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Review article

Cisplatin: The first metal based anticancer drug

Sumit Ghosh

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India

A R T I C L E I N F O

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A B S T R A C T

Cisplatin or (SP-4-2)-diamminedichloridoplatinum(II) is one of the most potential and widely used drugs for the treatment of various solid cancers such as testicular, ovarian, head and neck, bladder, lung, cervical cancer, melanoma, lymphomas and several others. Cisplatin exerts anticancer activity via multiple mechanisms but its most acceptable mechanism involves generation of DNA lesions by interacting with purine bases on DNA followed by activation of several signal transduction pathways which finally lead to apoptosis. However, side effects and drug resistance are the two inherent challenges of cisplatin which limit its application and effectiveness. Reduction of drug accumulation inside cancer cells, inactivation of drug by reacting with glutathione and metallothioneins and faster repairing of DNA lesions are responsible for cisplatin resistance. To minimize cisplatin side effects and resistance, combination therapies are used and have proven more effective to defect cancers. This article highlights a systematic description on cisplatin which includes a brief history, synthesis, action mechanism, resistance, uses, side effects and modulation of side effects. It also briefly describes development of platinum drugs from very small cisplatin complex to very large next generation nanocarriers conjugated platinum complexes.

1. Introduction

Cancer is one of the most important health problems in the world and second cause of death in the United States. In 2018, 1,735,350 new cancer cases and 609,640 cancer deaths are projected to occur in the United States [1]. Cancer is defined as the uncontrolled growth of abnormal cells anywhere in the body. It is accepted that cancer can develop when normal mechanism of body stops working. Old cells do not die and instead grow out of control, forming new abnormal cells. These extra cells may form a mass of tissue, called tumor [2]. According to World Health Organization (WHO), cancer may arise due to interaction between a person's genetic factors and 3 categories of external agents, including physical carcinogens (ultraviolet and ionizing radiation), chemical carcinogens (asbestos, components of tobacco smoke, aflatoxin, and arsenic) and biological carcinogens (infections from certain viruses, bacteria, or parasites) [274,275]. Depending on the type and stage of cancer, patients are treated with either traditional therapies (such as surgery, chemotherapy, and radiation therapy) or newer forms of treatment (such as immunotherapy [276], targeted therapy [277], hormone therapy [278], gene therapy [279] and photodynamic therapy [280]. Surgery is the process of removing cancer by doing operation and it is generally used only when cancer is localized [281]. Radiation therapy uses high doses of radiation to shrink or kill cancer cells [282]. On the other hand, chemotherapy is an effective and widespread way of cancer treatment in which one or more chemotherapeutic or alkylating agents are used [3–5].

Cisplatin is one of the best and first metal-based chemotherapeutic drugs (see Fig. 1 for 3D structure of cisplatin) [10,287]. It is reported that ~2 billion U.S. dollars of platinum-based anticancer drugs are sold worldwide [6,7] and nearly about 50% of all patients are treated with cisplatin [8]. Cisplatin was discovered in 1845 by Michele Peyrone but its biological property was hidden until 1965 when a biophysicist, Dr. Barnett Rosenberg [9] discovered its inhibiting cell division property. It is used for wide range of solid cancers such as testicular, ovarian, bladder, lung, cervical, head and neck cancer, gastric cancer and some other cancers [11,12,285]. Studies confirmed that cisplatin exerts its anticancer activity by attacking more than one place [14]. It generally binds with genomic DNA (gDNA) or mitochondrial DNA (mtDNA) to create DNA lesions, block the production of DNA, mRNA and proteins, arrest DNA replication, activate several transduction pathways which finally led to necrosis or apoptosis [13,15,40,283,286]. However, cisplatin does not show its highest potential because of side effects and drug resistance. Resistance to cisplatin depends on multiple factors such as reduced drug accumulation, inactivation of drug by binding with different proteins, increase of DNA repairing, alteration of different proteins that signal to apoptosis [16,40,288,289]. The major toxicities arise from cisplatin therapy are nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal, neurotoxicity [12,17,290,291]. Furthermore,

E-mail address: ghoshsumit357@gmail.com.

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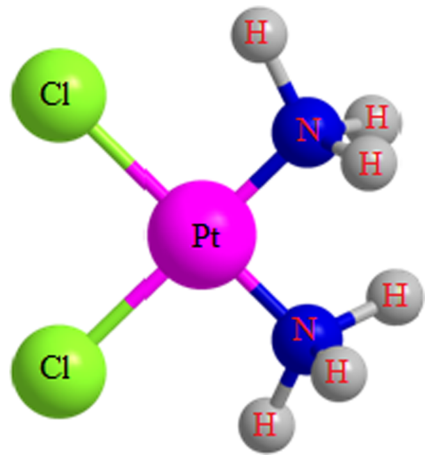


Fig. 1. 3D structure of cisplatin.

relapsing is also a very important drawback of cisplatin [18,284]. The clinical limitations of cisplatin motivate researcher to create thousands of cisplatin analogs [34,189]. But only two (carboplatin and oxaliplatin) have been approved worldwide and a few have entered in clinical trials [19]. But most of the platinum compounds do not show substantial advantage over cisplatin [20].

This article is divided in two parts. In the first part, a complete overview of cisplatin is sketched which includes a brief history of cisplatin, synthesis and clinical applications of cisplatin. Special attention is paid to mechanism of action and drug resistance. Next part of this article, development of different nonclassical platinum drugs such as *trans* Pt(II) compounds, monofunctional Pt(II) compounds, polynuclear Pt(II) compounds and Pt(IV) prodrugs are briefly explored. Different nanoparticle conjugated Pt(II) and Pt(IV) complexes are also discussed on this article.

2. Invention of 1st metal based chemotherapeutic agent

The compound cis-$[Pt(NH_3)_2Cl_2]$ was first prepared by Michele Peyrone in 1845 [21] and hence it was called Peyrone's salt for a long time. The structure of Peyrone's salt was properly deduced by Alfred Werner in 1893 [22]. But the mysterious property of inhibition of cell division was accidentally discovered by Barnett Rosenberg [23], a biophysicist on study of effects on electric field on bacterial growth where he used platinum as electrode and ammonium chloride as buffer. During his experiments, he found that the E-coli bacteria kept growing up to 300 times of their normal size instead of cell division on applying electric field and when electrical field was cut off, the bacterial cell again started dividing. Although the primary assumption was that electrical field was the cause of controlling cell division, but finally he proved that cell division was blocked by a platinum compound released from electrode. In 1969 Rosenberg [24] has demonstrated that cisplatin has the ability to inhibit sarcoma 180 and leukaemia L1210 in mice. The subsequent tests on the drug have found to be active against wide variety of animal tumor systems [25]. Results were so good that the National Cancer Institute (US) and the Wadley Institutes of molecular medicine started preclinical pharmacology and toxicology tests [26]. Finally, in 1971 National Cancer Institute started trial 1 and within just 7 years in 1978, it was approved by the US Food and Drug Administration (FDA) for testicular and ovarian cancer. One year later in 1979 United Kingdom also approved it [27]. Fig. 2 represents the milestones of cisplatin.

3. Synthesis

3.1. Synthesis of cisplatin

The most efficient method for synthesis of cisplatin was given by Dhara [28] which was published in 1970 entitled as "A rapid method for the synthesis of cis-$[PtCl_2(NH_3)_2]$". Dhara method (Scheme 1) is a multistep process in which aqueous $K_2[PtCl_4]$ is treated with excess KI in the first step to form $K_2[PtI_4]$. Ammonium Hydroxide is added in this dark brown solution of $K_2[PtI_4]$ which results in yellow precipitate of cis-$[Pt(NH_3)_2I_2]$. It is then collected and dried. To remove iodide ligands from the complex of cis-$[Pt(NH_3)_2I_2]$, 2 equivalents of aqueous solution of $AgNO_3$ is added resulting in formation of soluble $[Pt(NH_3)_2(H_2O)_2]^{2+}$ and insoluble AgI. The insoluble AgI is then filtered off and discarded. The filtrate containing $[Pt(NH_3)_2(H_2O)_2]^{2+}$ is then treated with excess KCl solution to get isomerically pure yellow solid of cisplatin. Cisplatin can be purified by recrystallization from hot water containing either 0.1 M HCl or 0.9% NaCl [29,30]. The first step i.e. conversion of $K_2[PtCl_4]$ into $K_2[PtI_4]$ is really important because stronger trans effect of iodide with respect to chloride helps to produce pure cisplatin [31].

3.2. Synthesis of transplatin

In 1844 Reiset [32,33] first gave a synthetic procedure for transplatin and hence it is known as Reiset's second chloride [34]. The most common method for synthesis of transplatin in modern days is a two-step process in which conversion of $K_2[PtCl_4]$ into $[Pt(NH_3)_4]Cl_2$ (colorless) by treatment of excess ammonia is the 1st step. In the next step, volume is reduced by evaporation and HCl is added to get precipitation of the desired product of transplatin. The intermediate $[Pt(NH_3)_3Cl]^+$ is charged species and hence soluble but transplatin is neutral species and hence very less soluble and so it precipitates out from solution. Formation of transplatin is possible because of the higher trans effect of chloride group than ammine group. Higher trans effect of chloride ligand makes more labile to ammine group which is trans in position with respect to it. So the second chloride replaces at trans position leading to transplatin. Scheme 2 represents the synthetic method of transplatin.

3.3. Separation of cisplatin and transplatin

The Soviet chemist Nikolai Semenovich Kurnakov [35,36] developed a quick distinguishing method between cisplatin and transplatin in 1894 and hence the method is known as Kurnakov test or Kurnakov's reaction (Scheme 3). In this method, aqueous cis/trans-platin is reacted with excess thiourea on gentle heating so that cisplatin produces deep yellow water soluble solution of $[Pt(Th)_4]Cl_2$ (Th = thiourea) while transplatin forms white water insoluble trans-$[Pt(NH_3)_2(Th)_2]Cl_2$ and hence they can be distinguished only by visual identification. The Kurnakov test is basically a result of trans effect. Thiourea has greater trans effect as compared to chloride and ammine ligands as thiourea coordinated through sulfur atom. Therefore for cisplatin when the first thiourea displaces a chloride ligand, the amine group present trans to it becomes more labile and hence is displaced by thiourea. Similarly, when the second chloride is replaced by another thiourea, its trans ammine group become more labile and hence is displaced by thiourea so that all four ligands become thiourea to form $[Pt(Th)_4]Cl_2$. But for transplatin, if one chloride replaces to thiourea, the trans position i.e. the second chloride ligand becomes more labile and hence is displaced by thiourea so that only two thiourea keep in trans position with respect to each other to form trans-$[Pt(Th)_2(NH_3)_2]Cl_2$. No other ammine group present at trans to thiourea and hence remains coordinated to platinum ion. Kurnakow test in conjugation with HPLC has developed to separate cis and transplatin and detect trace quantities of transplatin in samples of cisplatin which can be used in clinic [37,38]. Several other

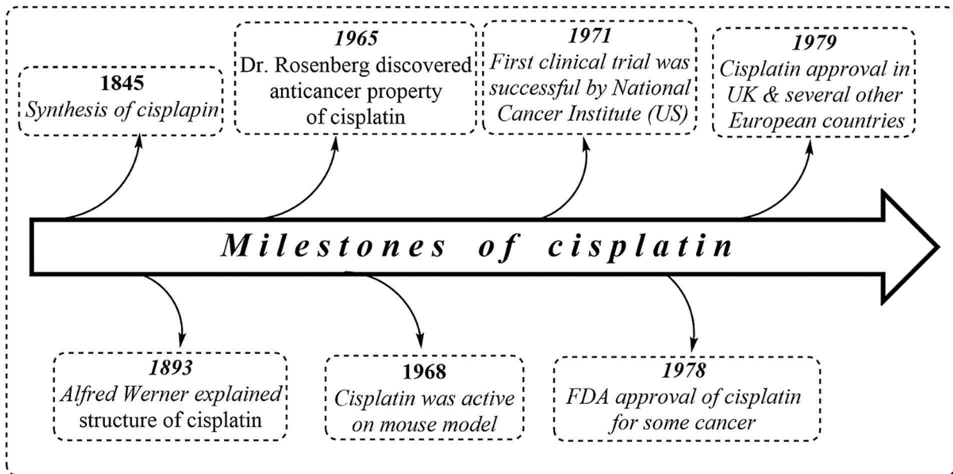
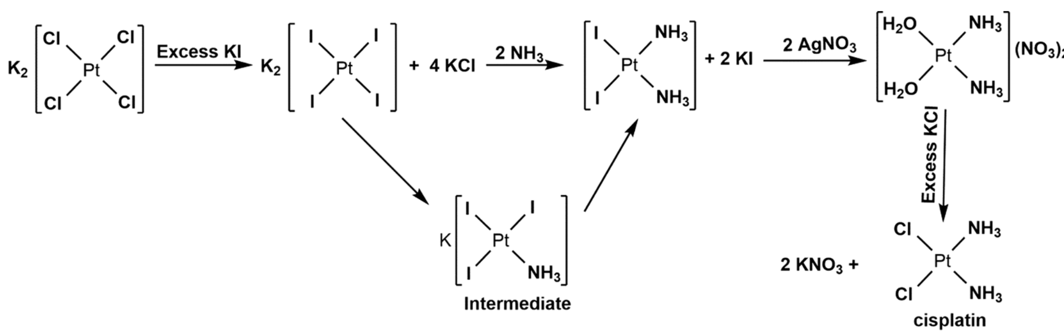


Fig. 2. Milestones of cisplatin.



Scheme 1. Synthetic Scheme of cisplatin (Dhara method).

distinguishing methods for cisplatin and transplatin are also known [39].

4. Action mechanism of cisplatin:

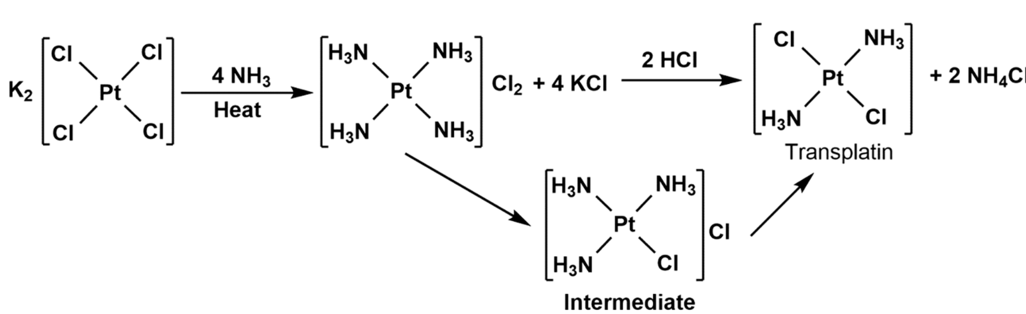
The detail molecular mechanism of cisplatin anticancer activity goes beyond this review and remains elsewhere [14,40,41,42]. Here a brief overview of mechanism of cisplatin activity is explained.

Cisplatin is administered intravenously to the patients as a sterile saline solution [43]. In the bloodstream the concentration of chloride is relatively high (approximately 100 mM) and hence cisplatin remains unchanged and neutral [31,44]. This unchanged cisplatin keeps flowing over the whole body through bloodstream. The plasma proteins albumin, transferring, cysteine etc. can bind strongly with cisplatin resulting in deactivation of large amount of applied cisplatin [31,45]. It is reported that 65–95% of cisplatin may bind with blood plasma protein just within 24 h of administration [46].

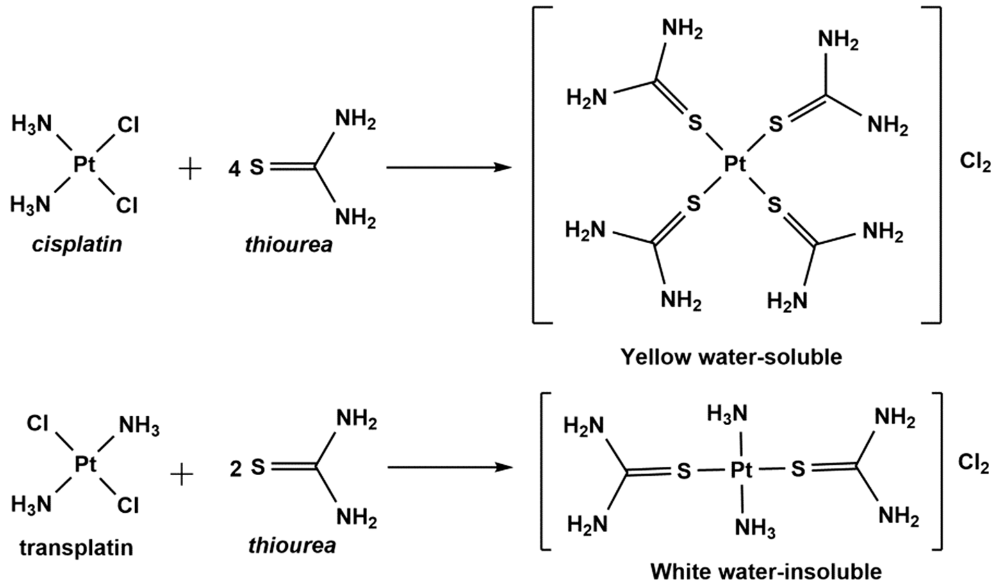
The remaining cisplatin can transport to tumor cells by passive diffusion through plasma membrane [31,44,47]. Modern studies reveal that copper transporter protein CTR1 is also responsible for cisplatin uptake [48]. Cisplatin causes degradation of concentration of CRT1, resulting in lower cisplatin accumulation by the cancer cells. Cells with higher CTR1 expression can have higher accumulation of cisplatin which makes higher sensitivity to cisplatin [12].

Once cisplatin enters into the cell it becomes activated by replacing one of the chloride ligands into water ligand (i.e. monoaquation of cisplatin does take place). This mono and/or diaquation of cisplatin occur because concentration of chloride in cytoplasm is relatively low (approximately 4–20 mM) and they are potent electrophile. They can react with a number of nucleophiles like sulfhydryl groups of protein and nitrogen donor atoms of nucleic acids etc [12] because water is better leaving group than chloride [49]. In vitro studies have confirmed that monoaquated platinum is more reactive than diaquated platinum towards DNA binding [50]. DNA binding properties of cisplatin are discussed in the next part of this article.

Oxidative stress is a very common mechanism in cisplatin



Scheme 2. Synthetic scheme of transplatin.



Scheme 3. Schemetic representation of kurnakow test.

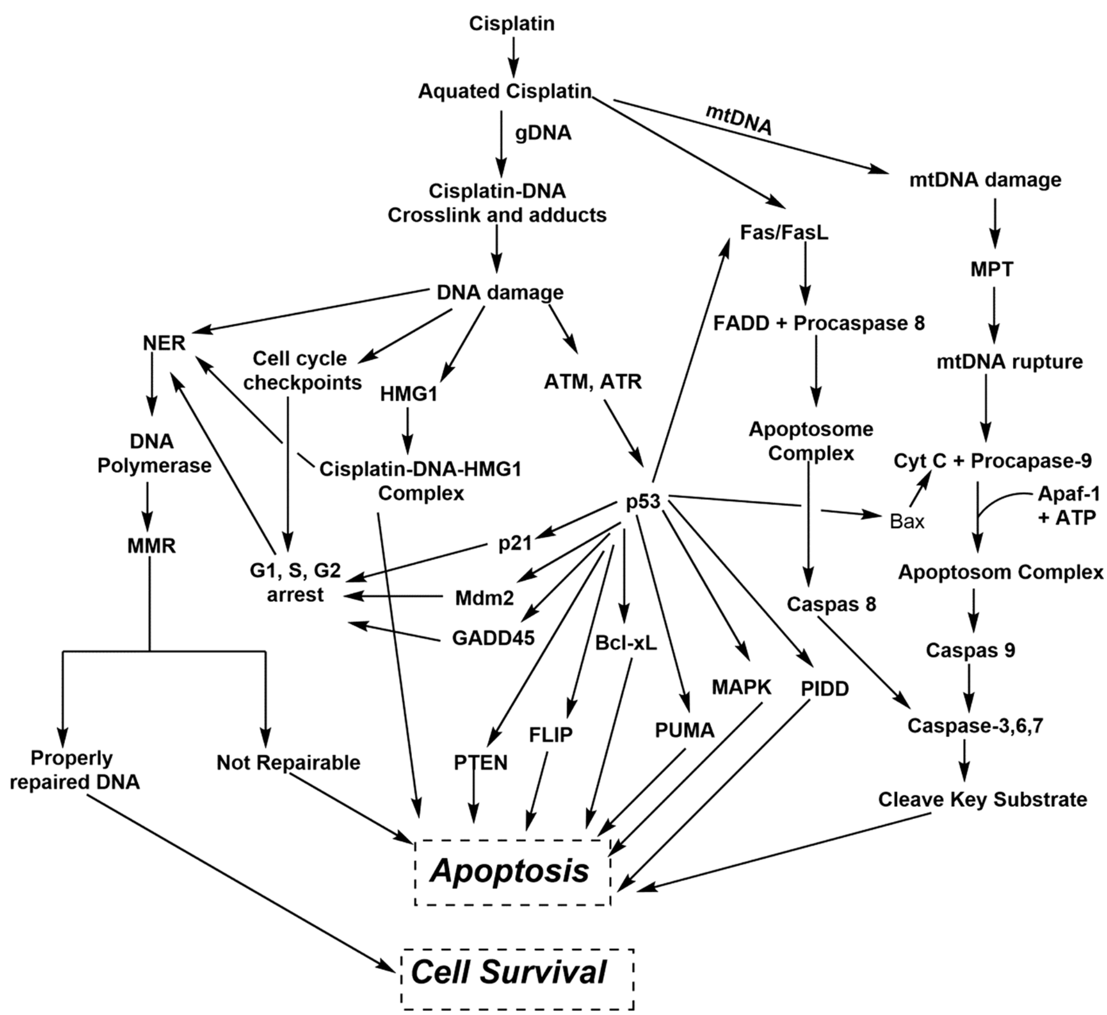


Fig. 3. Action mechanism of cisplatin anticancer activity.

cytotoxicity. Cisplatin induces oxidative stress by forming reactive oxygen species (ROS) like hydroxyl radicals, superoxide which depends on the concentration of cisplatin and time of exposure [51]. ROS is thought to be responsible for peroxidation of lipid, depletion of sulfhydryl groups, changed different signal transduction pathways, Ca-homolysis etc. which can cause DNA damage and consequently apoptosis of cells [14]. The mitochondrion is one of the most important targets of oxidative stress and ROS may affect on mitochondrial

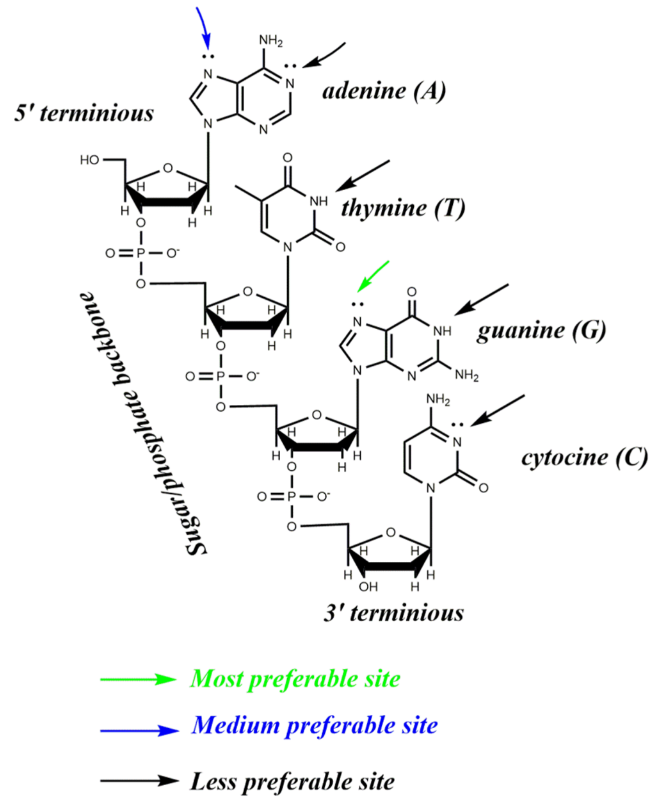


Fig. 4. Schematic representation of different binding sites of bases of DNA with cisplatin moiety.

respiratory function and cause cellular dysfunction [52]. ROS together with Bax (Bcl2 associated X) and Ca^{2+} cause mtDNA damage and fall in MPT (Mitochondrial permeability transition) [53] which facilitate rupture of mitochondria [54]. The rupture of mitochondria releases Cyt C (cytochrome *C*) and procaspase-9 (caspase is cysteine aspartate-specific proteinase) that bind with cytosolic Apaf-1 (apoptotic protease activating factor 1) and ATP (adenosine triphosphate) to form an apoptosome complex which activates caspase-9 [42]. The activated caspase-9 is then interacted with other caspases to activate caspase-3, caspase-6 and caspase-7 which lead to apoptosis through cleavage of key substrates (see Fig. 3) [55]. Apoptosis is ATP dependent "programmed cell death" or "cell suicide" [56].

Cisplatin may also induce cell apoptosis from cell membrane [57]. The type II transmembrane protein and Fas ligand (FasL) activate Fas receptor which is then facilitates to form apoptosome complex from FADD (Fas-associated death domain) and procaspade-8 [49]. This apoptosome complex activates caspase-8 which subsequently activates caspase-3, caspase-6 and caspase-7 that finally cleaves key substrate and leads to cell apoptosis (see Fig. 3).

The main target of cisplatin is genomic DNA (gDNA) but a very little amount (~1%) of intercellular cisplatin is generally bound to gDNA [58]. Several proteins like HMG (high mobility group) proteins can easily recognize cisplatin-DNA bindings. HMG1 protein selectively recognizes 1,2-cisplatin-DNA adduct, binds with them [59] and is able to shield and protect from repairing [60]. Three different pathways can be followed by cisplatin-DNA-HMG1 complex. The first path is to flow NER (nucleotide excision repair) mechanism to get repair of DNA and cell survives. The second path is "repair shielding model" in which it is postulated that HMG protein could protect cisplatin-DNA adducts from recognition by DNA repair enzymes [42]. The third one, "hijacking model" establishes that HMG proteins such as SSRP1 could be able to modulate cell cycle events after DNA damage and trigger cell death (see Fig. 3) [42,61].

The DNA repairing mechanism is one of the most important parts of cisplatin cytotoxicity. The proteins related to DNA repairing are NER and MMR (mismatch repair). The NER system contains 17 different proteins which recognizes Pt-DNA intrastrand crosslinks and then excises DNA sequences up to 20–29 base pairs [62]. DNA polymerase fills the remaining gaps [63]. The MMR would try to input correct nucleotide on the nondamaged strand opposite to the intrastrand adduct between two adjacent guanines [44,64]. When it failed to repair the damages, apoptosis of the cell occurs (see Fig. 3).

Cell apoptosis is also possible through cell cycle arrest (G1, S and G2 phase) caused by cisplatin [65]. These arrests allow time for repairing of damaged DNA before DNA synthesis. Cisplatin activates checkpoint kinases Chk1 and Chk2 which are responsible for G and S phase arrest [66]. Abrogating these arrests may cause killing the cancer cells by forcing them to reenter the cell cycle prematurely in the face of unrepaired DNA damage [67] which facilitates cell apoptosis through NER pathway (see Fig. 3).

The tumor suppressor protein p53 is a short lived protein which plays a central role in cisplatin induced apoptosis. It is also known as "guardian of genome" due to its role in conserving stability by preventing genome mutation [68]. p53 is activated by two different kinases ATM (ataxia telangiectasia mutated protein) and ATR (ATM and RAD3-related protein). Cisplatin first activates ATR kinase [69] which then activates p53 by phosphorylating at serine-15 [70]. p53 activates p21, Mdm2 and GADD45 genes which are responsible for cell cycle arrest and lead to apoptosis through DNA repair pathway [44]. p53 causes apoptosis directly by different mechanisms like: Degradation of FLIP (flice-like inhibitory protein), direct binding and counteracting the antiapoptotic function of Bcl-xL (B-cell lymphoma-extra-large), over expression of PTEN (phosphatase and tensin homolog) [12,71]. Again p53 actives PUMA [72], PIDD [73] and MAPK protein family [12] which are responsible for cell apoptosis. It is possible to enter mitochondrial path though activating Bax (present in cytosol) to gain apoptosis [74]. It is also reported that p53 facilitates Fas/FasL which lead to apoptosis through caspase 8, caspase 3 pathway (see Fig. 3) [51].

5. Cisplatin binds with DNA

DNA is the main target for cisplatin to show anticancer activity [75,76]. The mono or dihydrated platin entered in nucleus is vulnerable enough to react with bases of DNA. The potential binding sites on each bases of DNA are given in the Fig. 4. It is reported for in vitro studies that the N7 position of the imidazole ring of guanine is more preferable to attack over adenine or any other bases present in DNA (i.e. cytosine and thymine) [77,78,79]. Though adenine N7 is less reactive than guanine N7 but more reactive than any positions of cytosine and thymine. Lippard and his coworkers [79] proved that a strong hydrogen bond between the hydrogen of the amine on Pt and the oxo group at C6 position of guanine plays a pivotal role in stabilizing the Pt-guanine adduct by comparison to the Pt-adenine adduct. The computational study for binding efficiency of $Pt(NH_3)_3^{2+}$ with different sites of four bases of DNA follows the order as: G(N7) > C(N3) > C(O2) > G(O6) > A(N3) ≈ A(N1) > A(N7) > G(N3) > T(O4) > T(O2) based on differential Pt(II) binding energies [12]. Different types of adduct such as monoadducts, intra-stand crosslinks and inter-stand crosslink can be formed between cisplatin and DNA bases (Fig. 5). Monofunctional DNA adducts are formed first as only one chloride ligand is replaced by a water molecule in the first step. But bifunctional adducts may be formed either by ring closing of monofunctional adducts with reacting another DNA base (adenine or guanine) or by replacing second chloride ligand and then ring closing [31]. 90–95% of crosslinks are intrastrand in which 60–65% is for 1,2-d(GpG) and 20–25% is for 1,2-d(ApG) while others [monoadduct ~ 2%, 1,3-d(GpXpG) = 2% etc.] are less frequently formed [78].

Formation of crosslinks (Both intra and inter) create contortion of

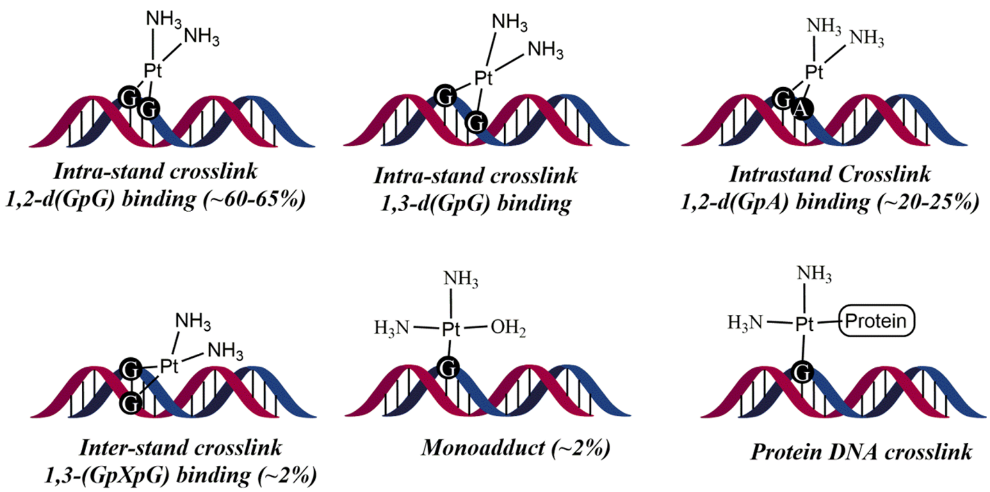


Fig. 5. DNA adduct formation with cisplatin moiety.

DNA [76]. Bending of DNA double helix toward major groove is seen by 32–35° for three types of intrastrand crosslink adducts and unwinding for both 1,2-d(ApG) and 1,2-d(GpG) crosslink adducts are 13°, while for 1,3-d(GpXpG) intrastrand unwinding is 23° [42]. Interstrand crosslink adducts result in more static changes in DNA [76] and create 20–40° bending of helix axis toward minor groove and ~80° of unwinding [80].

There are still continuous debates on which of the cisplatin-DNA adducts are most significant toward cell death. But majority accept that 1,2-intrastrand adducts induce cytotoxicity more effectively than 1,3-intra adducts [12,76,81]. It is also reported that DNA repair enzymes can remove 1,3-intrastrand adducts from DNA more effectively than 1,2-intrastrand adducts i.e. 1,3-intrastrand adducts are more rapidly repaired than 1,2-intrastrand adducts [31]. Some high mobility group (HMG1) proteins can recognize specifically this 1,2-intrastrand platinum-DNA adducts [81]. The transplatin does not form 1,2-adducts and that is why they are inactive towards anticancer activity. Though very high reactivity (like aquation, ammonolysis, reaction with glutathione etc) of transplatin is another reason for inactivation toward anticancer activity [31]. But some transplatin derivatives are known which are active toward cancer [82].

6. Resistance of cisplatin

The most serious drawback of cisplatin therapy is its resistance toward cancer cells. Resistance of cisplatin depends on types of cancer. For example, testicular cancer, ovarian cancer, head and neck cancer and small cell lung cancer are very sensitive to cisplatin, while non-small cell lung cancer and colorectal cancer are very resistant to cisplatin [42,83]. There are two forms of resistance exist: intrinsic resistance and acquired resistance. Intrinsic resistance is the resistance which occurs from beginning of treatment with drug, while for acquired resistance drug is initially active but become inactive over time [14]. Cisplatin resistance may be possible by lowering in cellular uptake of drug, decreasing influx or increasing efflux of drug, drug detoxification by cellular thiols, altering in drug target and repairing of DNA [84,85,86].

In this article it is accepted that cisplatin resistance may be occurred at four different moments: During drug circulation through bloodstream, during drug influx and efflux through cell membrane, during present in cytoplasm and finally after DNA binding.

6.1. Resistance during drug circulation through blood stream

Cisplatin is administered intravenously and hence it circulates through blood before entering cancer cells. The proteins present in bloodstream can bind with cisplatin, particularly those have thiol group like human serum albumin and cysteine. This protein binding is responsible for deactivation of cisplatin [87]. It is mention earlier that 65–95% of cisplatin binds with plasma protein just after one day of administration [46]. The strong binding nature between soft platinum and soft sulfur of HSA protein and cysteine can be explained by Hard-Soft Acid-Base principle [88]. The detail mechanism of cisplatin binding with GSH remains anywhere else [89].

6.2. Resistance during influx or efflux of drug through cell membrane

Decreased influx and increased efflux of cisplatin cause lower drug accumulation to the cancer cells [90]. Fuertes et al. [42] mentioned that the reduced cisplatin accumulation is due to reduced drug uptake rather than to increased drug efflux. It is known that passive diffusion and copper transport protein Ctr1 are responsible for cisplatin influx. Presence of cisplatin causes degradation in concentration of Ctr1 and therefore cisplatin influx decreases significantly which results resistance to the drug [58]. A membrane protein TMEM205 is also responsible for cellular resistance to cisplatin [12]. Two other copper transporter ATP7A and ATP7B help to export cisplatin from cell and lead to resistance [91]. It is also in literature that multidrug resistance proteins (MRP) preferably export cisplatin outside the cell by conjugation with sulfate, glucuronate or GSH [12,92].

6.3. Resistance during cisplatin present in cytoplasm

One of the most important mechanisms of cisplatin resistance is intracellular inactivation of cisplatin through binding with glutathione and metallothioneins. The complex of GSH and cisplatin is then excreted by a GS-conjugated export pump [93]. It is reported that either glutathione S-transferase enzyme (GST) helps this reaction or it spontaneously occurs [94].

6.4. Resistance after cisplatin-DNA binding

NER is the best way to remove DNA lesions to induce resistance of cisplatin [95]. NER system excises damaged nucleotides on both strands and then synthesizes DNA to reconstitute integrity of gene [96]. Cells with over expression with NER denote very lower sensitive to cisplatin [97]. MMR protein is very important protein which generally attempts to repair DNA-cisplatin lesion. If it fails to repair then it leads to apoptosis [64]. But if it repairs DNA perfectly then cell survives. It is well established that alterations expression of oncogenes like c-fos, H-ras, c-abl and c-myc and tumor suppressor gene like p53 can create cellular resistance to cisplatin [86]. Cisplatin resistance is also possible due to drug induced dysregulation of microRNA function [14]. This dysregulation of microRNA can causes problems in cell signaling, DNA methylation and invasiveness or cell survival which result in resistance of cisplatin [98]. The detail for mechanism of cisplatin resistance remains elsewhere [99].

7. Use of cisplatin for cancer treatment

7.1. Use of cisplatin for treatment of lung cancer

One of the most common fatal malignancies is lung cancer [100]. Two types of lung cancers are generally known in literature: Small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC). These two types of cancer can be differentiated by the way of growing and spreading. SCLCs are most aggressive and readily growing of all lung cancers. Chemotherapy is the most effective treatment for SCLC [101] because these tumors are generally widespread in the body when they are diagnosed. Cisplatin and carboplatin are two most important drugs generally used in SCLC chemotherapy [102]. But cisplatin is selected more preferably than carboplatin because of its strong antitumor activity though it has some adverse effect like renal toxicity [103], nausea and vomiting [104]. For treatment of non-small cell lung cancers, surgery is used at stage I and stage II to remove tumors and after that chemotherapy is used which is known as 'adjuvant chemotherapy'. For the people with stage III and stage IV lung cancer that cannot be removed surgically, chemotherapy is most effective along with radiation therapy [105].

7.2. Use of cisplatin for treatment of ovarian cancer

Ovarian cancer or cancer of the ovaries is one of most common types of cancer in woman and ovarian cancer has the highest death among the gynecologic cancers. Though exact cause behind ovarian cancer is unknown but it can be seen that it may arise from hereditary background and or who has breast or colon cancer [106]. It is very difficult to detect ovarian cancer at an early stage due to lack of effective screening strategies and specific symptoms associated with early-stage disease [12]. Surgery is the main treatment for most ovarian cancers and in the next step systemic chemotherapeutic treatment is given to the patient to kill very small amounts of cancer cells that may still be around after surgery [12]. Despite of several side effects, cisplatin is used as the most effective chemotherapeutic agent for ovarian cancer treatment. One of the most important drawbacks of cisplatin therapy in ovarian cancer is that even after successful treatment, there is a high chance that the cancer will come back within next few years and its resistance power to chemotherapy increases significantly. To avoid this problem combination therapy is used in which cisplatin is used along with one other chemical agents like honey venom [107], trichostatin A or 5-aza-2′-deoxycytidine [108], aferin [109].

7.3. Use of cisplatin for treatment of testicular cancer

Seminoma and non-seminoma are two important types of testicular cancer seen among young men. Seminomas are seen to occur in all age groups and tend to grow and spread more slowly than non-seminomas. Cisplatin-based regimens are the key to the treatment of seminomas. 85% of patients with advanced seminoma show cure with three or four cycles of cisplatin based therapy [110] while for single agent carboplatin this rate falls to 59% [111]. Non-seminomas are generally seen in men in between late teen and early 30 s and are mainly four subtypes such as embryonal carcinoma, yolk sac carcinoma, choriocarcinoma and teratoma. For the patients of teratoma, combination therapy with bleomycin, etoposide and cisplatin is the most efficient way of treatment and cure rate is at least 90% [112]. It is to be noted that the Food and drug administration (FDA) has approved cisplatin for the treatment of metastatic ovarian and testicular cancer in 1978 [113]. Though the actual reason behind the over sensitivity of cisplatin towards testicular cancer is unknown but several mechanisms are proposed to explain it, such as: Gong et al. [114] proved that prostate cancer cells over express Kindlin-2 which regulates cancer cell death, Usanova et al. [115] revealed that cisplatin sensitivity of testis tumour cells is due to deficiency in interstrand-crosslink repair and low ERCC1-XPF expression, Koster et al. [116] demonstrated that the presence of wild-type p53 protein and high levels of Oct4 and consequently high cellular levels of proapoptotic Noxa protein and miR-17/106b seed family members and low cytoplasmic levels of anti-apoptotic p21 protein are important parameters for the exquisite sensitivity of TC cells to cisplatin. Awuah et al. [190] proved that high-mobility group box protein 4 (HMGB4), a protein preferentially expressed in testes, uniquely blocks excision repair of cisplatin-DNA adducts, 1,2-intrastrand cross-links, to potentiate the sensitivity of TGCTs to cisplatin therapy.

7.4. Use of cisplatin for treatment of other cancers

Cisplatin is not limited for treatment of testicular, ovarian and lung cancers, it is broadly used for treatment of childhood brain tumors [117], gastric cancer [118], leukemia [119], anal cancer [120], etc. For treatment of breast cancer, cisplatin is very beneficent which causes enhancement of patient's lifespan [121]. For head and neck squamous cell carcinoma (HNSCC), cisplatin is not an effective drug but 32 percent of overall responsibility is seen [27]. So it can be concluded that cisplatin is a shining star among chemotherapeutic agents which can be used for the treatment of variety of cancers like ovarian, breast, testicular, head and neck, cervical, prostate, bladder, lung and refractory non-Hodgkin's lymphomas [122,123]

8. Side effects of cisplatin

Though cisplatin is very successful for the treatment of testicular and ovarian cancer, it induces a large number of toxic side effects [124]. These side effects may be seen due to overdose of cisplatin [17].

Table 1
Cisplatin dosages for different types of cancer.

Type of cancer	Cisplatin Dosage	Input type
Metastatic testicular cancer	20 mg/m^2 once a day for five days per cycle	Intravenously
Metastatic ovarian Cancer	(1) 75–100 mg/m^2 on day 1, every 4 weeks (taken with cyclophosphamide 600 mg/m^2 day 1, every 4 weeks) (2) 100 mg/m^2 per cycle once every 4 weeks (As single agent)	Intravenously
Advanced bladder cancer	70 mg/m^2 on day 2, every 4 weeks (with gemcitabine)	Intravenously
Head and Neck cancer	75–100 mg/m^2 on day 1, every 3–4 weeks	Intravenously
Oesophageal cancer	75–100 mg/m^2 on day 1, every 3–4 weeks (with fluorouracil)	Intravenously
Gastric cancer	60 mg/m^2 on day 1, every 3 weeks, (with epirubicin, capecitabine)	Intravenously
Lung cancer	(1) 75–100 mg/m^2 on day 1, every 3–4 weeks (with vinorelbine (2) 50 mg/m^2 on days 1 and 8, every 4 weeks (with etoposide, radiation therapy)	Intravenously
Hodgkin's or non-Hodgkin's lymphoma	75 mg/m^2 on day 1, every 3 weeks (with dexamethasone, gemcitabine)	Intravenously
Osteosarcoma	100 mg/m^2 on day 1, every 3 weeks (with doxorubicin)	Intravenously

The proper dosages of cisplatin used in different types of cancer are given in the Table 1. The major side effects of cisplatin are nephrotoxicity, ototoxicity, hepatotoxicity, gastrointestinal toxicity, etc.

8.1. Nephrotoxicity

When a patient is treated with standard-dose of cisplatin intravenously, rate of elimination of cisplatin is about 25% within just 24 h and 50% within 5 days in which more than 90% of total excretion is occurred through renal excretion [125]. So renal excretion is the principal route of excretion of cisplatin and hence kidney can accumulate greater amount of cisplatin than any other organs which is responsible for nephrotoxicity. Renal toxicity is seen in 28–36% of patients when they are treated with cisplatin as a single agent of amount 50 mg/m^2 [43]. Acute oliguric or non-oliguric renal insufficiency can be seen within 2 to 6 days after cisplatin overdose while chronic renal failure may stay for more than 2 years when the patient is treated with 20 mg/m^2/day of cisplatin for 5 days intravenously every 5 weeks [125,126]. Nephrotoxicity is seen because of increase in blood urea nitrogen (BUN) and creatinine, serum uric acid and/or a decrease in creatinine clearance and imbalanced electrolytes [43,44,127]. Aggressive hydration of at least 3–6 L per day can decrease the risk of nephrotoxicity by decreasing more reactive monohydrated cisplatin form [125,128].

8.2. Ototoxicity

Cisplatin induced ototoxicity is seen to 10–90 percent of patients in which children are affected (22–70%) more than adults [44,129,130]. Generation of excess reactive oxygen species (ROS) in cochlea cells is responsible for hearing loss [130]. The hearing loss caused by toxic effect of cisplatin is generally in high frequency range, bilateral and permanent [127,130]. Several approaches are reported for treatment of ototoxicity caused by cisplatin among which local or systematic administration of antioxidants and anti-inflammatory agents are very important [131].

8.3. Hepatotoxicity

Cisplatin overdose may cause hepatotoxicity. This is mainly caused by oxidative stress [44,132] formed by elevation of transaminases and bilirubin in circulation [133]. Glutathione and glutathione reductase levels are decreased significantly whereas glutathione peroxidase, catalase and gamma-glutamyl transpeptidase show significant increase after cisplatin therapy [14]. It is also reported that cisplatin treatment can enhance the cytochrome P450 level [14] and cytochrome-P450-2E1 enzyme (a member of cytochrome P450) is also responsible for liver injury [134]. Use of high doses of selenium and vitamin E can reduce the effect of hepatotoxicity [135].

8.4. Gastrointestinal toxicities

Marked nausea and vomiting is generally occurred in almost all patients despite routine prophylactic antiemetic use [125]. This may start within 1–4 h after treatment and last up to 24 h [43]. Delayed nausea and vomiting which begins or persists more than 24 h after administration of cisplatin is also seen with high-dose cisplatin use [136] and last up to 2 weeks. Diarrhea [43,125], lost of taste or metallic taste [137], pancreatitis [125,137,138] and mucositis [125] are also reported. Gastrointestinal toxicities may become worst when combination therapies of cisplatin with other antineoplastic agents are used [125].

8.5. Other toxicities

Other cisplatin induced toxicities such as cardiotoxicity, renal and electrolyte disturbances, neurotoxicity, myelosuppression, hematological toxicity, vascular toxicities, hyperuricemia, ocular toxicity etc. are also known [12,43,125,139].

9. Modulation of cisplatin toxicity due to overdose

There are several strategies such as aggressive intravenous hydration, administration of sodium thiosulfate, antiemetic agents, etc. are reported to modulate toxicities of cisplatin [140]. No specific antidote is discovered for cisplatin till date.

9.1. Modulation of nausea and vomiting

Aggressive antiemetics are generally used to control nausea and vomiting caused by cisplatin [141]. Several reports confirm combination of serotonin 5-HT_3 receptor antagonist, dexamethasone and lorazepam is more effective than metoclopramide, dexamethasone and lorazepam [142,143,144]. Nurokinin-1 receptor antagonist aprepitant or fosaprepitant are also very useful [140].

9.2. Modulation of nephrotoxicity

Intravenous administration of large amount of water (3–6 L per day) or isotonic saline is the main option to reduce nephrotoxicity [145]. Addition of osmotic diuretic mannitol is also needed to increase urine output [146]. Excretion of Cisplatin occurs through urine to reduce nephrotoxicity [147]. Sodium thiosulfate is also used which binds strongly with free platinum(II) complex, inactivates it and then excretes through urine to show less nephrotoxicity [125]. It is reported that plasmapheresis is a promising method to reduce nephrotoxicity by binding of cisplatin with plasma proteins which results fall in blood platinum concentration [125]. It is also well established that ROS is responsible for cisplatin induced renal tubular injury [148]. So use of antioxidants such as selenium and vitamin E [149], Dimethylthiourea (DMTU) [148,150], ebselen and allopurinol [151], amifostine [152], etc. or natural source of antioxidant [148] are known to control cisplatin induced nephrotoxicity.

9.3. Modulation of neurotoxicity

Several reports confirm that glutathione may reduce cisplatin induce neurotoxicity without altering anticancer activity [153,154]. Similarly, thiol containing compound BNP7787 is also known to prevent neurotoxicity caused by cisplatin [154]. Vitamin E acts as neuroprotector against cisplatin induced neurotoxicity [155,156]. ORG 2766 was initially thought to have ability to reduce cisplatin induce neurotoxicity but it does not prevent neurotoxicity [154].

Some other compounds such as ditiocarb sodium, acetylcysteine, fosfomucin and colestipol are also used to reduce different cytotoxicity induced by cisplatin [125].

10. Combination therapy

Though cisplatin is very successful for some cancer treatment, a numerous problems like resistance to chemotherapy, low prognosis, drug relapse, large number of side effects, etc. are seen to the patients treated with cisplatin. To overcome these problems combination therapies are used sometimes. Combination therapy is a therapy where two or more drugs with different mechanism of actions are used. A list of different combination therapies with cisplatin is given on Table 2.

Combination of cisplatin with UFT (mixture of tegafur and uracil with 1:4 ratio) is much efficient for treatment of advanced non-small cell lung cancer with respect to single cisplatin or single UFT therapy [157]. Cisplatin and doxorubicin combination therapy is well tolerable and effective for diffuse malignant pleural mesothelioma (DMPM) [158]. Good results are seen for treatment of carcinomas of advanced

Table 2
Example of different combination therapies.

Composition	Type of cancer	Source
Cisplatin + UFT	Advanced non-small cell lung cancer	157
Cisplatin + Doxorubicin	Diffuse malignant pleural mesothelioma (DMPM)	158
Cisplatin + Cyclophosphamide + Doxorubicin	Advanced salivary gland origin	159
Cisplatin + Gemcitabine	Biliary cancer	160
Cisplatin + Honey bee venom	Ovarian cancer	107
Cisplatin + Osthole	Lung cancer cell lines	161
Cisplatin + Bleomycin + Methotrexate	Advanced squamous cell carcinoma	162
Cisplatin + Anvirzel	Brast, colon, prostate, lung, pancreatic cancer cell lines and melanoma	163
Cisplatin + Everolimus	Urothelial bladder cancer	164
Cisplatin + Doxorubicin + Fluorouracil + cyclophosphamide	Salivary gland carcinoma	165
Cisplatin + Oxaliplatin + Quercetin + Thymoquinone	Human ovarian cancer	167
Cisplatin + Tetraarsenic oxide	Cervical cancer	168, 169
Cisplatin and Vindesine	Non-small cell lung cancer	170
Cisplatin + Paclitaxel	Ovarian cancer, breast cancer, lung cancer, head and neck	12

salivary gland origin, when combination therapy of cyclophosphamide, doxorubicin and cisplatin is applied [159]. For biliary cancer patients combination of cisplatin and gemcitabine is a good option [160]. Cisplatin along with different natural compounds are also known. A few examples are: cisplatin plus honey bee venom for ovarian cancer [107], cisplatin plus osthole for lung cancer cell lines [161], cisplatin, bleomycin and methotrexate for advanced squamous cell carcinoma of the male genital tract [162], cisplatin plus anvirzel for breast, colon, prostate, lung, pancreatic cancer cell lines and melanoma [163]. Combination therapy with everolimus and cisplatin has an important role in urothelial bladder cancer treatment [164]. Combination of cisplatin, doxorubicin, fluorouracil and cyclophosphamide is an appropriate option for advanced or recurrent salivary gland carcinoma [165]. It is reported that cisplatin along with metformin increase cytotoxicity suppressing Stat3 activity independently of the LKB1-AMPK pathway [166]. Nessa et al. [167] reported that combination of cisplatin and oxaliplatin with quercetin and thymoquinone is the best combination for human ovarian cancer. Tetraarsenic oxide combine with cisplatin induce apoptotic synergism by increasing calcium signaling and this combination therapy is used for treatment of cervical cancer [168,169]. Vindesine is a chemotherapeutic drug but combination of cisplatin and vindesine is more efficient for non-small cell lung cancer treatment than vindesine as single agent [170]. Photoactivated chemotherapy (PACT) is a growing area of interest in modern days [171,172,173,191] as it prevents damaging of healthy cells and platinum-diazido complexes are good example of PACT [174]. Combination of cisplatin and radiotherapy is also important treatment for different types of cancers [175]. Other possible combinations are listed elsewhere [12].

11. Some approved and under trial cisplatin analog drugs

Although cisplatin is a worldwide used chemotherapeutic drug but toxic side effects and drug resistance are two very important drawbacks of cisplatin. These drawbacks drive researchers to find out new cisplatin analogue drugs which may reduce side effects and resistance and which may improve efficiency towards anticancer activity. A large number of new cisplatin analogue drugs are designed based on "structure-activity relationship" but only carboplatin and oxaliplatin are approved and only a few entered in clinical trial [49].

Carboplatin has lower toxic profile and fewer side effects than cisplatin and hence can be administrated higher amount [176] and get better effects. The lower cytotoxic effect of carboplatin is due cyclobutanedicarboxylate which is a bad leaving group resulting in slower reaction. But the problems with the carboplatin are that it is active in the same range of tumor as cisplatin and it is administered intravenously and it is cross-resistant with cisplatin [49,176].

Oxaliplatin can overcome the resistance of cisplatin and it is used for colon cancer treatment. So France, United Kingdom and European countries have approved oxaliplatin for colon cancer in 1996 [31]. Oxaliplatin contains dicarboxylate instead of chloride as leaving group and 1,2-diamminocyclohexane instead of ammonia as carrier ligand. The carrier ligand 1,2-diamminocyclohexane increases the lipophilicity which results in higher penetration of the drug through cell membrane. Greater cellular uptaking property, and different conformation of DNA adduct formation are responsible for circumventing cisplatin resistance [177]. Very recently, Bruno et al. [192] demonstrated that oxaliplatin kills cancer cells cancer cells with different mechanism from that of cisplatin. Oxaliplatin creates fewer cross-links per base than cisplatin, yet remains its cytotoxicity. They suggested that oxaliplatin kills cells by inducing ribosome biogenesis stress. Oxaliplatin is neurotoxic and effective on limited types of cancer. So search continues to get more efficient cisplatin analogue anticancer drugs.

Nedaplatin i.e. Diammine[*hydroxyacetato*(2-)-*O*,*Ó*]platinum(II) has better anticancer activity than carboplatin but equal to the cisplatin [178]. But it is 10 times more soluble in water than cisplatin and less nephrotoxic and gastrointestinal toxic than cisplatin [179]. Nedaplatin is approved by Japan in 1995 for treatment of NSCLC, SCLC, oesophageal cancer, head and neck cancers [180]. A series of combination therapies with nepadaplatin is running in trials for different cancers [180]. But nedaplatin is crossresistant with cisplatin and it can cause thrombocytopenia.

Another Pt(II) complex, heptaplatin is under clinical trial and is approved by Korea in 1999 for treatment of gastric cancer [180]. Heptaplatin shows greater anticancer activity and lower toxicity than cisplatin. The extra advantage of heptaplatin is high solubility in water. Trials studies for different combination therapies with heptaplatin are known [178].

Lobaplatin has approved in China for treatment of chronic myelogenous leukemia (CML) and passed phase II trials in US, EU, Australia and South Africa for various cancers like breast, ovarian, CML, lung cancer [180]. It influences the expression c-myc gene, which is involved in apoptosis, oncogenesis and cell proliferation [181]. Lobaplatin can reduce renal, neuro and ototoxicity but it causes anemia, leucopenia, nausea and vomiting.

Cis-[$PtCl_2(NH_3)$(2-methylpyridine)] is also a cisplatin analogue drug which has entered in clinical trials in 1997 [31]. It has different names like picoplatin, AMD473, JM473 and ZD0473. The 2-methylpyridine ring tilts nearly about 102.7° which place methyl group over the square plane [176]. So steric hindrance come into play when deactivating agents like glutathione, methionine, albumin etc. try to react with it which results in slower reaction and hence lower deactivation of the drug and therefore it gets better effect on cancer treatment.

Pt(IV) complexes are also known which show anticancer activity [182] among which iproplatin, tetraplatin and satraplatin enter in clinical trials. Pt(IV) complexes are acted as prodrug and they need to reduce to Pt(II) by intracellular or extracellular reducing agents to show

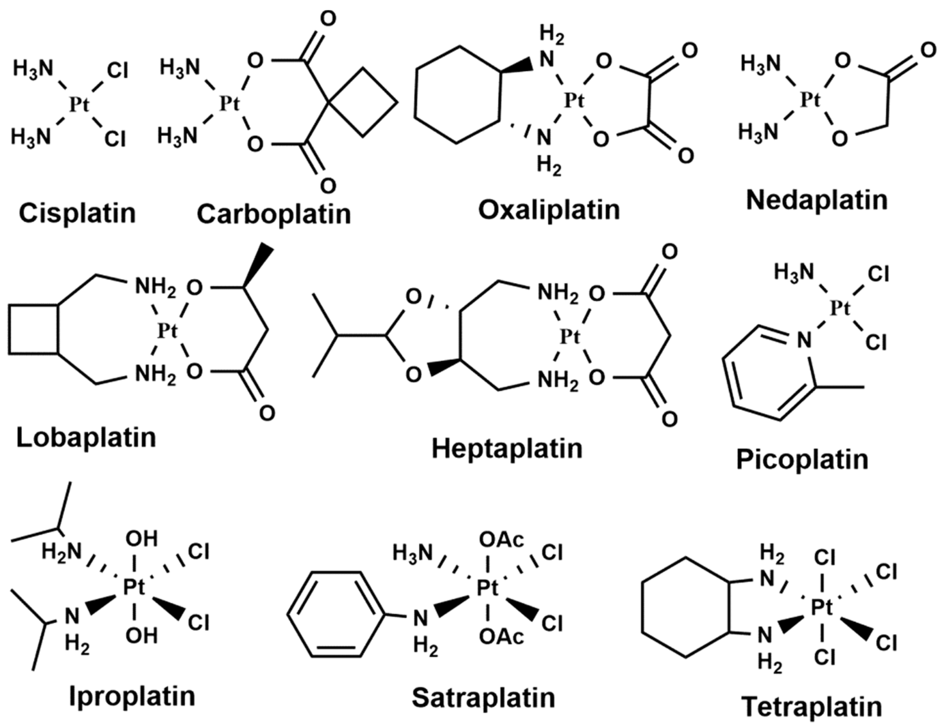


Fig. 6. Some approved and trial platinum anticancer drugs.

Table 3
Clinically approved Pt(II)-anticancer drugs.

Drug	Year of approval	Country approved	Type of cancer treated
Cisplatin	1978	Worldwide	Testicular, Ovarian, Bladder, Melanoma, NSCLC, Lymphomas, Myelomas cancer
Carboplatin	1989	Worldwide	Ovarian, Retinoblastomas, Neuroblastomas, Nephroblastomas Brain tumor, Head and neck, Cervix, Testis, Breast, Lung, Bladder cancer
Nedaplatin	1995	Japan	NSCLC, SCLC, Oesophageal cancer, Head and neck cancers
Oxaliplatin	1996	Worldwide	Colon cancer
Heptaplatin	1999	Korea	Advanced gastric cancer
Lobaplatin	2010	China	CML, SCLC, Inoperable metastatic breast cancer

anticancer activity. Iproplatin enter in clinical trials because it shows high solubility, activity towards different cancers and lower toxicity [183]. But it is less active than cisplatin and hence was abandoned after phase I and phase II trials. Tetraplatin though entered in clinical trials I, showed several neurotoxic side effects and hence abandoned [182]. The first orally active platinum drug, satraplatin is currently under phase II trials [184]. Fig. 6 contains structures of approved platinum drugs and some drugs which enter in clinical trial and Table 3 listed approval country, year and use of approved drugs.

Designing new platinum anticancer drugs is not limited to small Pt (II) or Pt(IV) complexes. Several multi nuclear platinum complexes are also reported [185,186]. In recent days lipids, nanoparticles are used as a part of platinum drug to improve selectivity and drug delivery [187,188,189].

12. Development of platinum based anticancer drugs

Detail study about development of platinum based anticancer drugs goes beyond this article and remains elsewhere [34,189,194,269]. A brief overview is described here.

12.1. First, second and third generation platinum drugs

Cisplatin is considered as first generation platinum based anticancer drug as it's anticancer property was discovered first. The second and third generation platinum drugs are similar to the cisplatin but leaving groups or ammine groups are different. Second generation drugs are formed only by varying either leaving groups or ammine groups. But for third generation platinum drugs, both leaving groups and ammine groups are different. Carboplatin and nedaplatin (see Fig. 6 for structures) are very important examples of second generation platinum drugs. The examples of third generation platinum drugs are oxaliplatin, lobaplatin, heptaplatin (see Fig. 6 for structures), etc.

12.2. Monofunctional platinum complexes

Those platinum complexes which have only one chloride ligand as leaving group and hence can bind with DNA through only one coordination site are known as monofunctional platinum complexes [193]. Monofunctional complexes were considered as inactive toward anticancer activity for a long time. But Engelhard Industries first demonstrated that monofunctional platinum(II) complexes of the form cis-$[Pt(NH_3)_2(Am)Cl]^+$, where Am is an aromatic *N*-heterocyclic amine, has the ability to inhibit tumor cell growth in vitro and in L1210 and P388 mouse leukemia models [195].These complexes bind with DNA with a different mechanism. It is accepted that a platinum moiety would be covalently linked to a nucleobase and an intercalator would additionally interact with DNA forming stable and structurally different adducts than cisplatin [194]. The advantage of this type of binding is that HMG protein can recognize this type of adducts very less efficiently [196]. A large number of monofunctional platinum complexes are known but only phenanthriplatin has greater in vitro cytotoxicity than

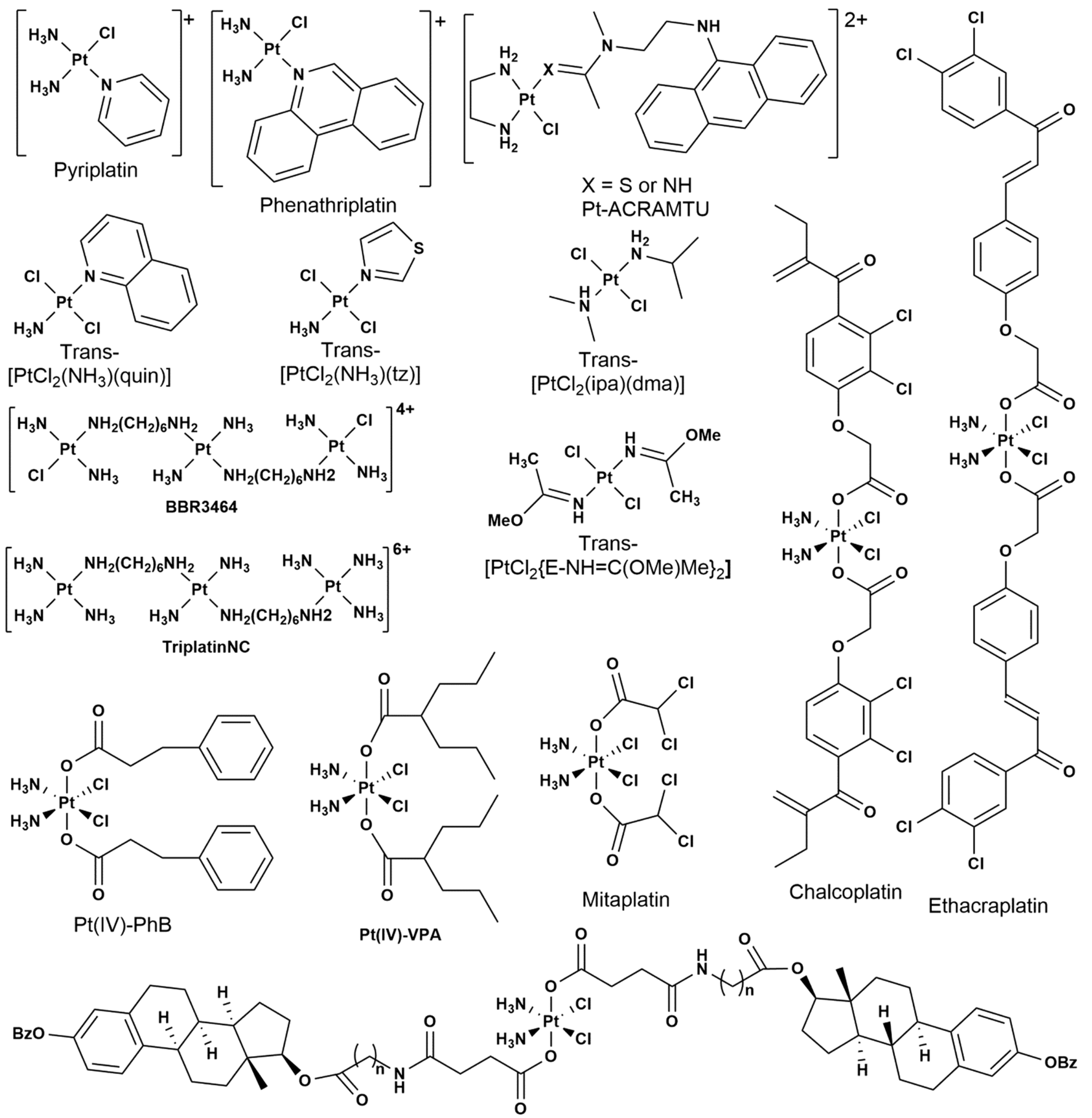


Fig. 7. Some different types of platinum based anticancer agents.

that of cisplatin across a broad range of cancer cell types [189,193,197] (see Fig. 7 for some structures of monofunctional complexes).

12.3. Trans-platinum(II) complexes

The trans-platinum(II) complexes were also considered as inactive due to inability of forming 1,2-intrastrand adduct with DNA. But in the last 30 years, several research group synthesized large number of trans-platinum(II) complexes which are showing efficiency toward anticancer activity [82,189,194,198]. According to Johnstone et al. [189] active trans-platinum complexes are three types: (i) trans-Pt(II) complexes with heteroaromatic ligands, (ii) trans-Pt(II) complexes with iminoether ligands, and (iii) trans-Pt(II) complexes with asymmetric aliphatic amine ligands. A few well established examples of trans-platinum(II) complexes are: trans-$[PtCl_2(py)_2]$, trans-$[PtCl_2(NH_3)(quin)]$, trans $[PtCl_2(NH)_3tz]$, trans-$[PtCl_2(E\text{-iminoether})_2]$, trans-$[PtCl_2(ipa)(dma)]$, etc (see Fig. 7 for structures). Trans-platinum complexes bind with DNA with different mechanism which cannot be either recognized by HMG proteins or repaired by NER system [204]. The detail advantages of these complexes are given elsewhere [194,204].

12.4. Polynuclear platinum(II) complexes

Polynuclear Pt(II) complexes having trans-$\{Pt(NH_3)_2Cl\}$ units bridging with alkanediamine linkers of variable length, are active toward cancer [199]. BBR3464 (see Fig. 7 for structure) is one of the best polynuclear Pt(II) which enters in clinical trial and active toward GFX214 and MKN45 gastric carcinoma in mice [194]. Tumor cells can

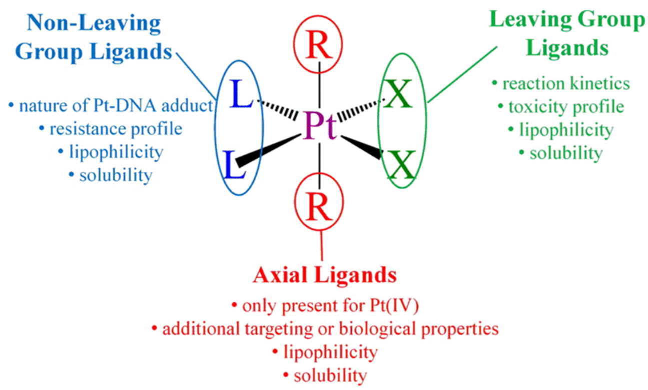


Fig. 8. Advantages of ligands in Pt(IV) prodrug. Ref. [34] Copyright ©2014 The American Chemical Society.

uptake higher amount of this compound and it can platinate DNA to higher extent than cisplatin. Summa et al. [200] proved that the tri-nuclear complex forms long-range delocalized intra- and interstrand cross-links between guanines spanning up to six base pairs which results in more flexibility and less distortion. Triplatin-NC (see Fig. 7 for structure) is another multinuclear Pt(II) complex which avoids deactivation by intrecellular nucleophiles and shows better antitumor activity [201]. The detail of polynuclear Pt(II) complexes are discussed somewhere else [202,203].

12.5. Platinum(IV) prodrugs

Development of six coordinated Pt(IV) prodrugs as a potential anticancer agents is an attractive and active field in chemistry [189,205–210]. Pt(IV) prodrugs are stable and substitution inert which inhibit to react with plasma proteins in blood [189]. Before DNA binding, Pt(IV) prodrugs are generally reduced by glutathione and ascorbate to form square planar active Pt(II) drugs [211,212]. The advantages of each types of ligands present on Pt(IV) prodrug are shown in Fig. 8. The most important point is that axial groups can used for increasing solubility, lipophilicity, targeting cancer cells or activating different biological properties [34]. The axial groups can also conjugate with nanoparticles or other carrier systems for cargo delivery of the Pt (IV) prodrugs [189,213,248,269]. Tetraplatin, iproplatin and satraplatin are very important examples of Pt(IV) prodrugs (see Fig. 6 for structures). A few Pt(IV) prodrugs are highlighted below.

12.5.1. Platinum(IV) complexes with bioactive ligands

There are several examples of Pt(IV) complexes with axial biological active groups in literature [206]. Here some very important examples are discussed. Pt(IV) complex with two phenylbutyrate (PhB) as axial ligands (see Fig. 7 for structure), shows up to 100 times more effective than cisplatin in many human cancer cells [214]. Pt(IV) conjugated with valproic acid (VPA) in two axial positions (see Fig. 7 for structure) binds to DNA to a higher extent than that of cisplatin. This is because VPA is a potent histone deacetylase inhibitor which decondenses chromatin and increases the accessibility of DNA within chromatin for DNA binding agents [194,215]. It is well established that pretreatment with estrogen increases the expression level of HMGB1 in estrogen-receptor positive, ER(+), MCF breast cancer cell resulting in increase the sensitivity of cisplatin [216]. Therefore Pt(IV) with axial estradiol ligands (see Fig. 7 for structure) shows higher response rate compare to cisplatin toward ER(+) breast cancer cell [217]. Another very important Pt(IV) prodrug entered in clinical trials is mitaplatin consisting two dichloroacetate (DCA) in the axial positions (see Fig. 7 for structure). Mitochondrial membrane potential of cancer cells is altered by DCA released from reduction of mitaplatin. As a result, the Cyt C is released and apoptosis inducing factor is translocated to nucleus [218]. Ethacrapltin (see Fig. 7 for structure) on reduction produces cisplatin and ethacrynic acid which inhibits glutathione S-transferase (GST) [273]. As a consequence platinum drug reacts with GSH with a very low rate and hence drug resistance decreases significantly.

12.5.2. Nanomaterial conjugated platinum(IV) complexes

Nanoscale drug delivery is the use of nanoparticles to transport pharmaceutically active drugs. The main goals of nanodrug delivery are (a) more specific drug targeting and delivery, (b) reduction in toxicity while maintaining therapeutic effects, (c) greater safety and biocompatibility [219]. A large number of nanoparticles with dimension 50–200 nm (for example: carbon based nanomaterials, gold nanoparticles, coordination polymers, metal-organic-frameworks, polymeric micelles, etc.) are generally used as nanodelivery of platinum(IV) anticancer drugs [189,220–223,259]. These nanoparticles are generally absorbed by the cancer cells with the help of enhanced permeability and retention (EPR) effect [224–226]. One of the most important points about nanodelivery is that if the surface of the nanoparticle is decorated with a ligand for a receptor expressed selectively on the surface of the cancer cells, then the particle is more likely to be taken up by those cells via receptor-mediated endocytosis [189,227].

12.5.2.1. Carbon-based nanomaterials. Carbon nanomaterials such as single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), carbon nanoparticles are very important which act as drug delivery vehicles of platinum(IV) anticancer drugs [228,229]. An early example of SWCNT tethered Pt(IV) drug is cis,cis,trans-[Pt$(NH_3)_2Cl_2$(OEt)$(O_2CCH_2CH_2COOH)$] tethered through amine-PEG-phospholipid (see Fig. 9A) to the SWCNT and each SWCNT can able to conjugate with 65 platinum(IV) prodrugs [189,230]. For the compound cis,cis,trans-[Pt$(NH_3)_2Cl_2$$(O_2CCH_2CH_2CO_2H)$$(O_2CCH_2CH_2CONH$-PEG-folic acid)], the one axial succinate group can able to attach with amine-functionalised SWCNT and other axial succinate group is conjugated with PEG spacer and folic acid [231]. Folic acid helps to target folate receptor which is over-expressed in some cancer cells (ovarian, breast, lung, kidney and colon cancer cells) and PEG spacer helps to soluble and biocompatible of the nanotube [189,231]. On the other hand, diameter of MWCNT is higher than that of SWCNT and hence hydrophobic cisplatin prodrug cis,cis,trans-[Pt$(NH_3)_2Cl_2(O_2CC_6H_5)_2$] can be loaded to the internal cavities of MWCNT by nanoextraction over a period of several days (see Fig. 9B) [189,232]. On reduction of the prodrug by internal reducing agent such as ascorbic acid or glutathione, the hydrophobic parts remove and resulting cisplatin release. Another very important example of Pt(IV)-carbon nanomaterial is photoactive cis,trans,cis-[Pt$(N_3)_2(OH)_2(NH_3)$(3-NH_2Py)] conjugated to carboxylate-functionalized carbon nanoparticle and folic acid was attached to this carbon nanoparticle through ethylenediamine linker (see Fig. 9C) [189,233]. Recently nanosized graphene oxide is also used for cargo delivery of Pt (IV) anticancer drugs [234,235].

12.5.2.2. Gold nanoparticles. Gold nanoparticles are generally nontoxic, biocompatible, inert and easily modified and hence they are promising and attracting for drug delivery vehicles of platinum anticancer drugs [236,237]. The main advantages of using gold nanoparticles are the ability to image and diagnose diseases sites, increase platinum uptake, selectivity of drug targeting, reduction of glutathione mediated detoxification, capacity of sensitizing the cells to anticancer drugs and resistance to enzymatic degradation [238]. It was proved that gold nanoparticles generally enter into cells through endocytosis [237,239]. Lippard and his coworkers [240] first showed the study of Pt(IV) complex cis,cis,trans-[Pt$(NH_3)_2Cl_2$(OH)$(O_2CCH_2CH_2COOH)$] tethered with gold nanoparticles via thiolated oligonucleotide linker (see Fig. 9D). This nanoparticle binding drug Pt (IV)-DNA-Au was more effective than free state on lung cancer cells A549, human osteosarcoma U2OS cells and almost 12-fold more

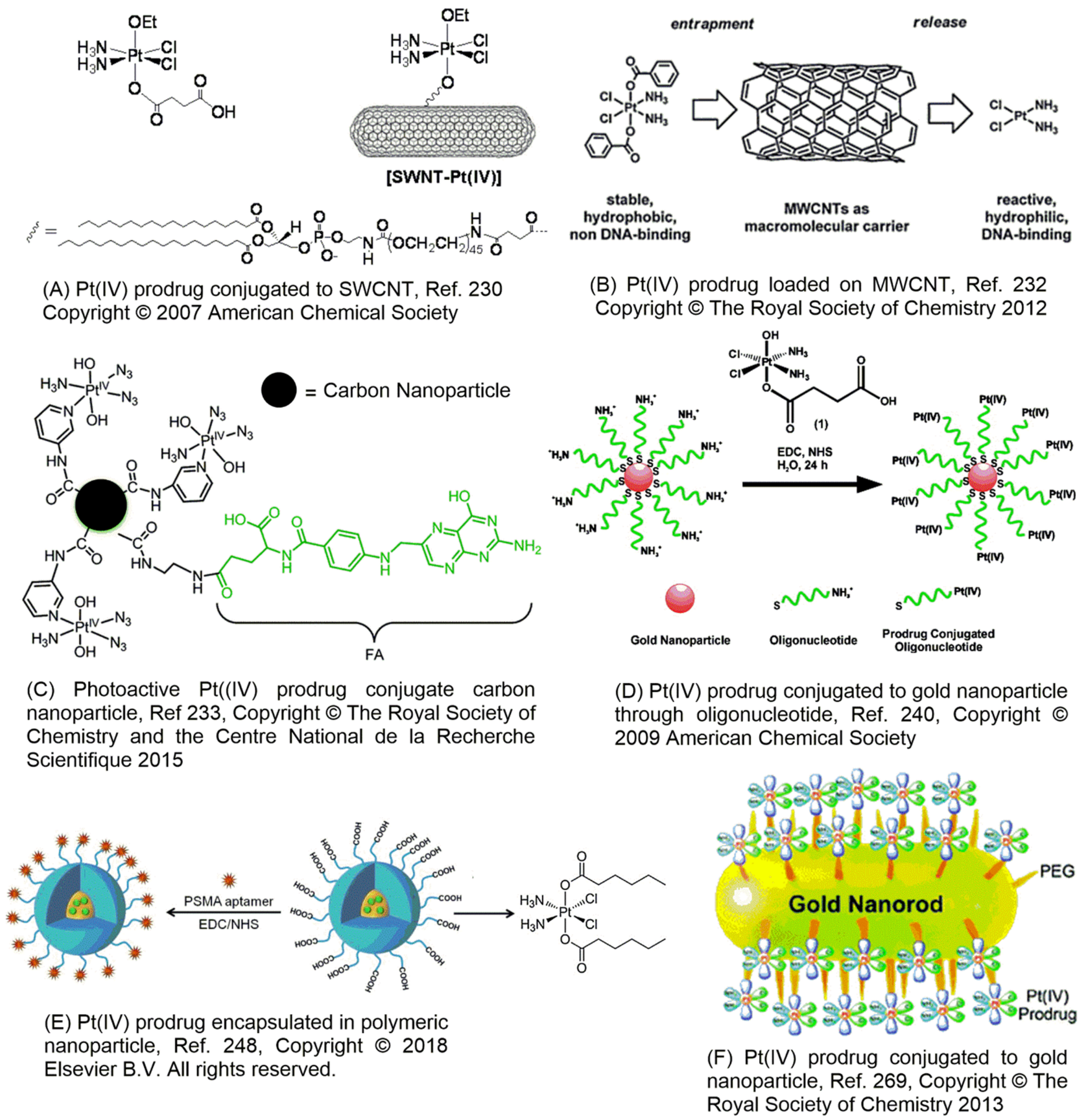


Fig. 9. Some examples of Pt(IV) prodrug nanodelivery systems.

cytotoxic than free state on A549 lung cancer cells. Kumar et al. [241] synthesized glutathione-stabilized gold nanoparticles (Au@GSH + CRGDK) to target prostate cancer cells. The thiol functional gold nanoparticles were conjugated to cis,cis,trans-[Pt$(NH_3)_2Cl_2(O_2CCH_2CH_2COOH)_2$] and CendR peptide ligand Cys-Arg-Gly-Asp-Lys (CRGDK) which is a neuropilin-1 receptor targeting peptide. Gold nanorods are also used for platinum(IV) drug delivery. Yangzhong Liu and his coworkers [242] demonstrated that PEGylated nonorods conjugated with cis,cis,trans-[Pt$(NH_3)_2Cl_2(O_2CCH_2CH_2COOH)_2$] (see Fig. 9F) showed superior cytotoxicity towards cervical cancer HeLa, human lung carcinoma A549 and human breast adenocarcinoma MCF-7 cell lines.

12.5.2.3. Other inorganic nanoparticles. Some other inorganic nanomaterials such as Fe_3O_4 nanoparticles [243,244] rare earth element based upconversion nanoparticles [245,246], silica nanoparticles [272] are used as platinum drug delivery system. Among these Fe_3O_4 nanoparticles are very attracting due to their exclusive characteristics of magnetic field mediated targeting and magnetic resonance for diagnostic and therapeutic application [238]. Very recently Ping'an Ma et al. [244] showed a programmed strategy of delivering cisplatin(IV) prodrug by use of iron oxide nanocarriers that can preferentially increase the Pt and Fe accumulation in the tumor site via magnetic-field mediated-localization and monitoring by MRI-guided delivery. Dai et al. [245] reported a system of trans,trans,trans-[Pt$(N_3)_2(NH_3)(py)(O_2CCH_2CH_2CO_2H)_2$] conjugated with core–shell upconversion nanoparticles in which core was made by $NaYF_4$ doped with ytterbium(III), thulium(III) and shell was made by $NaGdF_4$ doped with ytterbium(III). This Pt(IV) conjugated core–shell upconversion nanoparticles released Platinum drug at 980 nm light radiation and showed toxicity in cancer cells. Similarly, Ruggiero et al. [247] synthesized thulium(III) doped $NaYF_4$:Yb(III) nanoparticles conjugated with cis,cis,trans-$[Pt(NH_3)_2Cl_2(O_2CCH_2CH_2CO_2H)_2]$ through phospholipid-functionalized PEG chain. This system released Pt(II) compound on irradiation with 980 nm light. CdSe-ZnS quantum dot and layered doubled hydroxide nanoparticles are also known in literature which can act as platinum drug delivery vehicles [189]. More detail about inorganic nanocarrier of Pt(IV) remain elsewhere [238].

12.5.2.4. Polymer and polymeric micelles nanomaterials. Polymeric micelles are also very important for delivering of platinum anticancer drugs [98]. Polymeric micelles are aggregates of block copolymers featuring core-shell architecture [222]. The polymer poly(lactic-*co*-glycolic acid)-*block*-poly(ethylene glycol) or PLGA-*b*-PEG has been used frequently for platinum drug delivery [248] in which PEG is hydrophilic, PLGA is hydrophobic, biocompatible and biodegradable. Lippard et al. [249,250] synthesized a novel Pt(IV) prodrug delivery system in which cis,cis,trans-$[Pt(NH_3)_2Cl_2(O_2CCH_2CH_2CH_2CH_2CH_2)_2]$ was encapsulated within PLGA-*b*-PEG-COOH nanoparticles and theses nanoparticles were then functionalized with aptamers (Apt) that targeted to prostate-specific membrane antigen (see Fig. 9E). The group demonstrated that Pt(IV)-PLGA-*b*-PEG-Apt-NP was more cytotoxic than cisplatin on LNCaP prostate cancer cells [250]. His group also demonstrated that similar system of Pt(IV)-PLGA-*b*-PEG functionalized with cyclic pentapeptide c(RGDfk) was able to target breast prostate cancer cells [251].

Xiao et al. [252] demonstrated that cisplatin or oxaliplatin reacted with guanosine monophosphate or B-cell lymphoma 2 (BCL-2) siRNA to form Pt-guanosine adduct very rapidly but Pt(IV) analogues [OxaPt(IV) or CisPt(IV)] did not form Pt-siRNA adduct. However self assembled micelles from methoxy-poly(ethylene glycol)-*block*-poly(ε-caprolactone)-*block*-poly(L-lysine) (mPEG-*b*-PCL-*b*-PLL) were able to conjugate covalently with OxaPt(IV) and electrostatically with siRNA. Therefore concentration of BCL-2 mRNA decreased and hence in vitro antiproliferative activity increased significantly for corresponding Pt(II) agents.

Cong et al. [271] reported a novel system where axial groups of Pt (IV) prodrug were demethylcantharidin (DMC) and this prodrug was then polymerized with ethylenediamine into dual sensitive dual drug backboned shattering polymer (DDBSP) that self assembled into nanoparticles (DD-NPs). The system has two advantages: (a) DMC is a protein phosphate 2A (PP2A) inhibitor and hence the system showed enhancement in antitumor activity, (b) DD-NP with extremely high platinum heavy metal content in the polymer chain can directly track the drug itself via platinum based drug-mediated computer tomography and ICP-MS both in vitro and in vivo.

12.5.2.5. Other nanomaterials. Many other platinum drug carrier such as liposomes [253,254], lipid particles [255], dendrimer [256,257], etc. are also known.

12.6. Nanodelivery of Pt(II) anticancer drug

Considerable research attention has been paid to nanodelivery of Pt (II) drugs [258,259]. A few examples are given here. Wheate et al. [260] developed a system where Pt(II) anticancer drug oxaliplatin was chelated to gold nanoparticles that were functionalized with thiolated PEG monolayer capped with a carboxylate group (see Fig. 10A). Each of these gold nanoparticles was able to contain ~280 drugs molecules and showed better toxicity on HCT116, HCT15, HT29 and RKO cell lines. Wheate et al. [261] also developed the similar system with cisplatin and which showed enhancement of drug loading, with the number of platinums per nanoparticle ranging from 700 to 70000.

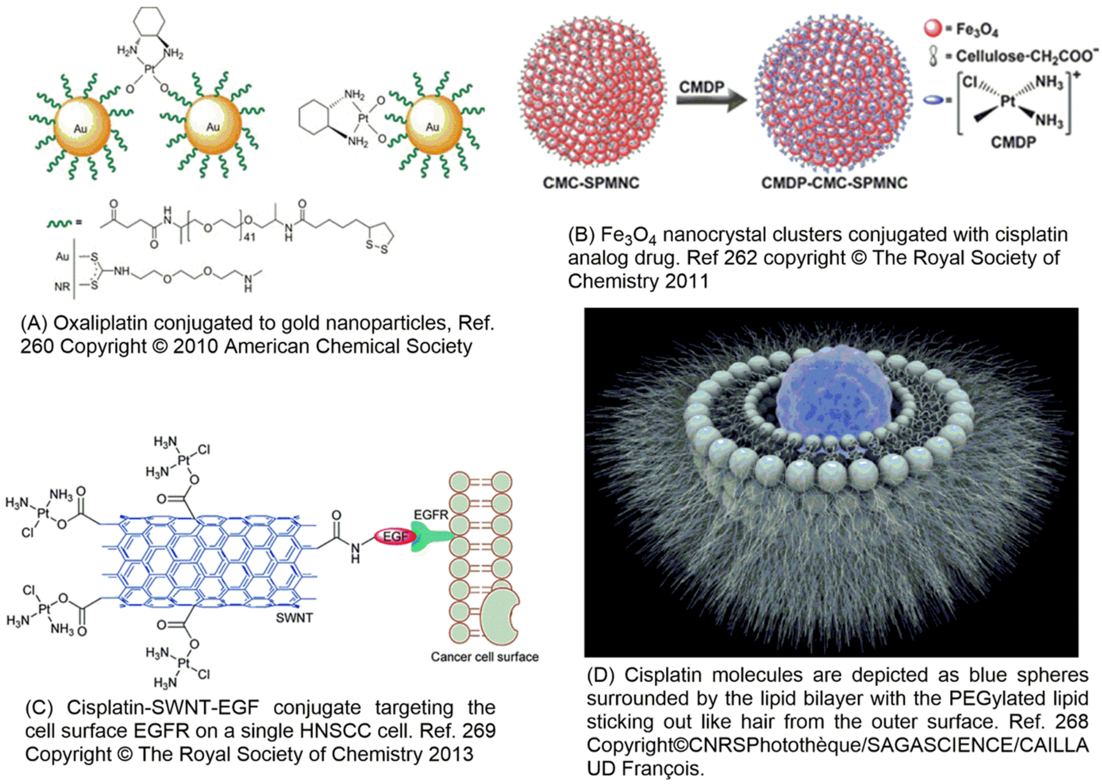
Guo et al. [262] synthesized super magnetic iron oxide nanoparticles coated with carboxymethylcellulose and this carboxylate end was then chelated with cisplatin (see Fig. 10B). In comparison with cisplatin, the conjugate can more readily enter cancer cells and exert higher cytotoxicity towards the human cervical cancer HeLa cells and the human hepatocarcinoma HepG2 cells. Sun et al. [263,264] synthesized a novel system where cisplatin was loaded in the cavities of the porous hollow iron oxide nanoparticles. Release of drug from these nanoparticles depended on the size of the cavities and pH value of the medium. When these nanoparticles were conjugated to herceptin, the conjugated drug was very selective and effective toward Her-2 positive breast cancer. Travnick et al. [265] reported maghemite/gold nanoparticles covered with lipoic acid for efficient transport of cisplatin.

Another very important example is lipoplatin (see Fig. 10D). In this 110 nm nanoparticle, aqueous core loaded cisplatin was bound by liposomal vesicle. This liposomal vesicle is composed of soy phosphatidyl choline (SPC-3), cholesterol, dipalmitoyl phosphatidyl glycerol (DPPG), and methoxy-polyethylene glycoldistearoyl phosphatidylethanolamine (mPEG 2000-DSPE) [266]. Lipoplatin has successfully entered in phase I, phase II and phase III clinical trials [267]. Boulikas et al. demonstrated that the accumulation of lipoplatin was up to 200-fold higher in colon tumor compared to normal tissue [268]. The clinical data confirmed that the lipoplatin shows similar efficiency to that of cisplatin in pancreatic, head and neck, breast cancers, and NSCLC [266] but shows lower side effects, lesser resistance [267].

Bhirde et al. [270] synthesized a system where cisplatin and epidermal growth factor (EGF) were conjugated to carboxylate functional SWNTs (see Fig. 10C). In vitro and in vivo study confirmed that this system showed more efficient than cisplatin for treatment of head and neck squamous carcinoma (HNSC) as these cancer cells overexpress EGF receptor. However one disadvantage of Pt(II) tethered SWNTs is that they are not stable enough and release prematurely and able to bind with endogenous nucleophiles [269].

13. Conclusions

Cisplatin is one of the most used anticancer drugs without any doubt for the treatment of solid cancer such as prostate cancer, ovarian cancer, head and neck cancer, bladder and lung cancer and some other cancers. Oversensitivity of cisplatin toward testicular cancer is due to overexpression of some proteins and low ability of interstrand-crosslink repairing. It is a cytotoxic drug which causes apoptosis by damaging DNA, activation of several signal transductions, and then inhibiting replication and mitosis. Multiple mechanisms of action of cisplatin are known in literature and each of them has proper evidence but none of them can explain the actual complete mechanism. Therefore, action mechanism is a great interest in chemistry, biology and medical science. A deep knowledge of mechanism in action may lead to design new drugs with superior efficiency and provide new therapeutic strategies in cancer treatment. Toxic side effects, drug resisance and relapsing are the major challenges of cisplatin. Drug resistance is generally seen due to changes in cellular uptake, decreased influx and increased efflux of drug, drug detoxification by cellular thiols, alterations in drug target and repairing of DNA. The side effects such as nephrotoxicity, neurotoxicity, gastrointestinal toxicity, ototoxicity are serious concern to the researcher. Sometime antioxidants, antiemetic agents, aggressive intravenous hydration are used to diminish side effects of cisplatin. Again, drug relapse is also seen most of the time for the patients of small cell lung cancer. Combinational therapy may be one important way to avoid these drawbacks. Carboplatin, oxaliplatin, nedaplatin are though less cytotoxic but they are cross-resistant with cisplatin and they generally do not show substantial advantage over cisplatin. Among nonclassical platinum compounds, Pt(IV) prodrugs shows very promising as they are very kinetically inert and axial groups may be lipophilic that can enhance passive uptake, cancer cell targeting agents, subcellular targeting



(A) Oxaliplatin conjugated to gold nanoparticles, Ref. 260 Copyright © 2010 American Chemical Society

(B) Fe_3O_4 nanocrystal clusters conjugated with cisplatin analog drug. Ref 262 copyright © The Royal Society of Chemistry 2011

(C) Cisplatin-SWNT-EGF conjugate targeting the cell surface EGFR on a single HNSCC cell. Ref. 269 Copyright © The Royal Society of Chemistry 2013

(D) Cisplatin molecules are depicted as blue spheres surrounded by the lipid bilayer with the PEGylated lipid sticking out like hair from the outer surface. Ref. 268 Copyright©CNRSPhotothèque/SAGASCIENCE/CAILLAUD François.

Fig. 10. Some examples of Pt(II) nanodelivery systems.

agents, bioactive moieties such as drugs, enzyme inhibitors, pathway activators or suppressors, epigenetic modifiers, antimetabolites etc. and therefore designing of Pt(IV) prodrugs is another very important way to improve efficiency of chemotherapeutic drugs in future. Development of nanoparticle conjugated Pt(IV) drugs will be future crush on researcher as nanoparticles can carry higher no. of Pt(IV) compounds, target cancer cells by attaching targeting agents, increase solubility by attaching hydrophilic moieties, increase distribution on tumor sites and have some other effective advantages. Finally, more research is needed to improve anticancer activity, reduced toxicity and cross-resistance or improve pharmacological characteristics as compared with the parent compound, cisplatin.

14. Area of interest

None.

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Appendix A. Supplementary material

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