment is associated with considerable side effects which include hepatotoxicity, nephrotoxicity, cardiotoxicity, neurotoxicity and hepatotoxicity. To develop better compounds, inorganic and medicinal chemists need to understand the mode of action and the rationale based approach for the synthesis of new metallo based drugs physiologically. Applying new methodologies like combination chemotherapies would be highly advantageous for developing future inorganic compounds as therapeutic agents. Studies have proposed that when one or more compounds get

combined with cisplatin it becomes the excellent therapeutic methodology to overcome drug resistance and minimize the unwanted side effects.

References: -

1. World Health Organization (WHO). (2018). WHO Reports.

2. American Cancer Society, (2018).

3. Orvig C, Abrams MJ. (1999). Medicinal inorganic chemistry: introduction. *Chem. Rev*. 99, 2201-3.

4. Greenwood N, Alan E.

5. Sadler PJ, Li H, Sun H. (1999). Coordination chemistry of metals in medicine: target sites for bismuth. *Coord Chem Rev*. 185, 689-709.Chemistry of the Elements (2nd ed.).

6. Volkert WA, Hoffman TJ. (1999). Therapeutic radiopharmaceuticals. *Chem Rev.* 99, 2269-92.

7. Ndagi U, Mhlongo N, Solemon ME. (2017).Metal complexes in cancer therapy- an update from drug design perspective. *Drug Design, Development and Therapy*. 11, 599-616.

8. Zhukova OS, DobryninIaV. (2001). Current results and perspectives of the use of human tumor cell lines for antitumor drug screening. *VoprOnkol*. 47, 706-9.

9. Graham RD, Williams DR. (1979). *J. Inorg. Nucl. Chem*. 41, 1245

10. Tusek-Bozic LJ, Matijasic I, Bocelli G, Calestani G, Furlani A, Scarcia V and Papaioannou A. (1991). *Dalton Trans.* 195-201

11. Bergamo A, Gaiddon C, Schellens JHM, Beijnen JH, Sava G. (2012)."Approaching tumour therapy beyond platinum drugs". *Journal of Inorganic Biochemistry*.106 (1), 90-9

12. Enzo A. (2017). "Thirty Years of the Drug Candidate NAMI-A and the Myths in the Field of Ruthenium Anticancer Compounds: A Personal Perspective". *European Journal of Inorganic Chemistry*. (12), 1549-1560.

13. Senthil SK, Kashinath L, Rajendran AJ. (2017). Antibacterial properties and mechanism of gold nanoparticles obtained from pergulariadaemea leaf extract. *Nanomed. Res*. 6(1), 00146

14. Teikink ERT. (2008). Anticancer potential of gold complexes. *Inflammopharmacology*. 16, 138-142.

15. Timothy CJ, Kogularamanan S, Stephen JL. (2016). The next generation of platinum drugs: Targeted Pt (II) agents, nanoparticle delivery and Pt (IV) prodrugs. *Chem. Rev.* 16(5), 3436-3486.

16. Rosenberg B, VanCamp L, Trosko JE, Mansour VH. (1969). Platinum compounds: A new class of potent antitumour agents. *Nature*. 222, 385-386. [PubMed: 5782119]

17. Wang X, Guo Z. (2015). *Acc. Chem. Res.* 48, 2622-2631

18. Wheate NJ, Walker S, Craig GE, Oun R. (2010). *Dalton Trans*. 89, 8113-8117.

19. Olszewski U and Hamilton G. (2010). *Anticancer Agents Med. Chem*. 10, 293-301

20. Mc Whinney SR, Goldberg RM, McLeod HL. (2009). *Mol. Cancer Ther*. 8, 10-16.

21. Hellberg V, Wallin I, Eriksson S, Hernlund E, Jerremalm E, Berndtsson M, Eksborg S, Arnér ESJ, Shoshan M, Ehrsson H, Laurell G. (2009). *J. Natl. Cancer Inst*. 101, 37-47

22. Oun R, Moussa YE, Wheate NJ. (2018). The side effects of platinum-based chemotherapy drugs: a review for chemists. *Dalton Trans*. 47 (19), 6645-6653.

23. Coluccia M, Natile G. (2007).Trans-platinum complexes in cancer therapy. *Anticancer Agents Med Chem*.7, 111-123.

24. Pinto A, Pocard M. (2019). Hyperthermic intraperitoneal chemotherapy with cisplatin and mitomycin C for colorectal cancer peritoneal metastases: A systematic review of the literature. *Pleura and Peritoneum*, 10.1515/pp-2019-0006.

25. National Institute for Health and Care Excellence (NICE), British National Formulary (BNF), '*Platinum Compounds'*, October (2016)

26. Casini A, Reedijk. (2012). *J. Chem. Sci.* 3, 3135-3144

27. Gibson D. (2009). *Dalton Trans*.10681-10689

28. Klein AV, Hambley TW. (2009). *Chem. Rev*. 109, 4911-4920.

29. Reedijk J. (2009). Platinum Anticancer Coordination Compounds: Study of DNA Binding Inspires New Drug Design. *Eur. J. Inorg. Chem*. 1303-1312

30. Yousef MI, Saad AA, El-Shennawy LK. (2009). Protective effect of grape seed pro anthocyanid in extract against oxidative stress induced by cisplatin in rats. *Food Chem. Toxicol*. 47, 1176-1183

31. Gi-Su oh, Kim HJ, Shen AH, Lee SB, Khadka D, Pandit A. (2014). Cisplatin induces kidney dysfunction and perspective on improving treatment strategies. *Electrolye Blood Pressure.* 12(2), 55-65.

32. Al-Majed AA. (2007). Carnitine deficiency provokescisplatin-induced hepatotoxicity inrats.*Basic Clin. Pharmacol.Toxicol*.100, 145-150.

33. Kart A, Cigremis Y, Karaman M, Ozen H. (2010). Caffeic acid phenethyl ester (CAPE) amelio rates cisplatin-induced hepatotoxicity in rabbit. *Exp.Toxicol. Pathol*. 62, 45-52.

34. dos Santos NA, Martins NM, Curti C, Pires Bianchi ML, dos Santos AC. (2007). Dimethyl thiourea protects against mitochondrial oxidative damage induced by cisplatin in liver of rats. *Chem. Biol. Interact*.170, 177-186.

35. Yilmaz HR, Iraz M, Sogut S, Ozyurt H, Yildirim Z, Akyol O, Gergerlioglu S.(2004).The effects of erdosteine on the activities of some metabolic enzymes during cisplatin-induced nephrotoxicity in rats. *Pharmacol.Res*.50, 287-290

36. Yilmaz HR, Sogut S, Ozyurt B, Ozugurlu F, Sahin S, Isik B, Uz E, Ozyurt H. (2005).The activities of liver adenosine deaminase, xanthine oxidase, catalase, superoxide dismutase enzymes and the levels of malondialdehyde and nitric oxide after cisplatin toxicity in rats: protective effect of caffeic acid phenethyl ester. *Toxicol. Ind. Health*. 21, 67-73

37. Caro AA, Cederbaum AI. (2004). Oxidative stress, toxicology, and pharmacology of CYP2E1. *Annu. Rev. Pharmacol. Toxicol*. 44, 27-42.

38. Hegazy AA. (2018). Effect of Administration of Acrylamide and Possible Protective Role of Vitamin E on Postnatal Rat Liver Structure. *J. Embryol Stem Cell Res*. 2(2), 000114

39. Liao Y, Lu X, Lu C, Li G, Jin Y, Tang H. (2008). Selection of agents for prevention of cisplatin-induced hepatotoxicity. *Pharmacol. Res*. 57, 125-131.

40. Iraz M, Kalcioglu MT, Kizilay A, Karatas E. (2005). Amino guanidine prevents ototoxicity induced by cisplatin in rats. *Ann.Clin.Lab.Sci*. 35, 329-335.

41. Al-Majed AA, Sayed-Ahmed MM, Al-Yahya AA, Aleisa AM, Al-Rejaie SS, Al-Shabanah OA. (2006). Propionyl -L-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine – depleted rat model. *Pharmacol. Res*. 53, 278-286.

42. Kuhlmann MK, Burkhardt G, Kohler H. (1997). Insights into potential cellular mechanisms of cisplatin nephrotoxicity and their clinical application. *Nephrol. Dial. Transplant*.12, 2478-2480.

43. Arany I, Safirstein RL. (2003). Cisplatin nephrotoxicity.*Semin.Nephrol*. 23, 460-464.

44. Hartmann JT, Lipp HP. (2003).Toxicity of platinum compounds. *Expert Opin. Pharmacother*.4, 889-901.

45. Kelland L. (2007).The resurgence of platinum-based cancer chemotherapy. *Nat. Rev. Cancer*. 7(8), 573-84.

46. Li S, Li C, Jin S, Liu J, Xue X, Eltahan AS.(2017). Overcoming resistance to cisplatin by inhibition of glutathione S-transferases (GSTs) with ethacraplatin micelles *in vitro* and *in vivo*. *Biomaterials*.144, 119-29.

47. Dempke W, Voigt W, Grothey A, Hill BT, Schmoll HJ.(2000).Cisplatin resistance and oncogenes-a review.*Anticancer Drugs*.11(4), 225-36.

48. Agarwal D, Gupta RD, Awasthi SK. (2017). Are Antimalarial Hybrid Molecules a Close Reality or a Distant Dream? *Antimicrobial agents and Chemotherapies*. 61(5), e00249-17.

49. Einhorn LH, Williams SD, Loehrer PJ. (1987). Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a South eastern Cancer Study Group protocol. *J. Clin. Oncol*. 7, 387-391