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Nanocarriers for delivery of platinum anticancer drugs☆

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Abstract

Platinum based anticancer drugs have revolutionized cancer chemotherapy, and continue to be in widespread clinical use especially for management of tumors of the ovary, testes, and the head and neck. However, several dose limiting toxicities associated with platinum drug use, partial anti-tumor response in most patients, development of drug resistance, tumor relapse, and many other challenges have severely limited the patient quality of life. These limitations have motivated an extensive research effort towards development of new strategies for improving platinum therapy. Nanocarrier-based delivery of platinum compounds is one such area of intense research effort beginning to provide encouraging preclinical and clinical results and may allow the development of the next generation of platinum chemotherapy. This review highlights current understanding on the pharmacology and limitations of platinum compounds in clinical use, and provides a comprehensive analysis of various platinum–polymer complexes, micelles, dendrimers, liposomes and other nanoparticles currently under investigation for delivery of platinum drugs.

Keywords

Platinum drugs; Drug delivery systems; Liposome; Polymer conjugate; Dendrime; Nanotube; Nanoparticle; Micelle; Block ionomer complex

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1. Introduction

It has been 48 years since Rosenberg and colleagues while studying the effect of electric field on bacteria made a serendipitous discovery that the products of hydrolysis of the platinum electrode can inhibit bacterial growth [1]. Of these products the most potent was cisplatin first described by Michele Peyrone in 1845, and known for a long time as Peyrone's salt. They also discovered that this compound can inhibit growth of cancer cells in mouse models of sarcoma and leukemia [2]. These seminal studies were followed by Higby and colleagues who carried out the clinical trial of cisplatin and reported response to the drug in testicular and other tumors [3]. Cisplatin and other platinate derivatives are now common in medical oncology, having a major impact in management of tumors of the ovary, testes, head and neck and other cancers [4,5].

However, the dose limiting toxicities associated with platinum therapy has presented a serious concern in clinic [6,7]. After decades of research the quest for new less toxic platinum compounds and treatment regimens or delivery methods, which would eliminate the associated toxicities and improve the anticancer efficacy, still goes on [8,9]. Carrier-based delivery of anticancer platinates to the tumor sites is one such area of intense research. It encompasses the use of polymeric conjugates and various other inclusions of platinates in liposomes, micelles, dendrimers, inorganic or other solid particles, and other carriers [10–12]. It is envisioned that such carriers may permit improved solubility of platinates, prolong their half-life in the body, increase distribution of them into tumor sites, enable sustained and/or triggered release of drugs in the tumors, decrease off-target distribution and effect of platinates, reduce side effects of platinum agents as well as suppress development of drug resistance [13,14]. Furthermore, carriers are now explored for simultaneous incorporation and delivery of platinum drugs with other anticancer drugs for combination therapy [15,16]. The following sections convey the current understanding of the pharmacology, mechanism of action and limitations of platinum compounds in clinical use, and analyze various polymeric carriers for anticancer platinates.

2. Platinum anticancer drugs in oncology

An overview of approved platinum complexes is presented in Table 1. The platinum complexes in worldwide clinical use, also termed *classical platinum complexes*, are uncharged, *cis*-configured, square planar complexes with platinum in its +II oxidation state (Pt(II)). The general formula to describe them is *cis*-$[PtA_2X_2]$, where A_2 represents two monodentate or one bidentate ligands with nitrogen donor atoms and X_2 represents two monodentate or one bidentate anionic ligand(s). Table 1 represents a summary of the ligands comprising clinically used platinum complexes. Based on studies pioneered by Cleare and Hoeschele [17], several structure–activity relationships have been recognized. The modification of the non-leaving group(s) A_2 results in formation of structurally different DNA adducts and thus alters the anticancer activity of the complexes. The modification of the leaving group X_2 affects the biodistribution of the complexes and thereby affects their side effects.

Cisplatin (*cis*-diamminedichloroplatinum(II)) was the first member of classical platinum complexes. It entered the Phase I clinical trials in 1971 and by the end of 1970s became the basis in combination chemotherapy for the treatment of advanced and metastatic testicular germ-cell cancer [18]. Combinations of cisplatin and etoposide are the current regimens of choice for this indication and have proven to be highly effective [19]. Although not curative, the cisplatin therapy has substantially improved the average progression-free survival and life span of patients in ovarian cancer [20]. Cisplatin is an essential component of chemotherapy regimens for lung, head and neck, endometrial, bladder and oesophageal cancers [21]. It is also accepted as alternative option in therapies of several other solid tumors, including liver, gastric, brain, melanoma and soft-tissue sarcomas. Moreover, this drug was shown to sensitize cancer cells to radiation and is widely used in combined radiotherapy–chemotherapy treatments in patients with advanced squamous cell carcinoma of the head and neck, lung and locally advanced cervical cancers [22–24].

The second-generation platinum drugs were developed to reduce the dose limiting toxicity of cisplatin by slowing down the rate of aquation reactions with bidentate X_2 ligands (discussed in Section 4). This, carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato) platinum(II)), was created by substituting the readily exchangeable chloride ligands with a bidentate 1,1-cyclobutanedicarboxylic acid ligand [25]. Its reduced toxicity profile makes it suitable for aggressive high-dose chemotherapy. This drug has been approved worldwide and nearly replaced cisplatin in combination regimens with paclitaxel for treatment of ovarian cancer [26]. This combination is also used in patients with non-small cell lung cancer (NSCLC) [19], albeit in these patients the carboplatin–etoposide combination is often preferred. At the same time carboplatin has limited effectiveness against testicular germ-cell cancers, squamous cell carcinoma of the head and neck and bladder cancer. As a result, cisplatin still remains the drug of choice for treatment of these cancers [19].

Nedaplatin or *cis*-diammineglycolatoplatinum(II), shows improved toxicological profile compared to cisplatin and pharmacokinetic properties similar to carboplatin [27]. So far it has limited regional approval in treatment of NSCLC, small cell lung cancer (SCLC), oesophageal cancer and head and neck cancers [28]. In a small pilot study, response rate against oesophageal cancers was shown to be good, and could further be improved with 5-fluorouracil (5-FU) [29]. The patients with renal impairment are expected to benefit from this regimen. In other clinical studies, nedaplatin activity in combination regimens, for example, with vindesine for untreated NSCLC, was shown to be equivalent to that of cisplatin [30]. However, nedaplatin still retains an advantage over cisplatin due to lower toxicity.

The third generation platinum complexes were designed to overcome cellular resistance to cisplatin and carboplatin. This design typically involves modification of the non-leaving A_2 (ammine) ligands (Table 1). For example, *cis*-dichloro(1,2-diamminocyclohexane) platinum(II) (DACHPt) is a potent anticancer agent with a broader spectrum of activity and no cross-resistance compared to cisplatin [19]. It is however, poorly soluble, which was addressed by further modification of the X_2 ligand. Among the various derivatives studied, oxaliplatin (1,2-diaminocyclohexane platinum(II) oxalate) having a relatively higher solubility compared to DACHPt has gained worldwide approval [31]. This agent has proven

to be effective and increased efficacy of standard 5-FU/leucovorin therapy in advanced colorectal cancer, whether its combination with 5-FU/leucovorin is now considered the first line treatment [32]. Oxaliplatin has also great potential as a treatment option after failure of cisplatin or carboplatin therapy. Clinical activity of oxaliplatin has been reported in both relapsed or refractory ovarian cancer [33] and refractory germ-cell cancers [34]. Its activity has also been shown in pretreated refractory or relapsed non-Hodgkin's lymphoma, anthracycline-resistant metastatic breast cancer and in NSCLC [35]. Additionally, oxaliplatin has shown much less toxicity than cisplatin or carboplatin.

The other notable representatives of the third generation complexes include lobaplatin and heptaplatin, which have found limited regional approval. Lobaplatin (1,2-diamino-methylcyclobutane) platinum(II) lactate) is currently approved for chronic myelogenous leukemia, metastatic breast cancer and SCLC [28]. Preclinical data suggested its favorable toxicological profile and lack of cross-resistance to cisplatin [36]. However, the clinical data regarding lack of cross-resistance is inconclusive. Heptaplatin (*cis*-malonatol [(4R, 5R)-4,5-bis(aminomethyl)-2-isopropyl-1,3-dioxolane]platinum(II)) is structurally similar to lobaplatin, but has a bulkier ammine ligand. It is currently used in the treatment of gastric cancer [37]. A recent Phase III study indicated that heptaplatin/5-FU regimen is comparable to cisplatin/5-FU regimen, but has less severe hematological side effects [38]. No study of this regimen in cisplatin resistant cancers has been reported so far.

Additionally a number of new platinum complexes, which have shown promising preclinical and early phase clinical results, are now being evaluated in advanced stage clinical trials. Some of these drug candidates are presented in Table 2. For example, picoplatin (ZD0473) was designed specifically to overcome intrinsic or acquired resistance due to elevated intracellular thiols [39]. Introducing the methyl group at the position 2 of the pyridine ring of this complex results in steric hindrance and reduced reactivity towards sulfur donors such as methionine and thiourea [39]. In Phase I and Phase II clinical trials, picoplatin demonstrated activity in a variety of solid tumors, including lung (SCLC and NSCLC), ovarian, colorectal and hormone-refractory prostate cancer [40]. However, in Phase III trials picoplatin failed to show efficacy in advanced NSCLC and second line SCLC. It is still being investigated in Phase II trials in metastatic colorectal cancer [41]. An interesting feature of this complex is its ability to be administered orally. It is the first Pt(II) drug to show good oral bioavailability and activity, and an oral formulation for clinical use is awaited.

The new candidates in clinical trials also include 'non-classical' complexes, which are structurally different from cisplatin such as the trans-geometry, trinuclear complex, BBR3464, and the octahedral Pt(IV) complex, satraplatin. In preclinical studies comparing BBR3464 to cisplatin the former derivative showed higher uptake [42,43], more rapid DNA binding and higher number of long persisting inter-strand cross-links, which were less inclined to repair [44]. Phase I studies of BBR3464 demonstrated its reduced toxicity profile, much different from that of cisplatin [45]. Although positive results were observed in Phase II studies with NSCLC [46], this drug candidate has not moved into Phase III. The results for Phase II studies in locally advanced and metastatic pancreatic cancer have not been reported yet.

Of particular interest are octahedral Pt(IV) complexes, which tend to be less reactive and are better suited for oral administration than their Pt(II) counterparts [47]. These compounds, also called fourth generation complexes, are characterized by higher oxidation state of the metal center + IV and presence of two axial leaving ligands. Their general formula is *cis*-$[PtA_2X_2Y_2]$, where Y_2 being two other axial monodentate anionic leaving groups. These complexes are prodrugs, which are eventually transformed into Pt(II) complexes due to reduction to Pt(IV) and loss of axial ligands. Of this group, satraplatin is currently under clinical evaluation [48]. It is readily absorbed by the gastro-intestinal mucosa and once in the blood is reduced to yield at least six different active Pt(II) complexes [48]. Phase I studies indicated a toxicological profile similar to carboplatin and different from cisplatin [49]. Phase II studies revealed activity in previously untreated patients with SCLC and prostate cancer. A Phase III trial evaluated satraplatin with and without prednisone in hormone-refractory prostate cancer and indicated a 40% reduction in risk of progression compared to placebo [50]. Currently satraplatin is undergoing variety of Phase I, II and III clinical trials in combination with various other drugs such as bevacizumab for prostate cancer, abraxane for advanced cancers, and vinorelbine for advanced solid tumors.

3. Mechanisms of action of platinum drugs

There are three major factors defining the cytotoxicity of the platinum drugs: 1) cellular accumulation of the drug; 2) intracellular aquation, sub-cellular distribution and binding to the cellular targets; and 3) cellular recognition of platinum-induced damage leading the cell to death (Fig. 1).

Cellular accumulation of the platinum drugs is directly related to their cytotoxicity. The majority of cases with acquired cellular resistance to platinum drugs are associated with a markedly reduced drug accumulation. The long held assumption that platinum is transported into cells largely by passive diffusion has recently been challenged by studies involving the role of various cellular transporters. In particular, the major copper influx transporter, copper transporter 1 (CTR1), is now considered the principal gateway for the accumulation of cisplatin and carboplatin in the tumor cells [51]. A positive correlation between decrease in CTR1 expression and increase in acquired cisplatin resistance was shown among ovarian cancer cell lines [52]. The CTR1 genetic knockout cells were shown to be resistant to cisplatin *in vivo* [53]. In contrast to cisplatin and carboplatin, the accumulation of oxaliplatin seems to be less dependent on CTR1 [51]. In addition, two copper efflux transporters, ATP7A and ATP7B have also been shown to regulate platinum drug accumulation. A small increase in ATP7A expression produced resistance to all three clinically available Pt drugs (cisplatin, carboplatin and oxaliplatin); however, the exact mechanism behind this effect is not clearly understood [54]. A more direct relationship between increased ATP7B expression and cisplatin and carboplatin efflux was shown by Katano et al. [55]. Moreover, in addition to copper transporters, organic cation transporters (OCTs) have also been implicated in the facilitated transport of platinum drugs. The nature of the non-leaving group coordinated to platinum, such as the DACH moiety in oxaliplatin, was shown to be a key for selective uptake of these platinum complexes by OCTs [56]. Thus, it appears that platinum drug accumulation is due to a combination of passive, active, and facilitated transport mechanisms.

Aquation is one of the key processes in the pharmacology of platinum drugs. In aqueous media, the platinum complexes undergo stepwise aquation reactions, in which the chloride ions are replaced by the water molecules resulting in the formation of cationic mono- and di-aqua complexes (the most active forms), and to a lesser extent hydroxo-bridged platinum(II) multimers (the least active forms) [57]. The rates of aquation of platinum complexes are determined mainly by the concentration of the chloride ions in biological fluids. Thus, the low concentration of chloride in the cells (4–12 mM) favors formation of the cationic aqua forms of the platinum complexes. In contrast, the high concentration of chloride in the blood (100 mM) favors existence of relatively stable neutral state of the platinum complexes [58]. The role of aquation in the pharmacology of platinum drugs is illustrated in Fig. 1 using cisplatin as an example. This process is believed to play two major roles. First, the cationic aqua derivatives of the platinum drugs do not readily diffuse out of the cell through the cell membrane and are trapped within the cell. Second, the aquation chemically activates the drug, which is essential for its binding to intracellular targets: proteins, RNA and, most importantly, DNA [58]. Furthermore, the rate of exchange of the X_2 ligands with water affects the toxicity of the platinum complexes. Rapid aquation in the blood produces highly active platinum species, which react with various molecules in the blood and cause severe systemic toxicity. Slower aquation reduces toxicity, prolongs plasma half-life, but also reduces the antitumor activity of the drug [59]. This concept is best exemplified by carboplatin, the better tolerability of which has largely been attributed to its higher stability and lower reactivity. The aquation rate of carboplatin in neutral chloride-free phosphate buffer is approximately 100 times slower than that for cisplatin [60]. Similarly, platinum compounds with bidentate X_2 ligands such as oxaliplatin also have slower rates of aquation and are therefore more stable in aqueous media and less toxic [61].

The ability to react with various cellular targets underlies the cytotoxicity of the platinum drugs. Of these cellular targets the DNA is undoubtedly the most important in exhibiting the anticancer effect [62]. Biochemical studies demonstrated that formation of Pt-DNA adducts significantly changes the structure of the target DNA, causing the unwinding, bending and destabilization of the DNA duplex [63]. The more common 1,2- or 1,3-intrastrand cross-links unwind the DNA duplex in the proximity of the site of platination and bend it toward the major groove [64]. In contrast, the less prevalent inter-strand cross-links bend the helix toward the minor groove [64]. The correlations between the Pt-DNA adduct levels and the cytotoxic responses of the cells to these drugs have been long known. Analysis of the DNA from the patients treated with cisplatin demonstrated formation of intra-strand Pt-adducts with approximately 65% of these adducts being 1,2-d(GpG), 25% 1,2-d(ApG), and 5–10% 1,3-d(GpNpG) [65]. Additionally, a small percentage of adducts display inter-strand cross-links or mono-functional modifications.

Platinum drugs containing different leaving groups X_2 may exhibit different kinetics of DNA binding and produce different DNA-adduct profiles [66]. Thus, oxaliplatin generates a disparate adduct profile compared to cisplatin [61]. The oxaliplatin adducts albeit being significantly less frequent are yet more cytotoxic than those of cisplatin. The chemical nature of the non-leaving group A_2 can affect the structures of Pt-DNA adducts and cause distinctive structural distortions of DNA, which, in turn, may alter the recognition of the

platinum lesions by the repair machinery and contribute to the differences in cytotoxicity of the platinum drugs [67].

The interaction between the Pt-DNA damaged site and nuclear proteins triggers the signal transduction pathways (AKT, c-ABL, p53, MAPK and others) that will ultimately seal the fate of the treated cells (Fig. 1). For example, the DNA-damage recognition proteins selectively recognize severely distorted DNA generated by formation of Pt-DNA cross-links (Table 3). Other proteins such as histones, DNA and RNA polymerases involved in DNA packaging are coming in frequent contact with the DNA duplex and unavoidably encounter Pt-DNA adducts (Table 3) [58]. There seems to be an individualized cellular response to these events, which is due to the heterogeneity of these interactions, further complicated by the differential expression of these proteins in different cell types, transcriptional, translational and post-translational regulation of their cellular levels, and cross-talk between the various downstream signaling molecules [58,68]. Numerous pathways are involved in the signaling DNA damage, arresting the cell cycle, repairing platinated DNA (transcription-coupled repair, global genomic repair) and triggering cell death through apoptosis or necrosis [4]. The knowledge of these processes is still incomplete and much remains to be elucidated.

Several additional mechanisms, other than DNA-platination, have also been implicated in the cytotoxicity of platinum drugs. Thus, platinum complexes can react with a number of non-DNA cellular components such as glutathione [69], which may play a part in cytotoxicity and toxicity profile of platinum drugs. There is evidence that cisplatin binds to tubulin, induces partial microtubule depolymerization and therefore leads to disruption of the cytoskeleton in tumor cells [70]. Cisplatin has been also reported to bind at C-terminal part of the molecular chaperone, Hsp90 and to interfere with its nucleotide binding [71]. Furthermore, cisplatin is prone to interact with phosphatidylserin and other phospholipid components of the cellular membranes and thus modulate their function [72]. A recent study reported that cisplatin induces redistribution of the death receptor CD95 into membrane lipid rafts of human colon cancer cell lines, which contributes to their sensitization to CD95-mediated apoptosis [73].

4. Limitations to platinum drug therapy

Majority of patients treated with platinum drugs, with the exception of the testicular cancer patients, experience only partial response with numerous systemic toxicities preventing administration of higher drug doses. Some of the toxicities to a varying degree are common to most platinum drugs. Some others are unique to specific platinum drugs.

For instance, nephrotoxicity is the major dose limiting toxicity associated with cisplatin. Irreversible renal failure requiring dialysis is observed with large doses (exceeding 100 mg/m^2/course) or multiple courses of cisplatin treatment. Cisplatin nephrotoxicity is often seen 10 days post administration and is manifested as permanent reduction in glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels [74–77]. These side effects are generally followed by histopathological changes, characterized by prominent tubular cell death due to necrosis and apoptosis [78]. The drug

induces injury and death of tubular cells [79] and stimulates robust inflammatory response, further contributing to renal tissue damage [80]. Moreover it may also induce injury to renal vasculature and result in decreased blood flow and ischemic injury to the kidneys [80]. These events, together, culminate in the loss of renal function during cisplatin nephrotoxicity, triggering acute renal failure. Additionally, cisplatin induces chronic nephrotoxicity characterized by altered nephron structure and continued nephron functional impairment [77]. The incidence of renal toxicities with carboplatin is generally lower and much less severe than that with cisplatin [81,82]. With continued carboplatin therapy some patients can experience subclinical tubular damage that can develop into overt nephrotoxicity [83]. The potential for renal failure in patients previously treated with cisplatin may be increased requiring a reduction in carboplatin doses [84]. Oxaliplatin is considered to be the least nephrotoxic amongst the platinum drugs in clinical use [85]. However, there have been several reported cases of renal failure with repeated cycles of oxaliplatin administration [86–88].

Neurotoxicity is another common side effect of platinum chemotherapy. Cisplatin treatment often results in the damage of the dorsal root ganglion [7]. The drug acts as a calcium channel blocker, changing intracellular calcium homeostasis and leading to apoptosis of exposed neurons of the dorsal root ganglion [89]. Predominant symptoms include numbness and tingling, abnormal sensation, disturbances of position, and relative sparing of motor units [90]. These adverse neurological effects, with peak severity around 1–4 months after the end of weekly cisplatin regimen, are usually reversible but are long-lasting in many cases [91]. With carboplatin where hematological toxicity is dose limiting the neurotoxicity is not generally observed at the clinically relevant doses. Oxaliplatin treatment is associated with two different forms of toxicity. First, after few infusions of this drug there is a transient acute syndrome accompanied with muscular cramps and spasms, which typically resolve within days of drug infusion [92]. Second, the drug causes gradual development of the dose limiting cumulative sensory neuropathy, which is similar to cisplatin effect. The characteristic symptoms include persisting abnormal sensation and paresthesias of the extremities, impaired sensory ataxia and deficits in fine sensory motor coordination, which may impair normal life [85].

Toxicity to sensory systems is more common with cisplatin than with carboplatin and oxaliplatin [93]. In particular, cisplatin causes ototoxicity especially in patients less than 5 years old, with adolescents/ adults being the least affected [94]. The ototoxicity of the drug is caused by the damage to the organ of Corti and manifested as high-frequency hearing loss and tinnitus [95]. There have been few reports of ototoxicity with carboplatin however their severity was much less than with cisplatin [96]. Moreover, high dose cisplatin therapy was reported to induce visual impairments due to retinal damage [97]. In contrast, carboplatin and oxaliplatin seldom induce visual disturbances [7].

Haematological side effects are more common with carboplatin compared to cisplatin and oxaliplatin. Carboplatin exerts potent myelosuppression resulting in thrombocytopenia and neutropenia [98]. High-dose carboplatin chemotherapy is generally associated with life threatening hematological toxicity, requiring prophylactic use of recombinant hemopoietic growth factors [99]. Cisplatin treatment causes anemia requiring the prophylactic use of

erythropoietin or transfusion of erythrocytes [100]. Oxaliplatin generally induces mild myelosuppression with only a small percentage of patients experiencing severe anemia [101].

Emetogenicity is most severe with cisplatin treatment amongst the clinically used platinum drugs [102]. A very high percentage of cisplatin-treated patients experience severe nausea and vomiting. While these adverse effects are also common with oxaliplatin and carboplatin treatment the symptoms are generally mild to moderate compared to those with cisplatin treatment [66,101].

Immunological side effects including hypersensitivity reactions associated with respiratory dysfunction, gastrointestinal discomfort and rashes, have been common for platinate drugs [103–105]. Cisplatin may also cause anaphylactic shock, asthma or hives [106]. These adverse effects are somewhat less frequent with carboplatin and oxaliplatin treatment but can be equally severe [107], necessitating either withdrawal from the drug use or premedication with steroids and antihistamines [108,109]. Interestingly, patients were reported to be cross-reactive to several platinum drugs [103].

There is some evidence indicating that platinum drugs are mutagenic. Particularly, the risk of developing secondary leukemia while receiving platinum based chemotherapy can increase by 4-fold [110]. Additionally, platinum compounds can cross the placenta and cause fetal damage.

Some of the adverse events have become manageable by concomitant clinical strategies. These include pre-hydration and forced diuresis, which reduces nephrotoxicity [111], continuous administration of anti-emetics such as serotonin antagonists, which reduce nausea/vomiting [112], co-administration of amifostine, which somewhat reduces the nephro- and neurotoxicity [113], and various other chemoprotectant approaches. However, these additional procedures have limited benefit, require complex dosage regimens to minimize drug–drug interactions, and at times have irreversible side effects of their own.

Another major problem associated with platinum therapy is the development of drug resistance. For example, 95% of patients with SCLC relapse after initial treatment because of acquired drug resistance, resulting in extremely low 5-year survival rates [114]. Studies have linked the development of platinum drug resistance to altered drug transport [115], glutathione system [116], DNA repair and apoptotic genes [117]. Approaches to overcome platinum drug resistance have also been widely investigated. Some of these approaches have shown limited success. In particular, intraperitoneal administration of cisplatin appears to be superior over intravenous administration in selected patients with ovarian cancer [118]. However, new drugs and modalities to overcome or prevent platinum drug resistance remain an unmet need for majority of malignancies.

Altogether, albeit platinum therapy enabled major advancements in oncology it is often hindered by adverse side effects of platinum drugs, and development of drug resistance. Additional hurdles include low bioavailability of platinum drugs and their low water solubility (which necessitates prolonged infusions of the drug in the patient). These hurdles severely limit the patient’s quality of life. In an extensive effort to overcome these

limitations many new platinum and other metal complexes were discovered and testing of as anticancer agents [119]. Nevertheless only few of these agents reached an advanced stage of clinical development (Table 2) and even less made it to the clinic (Table 1). Only three platinum drugs—cisplatin, carboplatin and oxaliplatin, have received a worldwide clinical approval. With the inventory of failed platinum complexes becoming ever more voluminous (Table 4), the prospect of finding active platinum complexes with a simple set of ligands and better therapeutic properties in comparison to cisplatin, carboplatin and oxaliplatin appears bleak. This has necessitated exploration of alternate strategies such as the use of targeted platinum complexes or carrier-based delivery approaches.

5. Platinum drug delivery using nanocarriers

Carrier-based delivery of anticancer drugs has received much attention in recent years because of its potential for improving drug efficacy, reducing unwanted side effects and circumventing cellular accumulation mediated drug resistance (Fig. 2). Such delivery approaches often exploit differences between normal tissues and tumors to increase the selectivity of the drug towards its intended target. Specifically, the enhanced permeability and retention effect (EPR effect) is based on the increased permeability of macromolecules in the tumor containing tissues coupled with poor lymphatic clearance and slow venous return in these tissues [120,121]. While most clinically used anticancer drugs have low molecular weight and rapidly pass through the membranes of both normal and cancerous tissues, the drugs coupled to liposomes, lipid particles, micelles and various other polymeric carriers selectively accumulate in tumors [122]. The nanoscale size of these carriers is important, since it prevents their extravasation in normal tissues and removal by renal clearance. As a result, long circulating polymeric carriers have greater exposure to the tumor sites compared to low molecular drugs, which are rapidly cleared from circulation. Thus EPR results in passive targeting of polymeric drugs to the tumors. This in some cases can be further enhanced by active targeting using ligands or antibodies attached to the polymeric drug that can selectively bind to tumor-specific moieties displayed at the target cells. Such moieties are generally transporters, antigens or receptors with increased quantity or functionality in tumors compared to normal tissues [123,124]. As further discussed below, the delivery of the platinum complexes using polymeric carriers has largely focused on passive targeting with relatively fewer examples of active targeting available (Table 5).

Generally, the drug is incorporated into polymeric carriers via encapsulation, covalent attachment (conjugation), or complexation/ coordination binding. Most of the platinum complexes are loaded into the carriers using encapsulation methods. Methods involving conjugation and coordination binding have mostly involved cisplatin or DACHPt derivatives due to the presence of replaceable X_2 ligands in these complexes, which are not required for drug activity. A few studies employed conjugation of drug to polymers containing amino groups, which replaced the A_2 ligands in the complexes.

A frequently occurring motif in the drug delivery systems is a hydrophilic polymer polyethylene glycol (PEG), also known as polyethylene oxide (PEO) or polyoxyethylene (POE). This polymer is inexpensive, has good biocompatibility and has been approved for internal applications in humans by regulatory agencies [124]. PEG chains of molecular

weights ranging from 1 to 15kDa have been widely employed as steric protectors in various nano-particulate systems [125]. Owing to its high aqueous solubility, high mobility and large exclusion volume, hydrated PEG forms a dense brush of polymer chains stretching out and covering the particle surface [126]. This minimizes the interfacial free energy of the particle surface and obstructs its interaction with other particles, proteins and other biomolecules in blood, and cells. PEG coating hence serves to reduce particle opsonization and is intended to make the carrier less recognizable by the reticuloendothelial system (RES) in the liver and the spleen [125,127]. Although a complete 'stealth' effect has rarely been demonstrated, prolonged blood circulation of the PEG coated carrier has widely been observed and is considered crucial to its passive accumulation into tumors. Beside surface characteristics, the size and shape of the nanocarriers also play roles in avoidance of various clearance mechanisms and contribute into EPR-mediated tumor accumulation. Although there is no ultimate answer on what is the size limit for tumor extravasation, it is generally considered that particles with diameters <200 nm are more effective [128]. It is expected that the particle characteristics favorable for the desired pharmacokinetic profile and therapeutic index need to be tailored for each particular nanocarrier.

5.1. Clinical stage liposomal formulations for platinum complexes

Liposomes are lipid bilayer vesicles with an aqueous interior, usually prepared from a variety of amphiphilic phospholipids (Fig. 3). Since their discovery by Bangham and colleagues [129], liposomes became the pharmaceutical carriers of choice for numerous practical applications. Several liposomal drug formulations have been approved, and many more are under clinical evaluation [130]. One major advantage of this technology is its ability to work with both hydrophobic and hydrophilic drugs; hydrophobic drugs can be enclosed within the phospholipid bilayers, while hydrophilic drugs can be entrapped in the aqueous cavity [131]. The physicochemical characteristics of liposomes (size, charge and surface properties) are manageable. Thus, the size of the carrier could be adjusted by the choice of an extrusion membrane of defined pore size, and the surface properties by appropriate composition of phospholipids [131]. To avoid the recognition by RES system and increase blood-circulation time, stealth liposomes with PEG molecules attached to their surface were developed. Moreover, by modification of the terminal PEG molecule, such liposomes can be conjugated with different targeting moieties (Fig. 3). Since the literature related to liposomal delivery of platinum complexes is extensive, the following discussion is limited to formulations, which currently are or had been in past under clinical evaluation (Table 5).

Lipoplatin (Regulon, Inc.) is one of the most promising liposomal platinum drug formulations under clinical investigation [132]. This formulation is prepared using soy phosphatidylcholine (SPC-3), cholesterol, dipalmitoyl phosphatidylglycerol (DPPG) and methoxy-PEG-distearoyl phosphatidylethanolamine (mPEG2000-DSPE). Lipoplatin comprises ~9% cisplatin and ~91% lipids (w/w) corresponding to a drug-to-lipid ratio of 1:10 [133]. Its particle size is about 110 nm. Pre-clinical studies of Lipoplatin in mice, rats and in severe combined immunodeficient mice reported that it has lower side effects, and notably less nephrotoxicity compared to cisplatin [134]. Studies in dogs demonstrated that Lipoplatin can be administered without the need for concurrent hydration protocols [135].

Same liposomal carriers (with a reporter gene incorporated) were shown to extravasate through defects of the leaky tumor vasculature and concentrate in solid tumors [136].

Phase I human studies of Lipoplatin albeit revealed its mild hematological and gastrointestinal toxicity, did not show most other side effects characteristic of cisplatin treatment such as nephro-, neuro- and ototoxicity, as well as hair loss [137]. Prolonged blood circulation of Lipoplatin with a half-life of 3–5 days depending on the dose was also observed, which was attributed to inclusion of PEGylated phospholipids [137]. In addition, elevated accumulation of platinum in tumor tissues (10–50 times) in comparison with adjacent normal tissues were detected [138].

Phase II studies of Lipoplatin in combination with gemcitabine also demonstrated significant clinical benefit of the combination regimen in a number of patients previously resistant to first- or second-line chemotherapy [139]. Lipoplatin has received orphan drug status by the European Medicines Agency (EMA) for treatment of pancreatic adenocarcinoma [140]. Its efficacy has been subsequently demonstrated in various Phase II/III studies, such as NSCLC [141], HER2/neu negative metastatic breast cancer [142] and advanced gastric cancer [143]. In other human studies using Lipoplatin platinum accumulation in tumors and metastases was shown to be higher than that in adjacent normal tissue 20 h after i.v. administration [138]. Increased entry of Lipoplatin into cells could be due to its high levels of accumulation in tumors as well as fusion of liposomes with the tumor cell membrane mediated by the fusogenic anionic lipid DPPG [138,140].

SPI-77 (Alza Pharmaceuticals formerly Sequus Pharmaceuticals) is another liposomal cisplatin, recently underwent clinical investigation. The formulation encapsulates cisplatin in stealth liposomes composed of hydrogenated soy phosphatidylcholine, cholesterol and PEG-modified phosphatidylethanolamine [144]. SPI-77 is prepared by adding the lipids dissolved in ethanol to an aqueous solution of cisplatin and subsequent size extrusion of the resulting dispersion through a 100nm pore size filter [145]. The drug loading is much lower (drug to lipid ratio ~1:70) compared to Lipoplatin. Preclinical studies in tumor-bearing mice indicated superior antitumor activity compared to cisplatin with higher cumulative doses of SPI-77 being well tolerated [145]. SPI-77-treated animals had a 28-fold higher tumor exposure to platinum with a 4-fold lower platinum exposure to kidneys relative to cisplatin-treated animals [145].

Phase I studies of SPI-77 were conducted in both adult and pediatric patients with advanced cancer not amenable to other cancer treatments. Despite about 100-fold higher plasma platinum levels than those reported following comparable doses of cisplatin, SPI-77 was well tolerated in all patients with lack of toxicities typical of conventional cisplatin regimen [146]. Haematological toxicities were also reported to be mild; majority of patients did not require antiemetics, lacked clinically significant peripheral neuropathy, and required no additional hydration or forced diuresis [146]. Similar safety results were obtained in Phase II trials in patients with advanced NSCLC, however the antitumor response was modest, which resulted in early closure of the trial [147]. This could be due to the high stability of liposomes and inefficient release of the drug from the carrier, as evidenced by very low concentrations of free cisplatin observed in plasma as well as significantly reduced tumor

DNA-platination [148]. Two other Phase I trials, one in combination with vinorelbine [149] and another in combination with radiation [150], has also produced modest results. Recent trials in advanced NSCLC [151] and in platinum-sensitive recurring ovarian cancer [152] again indicated moderate antitumor response. This drug did not progress to Phase III because of a lack of activity in Phase II trials. Nevertheless, all these trials demonstrated much higher safety margin with the liposomal-cisplatin and lack of toxicities typical of the free drug. These studies hence reflect the challenge of not only having to deliver platinum to the tumor in a relatively inactive form, but also the subsequent need to achieve good release and activation.

Liposomal formulations of oxaliplatin analogues have also been developed. Aroplatin (L-NDDP, originally Aronex Pharmaceuticals now Agenus, Inc.) is a liposomal formulation of *cis*-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) (NDDP), a structural analogue of oxaliplatin with two branched aliphatic leaving groups of ten carbon atoms, incorporated in a matrix of dimyristoylphosphatidylcholine and dimyristoyl phosphatidylglycerol (DMPG) (Table 5). Due to the lipophilic character of NDDP imparted by the aliphatic side chains of this drug efficiently incorporates in the lipid compartment of the liposomes (drug to lipid ratio ~1:15) [153]. Interestingly, NDDP is a liposome-dependent drug where the liposomal carrier plays a crucial role in mediating the cytotoxicity and antitumor activity of the drug, while the free drug itself has a very low cytotoxicity [154]. Suggested mechanism of biological activity of NDDP includes the formation of active intermediates *in situ* within the lipid bilayers, where the activation reaction was reported to be highly dependent on the presence of DMPG and the lipophilic leaving group of NDDP [155]. Preclinical studies in mice has shown L-NDDP activity against L1210 leukemia resistant to cisplatin, B16 melanoma and murine M5076 reticulosarcoma exhibited without any significant nephrotoxicity [156]. Studies in dogs also indicated better tolerability of L-NDDP, accompanied with minimal renal dysfunction, and no cumulative myelosuppression or liver dysfunction [157].

Subsequently, several Phase I trials of L-NDDP were conducted in patients with tumors localized to a body cavity such as in malignant pleural mesothelioma [158], ovarian cancer [159] and peritoneal carcinomatosis and sarcomatosis [160]. The drug was well tolerated in patients with high peritoneal exposure compared to the plasma compartment [161]. A Phase II trial of L-NDDP in mesothelioma patient population however revealed significant but manageable toxicity. Although pathologic responses were highly encouraging, areas of mesothelioma not in direct communication with the pleural space evaded drug exposure, resulting in limited efficacy in some patients [162]. In patients with advanced colorectal cancer that was refractory to 5-FU/leucovorin, capecitabine or irinotecan, a Phase II study reported good tolerability and modest tumor response with single-agent oxaliplatin [163].

Lipoxal (Regulon, Inc.) is a liposomal oxaliplatin formulation produced using similar technology as Lipoplatin. *In vitro* studies reported reduced cytotoxicity of Lipoxal against tumor cells [164] however *in vivo* experiments reported equivalent efficacy with lower toxicity compared to the free drug [165]. In Phase I study with advanced gastrointestinal cancer patients, Lipoxal was well-tolerated and exhibited greatly reduced side effects

compared to oxaliplatin, especially lower myelotoxicity and gastrointestinal tract toxicities [165]. There is however no reports of any ongoing Phase II study.

MBP-426 (Mebiopharm Co., Ltd) is a transferrin (Tf)-conjugated N-glutaryl phosphatidylethanolamine liposomal formulation of oxaliplatin, which can provide preferential tumor targeting by binding to transferrin receptors [166]. Direct drug binding to Tf receptor (TfR) and enhanced drug delivery mediated via uptake of MBP-426 by TfR was demonstrated in human cancer cells *in vitro* [166]. MBP-426 also demonstrated potent anticancer preclinical activity and has entered clinical trials. Results from Phase I clinical trials for solid tumors were recently reported [167,168] and Phase II studies are ongoing.

5.2. Lipid coated nanocapsules for platinum complexes

Burger et al. in 2002 reported a method for preparation of cisplatin nanocapsules containing platinum complexes with high encapsulation efficiency [169]. These nanocapsules are close relatives of the liposomal formulations described above but are characterized by much higher drug loading capacity (Fig. 2). According to this method nanoscale sized precipitates of cisplatin covered with lipid bilayer were obtained by repeated freeze thaw cycles of a concentrated aqueous solution of cisplatin mixed with negatively charged phospholipids (ζ-potential about −40 mV). The resulting nanocapsules were bean shaped, with a heterogeneous size distribution ranging from 50 to 250 nm, and a negative-potential [170]. Interestingly, analysis of the contents of the nanocapsules revealed a core composed of over 80% cisplatin covered with a lipid bilayer [170]. The average drug-to-lipid ratio in the nanocapsules exceeded than 10:1. This formulation was further improved by including cholesterol and PEG-modified lipids that increased stability of the lipid coat [171]. The cytotoxicity of the cisplatin nanocapsules was more than two-fold greater than that of the free drug. These nanocapsules were taken up in cells by caveolae-mediated endocytosis or clathrin-mediated in cells lacking caveolin-1 expression [172].

The cisplatin nanocapsules displayed rapid accumulation in the liver, and more gradual accumulation in the lung and the spleen, unexpectedly, similar plasma and tumor platinum concentrations compare to the free drug. This formulation of cisplatin did not show enhanced antitumor efficacy in an animal model of ovarian cancer [173]. The authors attributed this to insufficient accumulation at of the nanocapsules the tumor site, rapid adsorption of plasma proteins on the nanocapsules leading to disruption of capsule structure, and probably the wrong choice of tumor model [174]. It was also suggested that the high encapsulation efficiency could actually play and adverse role in drug delivery to the tumor. At the administered dose nanocapsules has much lower amount of particles compared to similar liposomal formulations, which could be insufficient to saturate the RES, leading to preferential delivery of the nanocapsules to the liver and spleen, and hence inadequate amounts available at the tumor [174].

Nonetheless, such nanocapsulation technology has shown promise, in its ability to remarkably improve the drug loading and to encapsulate other platinum drugs such as carboplatin [175]. The authors envision that further improvements, such as strategies to mediate endosomal escape, active targeting approaches and optimization of plasma stability, nanocapsules formulations might translate to the clinic.

5.3. Polymer–platinum conjugates

This concept, originally proposed by Ringsdorf [176], is based on covalent attachment of the drug to a hydrophilic polymer (Fig. 2). Built upon by Duncan, Kopeček and others [11,177], the approach has proven promising with nearly a dozen polymeric conjugates in clinical trials. Although most polymer–drug conjugates that have advanced to the clinic rely only on the EPR effect, numerous preclinical studies suggest opportunities for the tumor-specific targeting of polymer conjugates using antibodies, peptides and other targeting moieties [178]. Polymer biocompatibility, presence of proper drug-binding groups and a suitable linker chemistry allowing drug release and access to the pharmacological target are important parameters that need to be taken into account upon development of polymer–drug conjugates. Specifically, polymers containing nitrogen donors such as amines or oxygen donors such as carboxylates or hydroxyl groups can bind platinum complexes [179]. These groups can be present either in the polymer main chain, be terminal, or pendant. Depending upon the platinum complex structure and the drug-binding groups type the complexation of the drug to the polymer can be monodentate or bidentate.

The N-(2-hydroxypropyl)methacrylamide (HPMA) is the most frequently used polymer for conjugation of anticancer compounds (Fig. 4). Previously it was used safely as a plasma expander. The first promising HPMA anticancer drug conjugates used doxorubicin and paclitaxel as biological agents [11]. The HPMA-drug conjugates were optimized to ensure that polymer size is large enough to take advantage of the EPR effect, yet small enough to allow for the ultimate renal excretion. One of the HPMA–copolymer platinates, AP5280, contains cisplatin linked through a malonate end group of the polymer [180]. This conjugate with platinum loading of approximately 10% by weight was at least 20-fold less toxic than cisplatin *in vivo* and showed 19-fold increase in platinum accumulation in B16 mouse tumors. On the basis of the improved therapeutic index evidenced in several other murine tumor models [181], AP5280 (Access Pharmaceuticals, Inc.) was advanced into clinical trials. In Phase I/II studies much reduced platinum-related toxicity and promising efficacy was observed [182,183]. However, further development of the formulation was terminated as the company opted to focus its development resources on a third-generation polymer-conjugate AP5346, which is based on improved polymer carrier conjugated to a more potent DACHPt moiety.

AP5346 or ProLindac (Access Pharmaceuticals, Inc.) is the HPMA–platinum conjugate currently under clinical development (Table 5, Fig. 4). This 25 kDa polymeric drug conjugate contains DACHPt bound to hydrophilic HPMA through a pH-sensitive amidomalonate chelating group [184,185]. The amidomalonate–platinum chelate is stable at physiological pH but releases the DACHPt at lower pH of extracellular space of hypoxic tumors or intracellular endosomal–lysosomal compartments [186]. ProLindac has shown efficacy similar to oxaliplatin in a panel of breast, ovarian, lung and prostate cancer cell lines [187]. Pre-clinical studies in several mouse tumor models, including both syngeneic murine and human tumor xenograft models suggested that compared to oxaliplatin ProLindac displays superior tumor growth inhibition, reduced toxicity towards normal cells, increased and more sustained plasma platinum levels, and up-to 14-fold increased platinum delivery to the tumor [184]. Specifically, ProLindac has proven to be better than oxaliplatin

in three human colon xenograft models (Colo-26, HT-29, and HCT116), as well as in the L1210 murine leukemia and 0157 hybridoma models [188].

In a Phase I trial ProLindac was well tolerated and shown no neutropenia or significant hematologic toxicity in patients with advanced solid tumors [189]. Partial responses were observed in patients with relapsed melanoma, ovarian cancer, and stable disease was attained in patients with esophageal carcinoma, cisplatin-resistant carcinoma of the cervix, thyroid cancer, and melanoma [189]. The Phase I study demonstrated that high doses of ProLindac could be administered safely when patients were adequately pretreated with antiemetics and hydration [189]. A Phase I/II trial evaluated the anticancer activity of ProLindac as a single agent for advanced ovarian cancer, previously treated with organoplatins (except oxaliplatin) [188]. Considering the long half-life of ProLindac observed in patients, weekly doses were considered unsuitable and dosage was reduced to a two-hour i.v. infusion every two or three weeks [190]. This treatment was also well tolerated and resulted in the disease stabilization in a significant number of patients [188,190]. The side effects experienced by patients were mild at grades 1–2, and without any signs of acute neurotoxicity [188]. The company, Access Pharmaceuticals, has also tested a new ProLindac formulation manufactured using a scalable process, intended for future clinical trials. No adverse events were reported while the formulation retained the beneficial disease stabilization as seen previously [28]. ProLindac is currently in several Phase II combination studies with drugs such as paclitaxel and gemcitabine in patients with solid tumor indications including colorectal and ovarian cancer. In addition, ProLindac has been licensed to pharmaceutical companies in China and South Korea where further Phase II combination studies will be conducted in specific tumor types [191].

Polyphosphazenes are biodegradable linear polymers with an inorganic backbone composed of alternating nitrogen and organically functionalized phosphorus groups and reactive pendant side groups that may be organic, organometallic or inorganic in nature [192] (Fig. 4). Functionalization with amino acids makes the polymer hydrolytically degradable [193]. Sohn and colleagues have studied a variety of aspartic and glutamic acid derivatized polyphosphazenes conjugates of platinum drugs. From a series of conjugates incorporating platinum complexes, DACHPt containing complex glutamate derivatized polyphosphazene demonstrated high potency both *in vitro* and *in vivo*, lacked cross-resistance to cisplatin and maintained good water solubility [194,195]. A variety of other modified polyphosphazenes–platinum conjugates were also synthesized and evaluated *in vivo* [196,197]. The most promising results however involved amphiphilic polyphosphazene modified with PEG chains. The conjugate had high cytotoxicity against human cancer cell lines and was found to selectively accumulate in tumor tissue [198]. Recently, amphiphilic polyphosphazenes–platinum conjugates with the ability to assemble into stable nanoparticles of size 100–200 nm were also reported [199]. In addition, thermosensitive cyclotriphosphazene–platinum conjugates with critical solution temperature below body temperature were developed [196]. This conjugate had antitumor activity comparable to the cisplatin in murine leukemia L1210 model although possessed much lower toxicity.

Various other synthetic polymers have also been investigated as carriers for platinum drugs such as cyclodextrines, polyaminoacids and others. Neuse and colleagues have reported

several formulations where cisplatin was bound either to the main chain [200,201] or to pendant groups [202,203] of water-soluble polyamides. Polyaspartamides were found to be particularly useful for forming platinum complexes yielding a platinum loading ranging from 4 to 15% [202–204]. Platination was brought about by chelation of carriers containing ethylenediamine ligands with tetrachloroplatinate, yielding cisplatin-like species. The structural properties of the various polymers and particularly the nature of the ligand groups affected the release of platinum hence strongly influencing the anti-proliferative activity of the complexes [201,205,206]. Lack of cross-resistance with cisplatin was also shown in cisplatin-resistant A2780-cis cells [207]. Studies in mice demonstrated lower toxicity of these conjugates with up to 20-times higher maximum tolerated dose in some cases relative to cisplatin [208]. Platinum-conjugates, bound on polymeric carriers through chelation with carboxyl or hydroxyl functionalities have also been investigated. Such carriers incorporated from 5% to 15% of DACHPt as the platinum drug and exhibited a more rapid release profile compared to amine polymers [209–211]. Selected conjugates had cytotoxicity on par with cisplatin against the sensitive HeLa and A2780 cancer lines, and up to 10-times higher than cisplatin against the multidrug-resistant Colo 320 DM and A2780-cis cell lines [209,212]. Favorable pharmacokinetics, reduced toxicity and enhanced selectivity of antitumor activity were also reported for a set of these conjugates [213].

5.4. Dendrimers in platinum delivery

Dendrimers are of considerable interest for drug delivery and targeting of platinum-drugs to a large extent due to their highly uniform structure and narrow size distribution, a challenge with some of the other polymeric technologies [214]. Dendrimers are highly branched polymers with multiple end groups which allow encapsulation or conjugation of numerous drug molecules at the surface or in the core [214] (Fig. 2). The dendrimer generation refers to the number of repeated branching cycles performed during synthesis and defines the number of branches and terminal groups in the dendrimer structure. With increasing generation number, dendrimer diameter increases linearly, however the number of functional groups on the periphery increases exponentially [215]. This in-turn determines the extent of drug loading and kinetics of drug release. Further modulation in loading and release can be permitted by incorporation of various degradable linkages between the drug and dendrimer [216]. There are numerous forms of dendrimers that are made from polyamidoamines, polyamines, polypeptides, poly(aryl ethers), polyesters, carbohydrates or DNA [217].

The most frequently reported are polyamidoamines (PAMAM), which are available commercially with an extensive range of generations and end functional groups [218]. PAMAM dendrimers at the ends of their branches can carry either amino groups (the “full-generation” dendrimer) or carboxylate groups (the “half-generation” carries [219]. One of the earliest works on conjugates PAMAM dendrimers with platinum was reported by Duncan and co-workers [220]. In this cisplatin was linked to the dendrimer G3.5 through the functionalized sodium carboxylate surface. The conjugate demonstrated increased solubility, high loading capacity (20–25% by weight), decreased systemic toxicity, selective accumulation in solid tumors and anticancer activity. Specifically, dendrimer–cisplatin conjugate induced retardation of growth of the subcutaneous B16F10 murine melanoma,

while cisplatin alone failed to show any anti-tumor activity [220]. Interestingly, Kirkpatrick et al. showed that in such conjugates some drug remains bound to the dendrimer even after prolonged incubation (60 °C, over a week), which is in compliance with formation of additional bonds. Also drug loading and its release profile depend on the generation of dendrimers [221]. In another study amino-terminated PAMAM dendrimer was conjugated to potassium tetrachloroplatinate. However, along with the terminal modification of the PAMAM branches at the dendrimer surface, a considerable portion of platinum complexes could link with the secondary and terminal amino groups within the dendrimer core, which may slow down the drug release [222]. Additionally, the reaction of the PAMAM dendrimer with the tetrachloroplatinate can induce cross-linking and formation of large aggregates due to the presence of multiple conjugating groups. Such complication was for example observed by Bellis et al. who modified poly(propyleneimine) dendrimers [223].

DACHPt conjugation to dendrimers has also been reported. Howell et al. were able to produce well-defined conjugates of PAMAM dendrimers (G4.5) with carboxylic acid terminal groups containing up-to 40 DACHPt moieties at the surface [224]. In this study the bulky DACH ligand groups were expected to reduce the probability of inclusion of the platinum complexes with interior amines within the dendrimers of this size. These conjugates retained water solubility and displayed sustained release of active platinum species over a 24 h period under physiological conditions [225]. Current literature also presents few other studies on dendrimeric-platinum anticancer drugs [226–228], but no such study has warranted further development of these conjugates due to their relatively modest efficiency.

5.5. Platinum complexes in nanotubes

Nanotubes are tubular structures with at least one dimension, a diameter, in the nanometer scale [229] (Fig. 2). Examples include Single-Walled Carbon Nanotubes (SWCNTs) or Multi-Walled Carbon Nanotubes (MWCNTs) as well as cyclic peptide nanotubes and template-synthesized nanotubes. Nanotubes offer some interesting advantages relative to spherical nanoparticles for drug delivery applications. The presence of the open ends and large inner volume (relative to the volume of the tube) permit incorporation of pharmaceutical species at high loading capacities with ease. Additionally, the inner and outer surfaces of the nanotubes can be differentially modified with chemical or biochemical functionalities and this can be exploited for conjugating targeting ligands or grafting PEG to increase biocompatibility of the nanotubes [230]. The toxicity of SWCNTs appears to be low despite long term accumulation *in vivo* [231].

Ajima et al. demonstrated possibility to incorporate and release cisplatin in SWCNTs. The released cisplatin retained ability to kill human lung cancer cells while the SWCNTs themselves were not cytotoxic [232]. Molecular modeling studies have shown that to host cisplatin the radius of carbon nanotubes must be at least 4.8 Å while the maximum uptake of cisplatin is observed when nanotube radius is approximately 5.3 Å [233]. Although this model represents only a first approximation, it provides overall guidelines towards selection of appropriately sized nanotubes [234]. Cisplatin loading and release was also altered by chemical modification of the structural holes in the SWCNTs and the overall amounts of

incorporated and released cisplatin were increased by modification compared to unmodified nanotubes [235]. Moreover, the *in vitro* anticancer activity of cisplatin loaded in modified nanotubes was also increased and such drug, loaded nanotubes displayed a marked tumor suppression *in vivo* [236]. Interestingly the unloaded nanotubes also exhibited some anti-tumor effect.

Lippard and colleagues produced conjugates of amine-functionalized water-soluble SWCNTs with a platinum prodrug derivatized from cisplatin [237]. The Pt(IV) complex, c,c,t-[$Pt(NH_3)_2Cl_2(OEt)(O_2CCH_2CH_2CO_2H)$], was tethered to the surface of the carbon nanotubes through peptide linkages. The SWNTs were taken into testicular cancer cells by endocytosis, where the drop in pH facilitated reductive release of the Pt(II) core complex. The cytotoxicity of the free platinum(IV) complex was shown to increase by >100-fold upon conjugation with the nanotubes [237]. Further studies were carried out using a folate modiied nanotubes, which demonstrated selective accumulation and enhanced antitumor activity towards folate receptor-positive cancer cells [238]. Targeted nanotube–platinum conjugates have also been reported by Bhirde et al., who used epidermal growth factor (EGF) attached to SWNTs to specifically target EGF overexpressing head and neck squamous carcinoma cells [239]. The targeted nanotubes also showed selective accumulation in mice xenografts leading to significant regression of tumor growth compared to controls [240].

5.6. Platinum delivery using polymer micelles

Polymer micelles (Fig. 5) are aggregates of block copolymers with the core-shell architecture [241]. They can entrap drugs, generally in the micelle core and increase the apparent solubility of a drug, thus greatly exceeding its intrinsic solubility in water. The ease of micelle preparation and drug loading, along with the ability to alter chemical composition, total molecular mass, and block lengths of the block copolymers, permits to precisely control the size and morphology of the micelles, which is of importance for their pharmaceutical use [242]. Polymer micelle-based compositions of various drugs have been investigated for parenteral, oral [243–245], nasal [246,247], and ocular [248,249] delivery routes. Many of these studies demonstrated clear benefits including increased bioavailability or reduced adverse effects of the drugs. The block copolymer micelles can be sub-categorized in at least two main groups, depending upon the type of intermolecular forces driving the segregation of the core-forming block in the aqueous environment. The first group is amphiphilic block copolymer micelles having the core formed by hydrophobic interactions amongst the water-insoluble blocks of the block copolymer and the shell formed by the water soluble blocks [10]. They self-assemble due to aggregation of amphiphilic block copolymers having hydrophobic and hydrophilic blocks in water at concentrations above critical micelle concentration (CMC). The second group is block ionomer complexes (BICs) or polyion complex (PICs) micelles, which have the core formed by electrostatic interactions of the polyion block of the block copolymer with oppositely charged species—natural and synthetic polyelectrolytes (including ionic blocks of other block copolymers), surfactants, and metal ions [250–252]. One specific type of BICs, the block copolymer–metal complex micelles is spontaneously formed in aqueous media as a result of electrostatic

neutralization [253] and/or coordination of transition metal ions with the polyion blocks [254,255].

Amphiphilic block copolymer micelles are well-suited for solubilization of hydrophobic drugs [10,256,257]. Some of such micelles display unprecedented high loading capacity of nearly 50 wt.% with respect to very poorly soluble single drugs as well as drug combinations [258,259]. Generally, the spatial distribution of the solubilized drug within the micelle depends upon the drug polarity. Hydrophobic drugs distribute into the micelle core while drugs with intermediate and higher polarity occupy more peripheral positions [10]. The drug distribution correlates well with the strength of association between the micelle and the drug and in turn determines the release profile of the drug with more peripherally located drug more amenable to release [10]. Hydrophilic drugs can be adsorbed in the micelle corona, however this interaction is usually weak. The same holds true for cisplatin and some other platinum drugs, which are too soluble in aqueous media to be encapsulated in the hydrophobic micelle core. This limitation has been overcome using block ionomers, which can form polymer–metal complexes. Incorporation of platinum drugs into such complexes proceeds though formation of coordination bonds between these platinates and the polyion block of the block copolymer, which also induces the micelle formation [179]. Copolymers containing polycarboxylates as the ionic blocks has been the choice for this purpose due to the ability of carboxylic groups to substitute anionic ligands X_2 in the platinum complexes, such as chloride ligands in cisplatin. Most platinum complexes have two leaving groups and can form complexes with the copolymer through a bidentate binding. Thus loading of BICs with platinum drugs can also result in the cross-linking of the micelle core involving two carboxylic groups located in two separate block ionomer chains [254]. The low nucleophilicity of carboxylic groups permits release of the active platinates at the physiological concentrations of salts. The release of platinum complexes depends on the external salt conditions, pH and overall BIC micelle stability [260,261]. In *in vivo* conditions, it is likely that the micelle disruption precedes any significant drug release from the carrier. This may be due to strong dilution of the BIC micelles in the blood that favors the formation of the platinum-bound copolymer unimers. Biologically abundant counterions having access to the platinum–polymer complex may subsequently promote the drug release by ligand exchange [179].

Poly(amino acid) based copolymers, such as poly(aspartic acid), PAsp and poly(glutamic acid), PGlu, have been the most widely used for platinum drug delivery [262]. Kataoka and colleagues were the first to describe complexation of cisplatin with PEG–PAsp [254,263,264] copolymers, which led to the spontaneous formation of stable polymer micelles with high drug loading. Initial studies demonstrated 1) formation of such polymer micelles with the sizes ranging from 20 to 100 nm and narrow size distribution, 2) sustained release of platinum complexes from the micelles via exchange with chloride ions and 3) the dependence of the drug release on the PAsp block length [254]. Under the physiological salt concentrations the micelles were stable for about 10 h, which was followed by their gradual dissociation. Blending of the PEG–PAsp block ionomers with the PAsp homopolymer was shown to alter the micelle size, the micelle decay and the cisplatin release [263]. Studies in mice demonstrated that incorporation of cisplatin in such polymer micelles prevented the

kidney toxicity of the drug, increased circulation of the micelle bound drug in plasma and increased exposure of the drug to the tumors [264].

Further studies were carried out with PGlu-based micelles which have improved stability and drug release characteristics compared to PAsp-based micelles [265]. The sizes of these micelles are about 30nm. In preclinical studies they exhibited prolonged blood circulation and accumulation in solid tumors. Significant antitumor activity was observed in C26 tumor-bearing mice model with some animals showing complete tumor regression without any significant body weight loss typical of the free drug treatment [265]. Notably, histopathological and biochemical studies have not revealed any significant nephrotoxicity of the micelle bound drug, although some transient hepatotoxicity was observed post-treatment [266]. Moreover, these cisplatin-incorporating micelles were found to decrease ototoxicity in a guinea pig model, indicating a safer toxicity profile than cisplatin [267]. This formulation is at the final clinical stage, i.e. Phase III, in Asia under the development name NC-6004 (Nanoplatin; NanoCarrier Co., Ltd.; Japan). Phase I clinical studies demonstrated that NC-6004 has significantly better tolerability than free cisplatin, without inducing significant nephrotoxicity, while other side effects were generally mild [268]. A Phase II study of NC-6004, combined with gemcitabine, in patients with locally advanced or metastatic pancreatic cancer showed that Pt hypersensitivity could be completely inhibited by using prophylactic treatment, and there was no need for pre-hydration, opposing conventional cisplatin treatment. Moreover, in this study, 2 patients treated with NC-6004 showed partial response (11.8%; total number of patients: 17), while stable disease was found in 9 patients (52.9%), resulting in a disease control ratio of 64.7%. Importantly, median overall survival was 12.3 months, which is better than the 7.5 months overall median survival reported for cisplatin/gemcitabine combination [269]. These results suggest that NC-6004/gemcitabin combination could be a substitute for the cisplatin/gemcitabin combination therapy. As for Japan and the USA, a Phase I study of these micelles started in 2012 for various solid tumors and an application for investigational new drug (IND) was submitted to FDA in 2013, respectively.

A second generation of platinate micelles has been recently prepared by using the parent complex of oxaliplatin, i.e. DACHPt [270,271]. The diameter of these micelles was 30 nm, which was comparable to cisplatin-incorporating micelles. The relatively small size of these micelles allowed deep penetration to tumor tissues, even in poorly permeable tumors, such as intractable pancreatic cancer [272] and scirrhous gastric cancer [273], leading to enhanced antitumor efficacy. Moreover, the DACHPt-incorporating micelles were able to overcome acquired resistance to oxaliplatin *in vivo* due to their selective drug release at the perinuclear region, which increased the delivery of the Pt drug to DNA while circumventing resistance mechanisms in the cytoplasm [274]. The ability of these micelles for prolonged chemotherapy cycles was confirmed in a recent paper, by using a transgenic model of spontaneous pancreatic cancer. Accordingly, by injecting the micelles once a week, the mice survival was extended for more than 100 days, preventing the development of intraperitoneal metastasis, while for oxaliplatin, approximately 50% of the animals were dead after 50 days [275]. This micelle formulation is being developed under the name NC-4016 (NanoCarrier Co., Ltd.; Japan), and will be starting a Phase I/II clinical evaluation

at The University of Texas MD Anderson Cancer Center (Houston, TX), against various solid tumors.

Polymer micelles based on biodegradable polyester block copolymer PEG-*b*-polycaprolactone (PEG-*b*-PCL) were also used for incorporation of cisplatin with high encapsulation efficiency. Anti-tumor activity of such micelles was demonstrated *in vitro* and *in vivo* [276]. Another study by Xu et al. described pH responsive polymer micelles with poly2-(N,N-dimethylamino)ethyl methacrylate cores for cisplatin delivery capable of rapid endosomal release of the drug [277]. Such micelles were more active against ovarian tumors compared to non-pH sensitive PEG-*b*-PCL based micelles and cisplatin alone. Graft copolymers were also investigated for cisplatin delivery. Thus, biodegradable poly(beta-aminoester)-*g*-PEG reacted with cis-platin and formed 100–200 nm particles, which displayed similar anticancer activity against SKOV-3 tumor xenografts in mice as cisplatin alone [278]. PEG-*g*-poly((N-amino acidyl)-DL-aspartamide) formed with cisplatin 80–160 nm spherical particles [279]. Such cisplatin-loaded polymer micelles were also modified with folate groups and evaluated against folate receptor positive KB cell-derived tumors. The antitumor efficacy of the folate-modified polymer micelles was less than that of the free cisplatin [280]. However, the mi-cellar form of cisplatin demonstrated significantly lower toxicity than the free drug [280]. PEG-derivatized hyperbranched polyglycerols (HPGs) with hydrophobic cores further functionalized with carboxylate groups were shown to bind up to 10–20% cisplatin (w/w) and form small 5–10 nm micelles [281]. Carboxylated HPGs demonstrated good biocompatibility, and effectively inhibited proliferation of KU-7-luc bladder cancer cells.

Another type of polymer micelles for delivery of cisplatin was prepared by the metal ion condensation, self-assembly and cross-linking of ionic blocks of doubly hydrophilic block copolymers, such as PEG-*b*-(polymethacrylic acid) (PEG-*b*-PMAA). Following removal of the condensing metal ions the soft nanospheres were formed of about 100 nm in diameter, which contained cross-linked PMAA ionic cores surrounded by hydrophilic PEG shells. In aqueous environment such micelles behave as nanoscale ionic gels (nanogels), capable of swelling and changing charge in response to environmental changes (pH or ionic strength) [282].

An important variable in such polymer micelles was the extent of cross-linking which revealed an optimum for efficient drug delivery systems. While at low cross-linking extents the micelle structure was not adequately reinforced, the excessive cross-linking reduced the free volume of the core and led to a decrease in the drug loading capacity [261]. The cross-linked micelles with an optimal cross-linking density exhibited a cisplatin loading capacity of ~30% w/w, were stable against dilution in the body fluids and displayed ability for sustained release of the drug species [261]. They were rapidly internalized in human A2780 ovarian carcinoma cells in culture. Prolonged blood circulation, increased tumor accumulation, enhanced antitumor effect, and reduced toxicity relative to the free drug were also shown for this system [283]. Although a strong accumulation of drug-loaded micelles was also seen in the liver and the spleen, a detailed toxicity analysis did not reveal any untoward toxicity. Targeted delivery of platinum drugs was examined using such cross-linked polymer micelles decorated with the folate groups [284]. Folate-conjugated micelles

were shown to carry their drug cargo selectively to targeted cell populations expressing folate receptors. Furthermore, they also demonstrated superior antitumor efficacy in a xenograft tumor model and a decrease in renal toxicity associated with cisplatin. Recently similar approach was applied to encapsulate DACHPt. This formulation had properties similar to cisplatin-loaded micelles such as high drug loading (~25% w/w), controlled pH dependent release of platinum species, and an improved antitumor activity compared to the free drug (oxaliplatin) [285].

Studies on micelle delivery of platinum complexes other than cisplatin are scarce. Duong et al. reported incorporation of cisplatin derived Pt(IV) into 36 nm micelles while simultaneously cross-linking the micelle core [286]. The approach allowed reduction of Pt(IV) under reductive environment, such as inside the cell, leading to the disintegration of the core-cross-linked micelles. Jadhav et al. reported encapsulation of a hydrophobic and water-insoluble Pt(II) compound, *cis*-$(cha)_2Pt(NO_3)_2$ into amphiphilic cyclotriphosphazene-based micelles [287]. The micelle-encapsulated Pt(II) compound exhibited improved cellular uptake *in vitro*, along with improved pharmacokinetics profile and specific tumor accumulation in rats.

6. Conclusions

Platinum anticancer complexes have made a profound impact on cancer management, but their clinical use has its share of limitations. Almost half a century worth of research effort focused on finding superior platinum complexes, seems to have hit a roadblock. Nanocarrier-based delivery of platinum complexes is a viable alternative that has emerged during the last decade. Liposomal constructs at present numerically lead the domain of platinum-carriers under clinical evaluation, but other new polymeric technologies are becoming increasingly visible. While the focus so far has been on the EPR guided delivery of these constructs to tumor targets, active targeting using specific biomolecular interactions may hold the key to a future therapeutic approach. Recent years have also seen a shift in emphasis from first generation cisplatin analogues as the drug payload to the more effective third generation DACHPt analogues. Most studies described here, demonstrated the ability of carriers to deliver higher platinum dosage at the tumor site, reduce non-target toxicity, and in some cases evade platinum drug resistance, significant milestones as such. However, the potent antitumor response seen in preclinical studies has rarely been translated to humans, a limitation of the current technology, which might impede its rapid penetration to clinic. Regulatory agencies have denied approval to several platinum complexes, which demonstrated better safety profile, but lacked superior antitumor activity compared to free drugs. Clearly the strength of interaction between the platinum drug and the carrier is central to their performance. Therefore, future design of these carriers will have to insure efficient drug release in the tumor environment since only the free platinum complexes are therapeutically effective. Efforts need to be focused on engineering the drug delivery systems with tumor responsive cues to trigger drug release inside the tumors and tumor cells, and codelivery of platinum resistance modulators. Having said that, there are plenty of opportunities for further improvement in this field and the future of some of these technologies appears promising.

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Abbreviations

BIC	block ionomer complexes
CDDP	cisplatin
CMC	critical micelle concentration
CTR1	copper transporter 1
DACHPt	*cis*-dichloro(1,2-diamminocyclohexane) platinum (II)
DMPG	dimyristoyl phosphatidylglycerol
DPPG	dipalmitoyl phosphatidylglycerol
5-FU	5-fluorouracil
HPGs	hyperbranched polyglycerols
HPMA	N-(2-hydroxypropyl) methacrylamide
MWCNTs	multi-walled carbon nanotubes
NDDP	*cis*-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II)
NSCLC	non-small cell lung cancer
OCTs	organic cation transporters
PAMAM	polyamidoamines
PAsp	poly(aspartic acid)
PEG	polyethylene glycol
PEG-*b*-PCL	PEG-*b*-polycaprolactone
PEG-*b*-PMAA	PEG-*b*-(polymethacrylic acid)
PGlu	poly(glutamic acid)
PIC	polyion complex
RES	reticuloendothelial system
SCLC	small cell lung cancer
SPC-3	soy phosphatidylcholine
SWCNTs	single-walled carbon nanotubes

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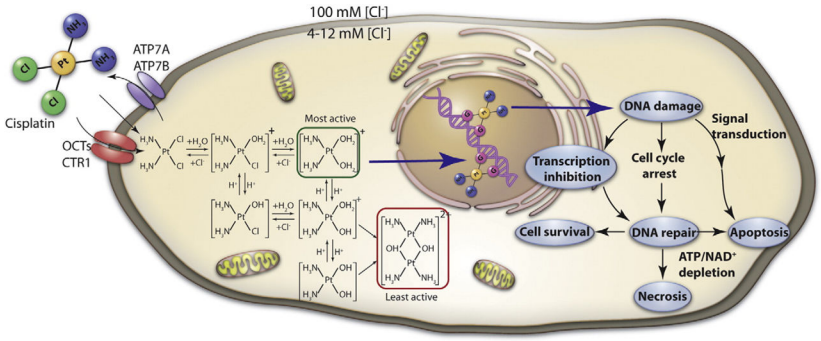


Fig. 1.

Schematic illustration of cellular accumulation of cisplatin, its intracellular aquation, activation of cellular signaling pathways by platinum induced DNA damage and the resultant cell death.

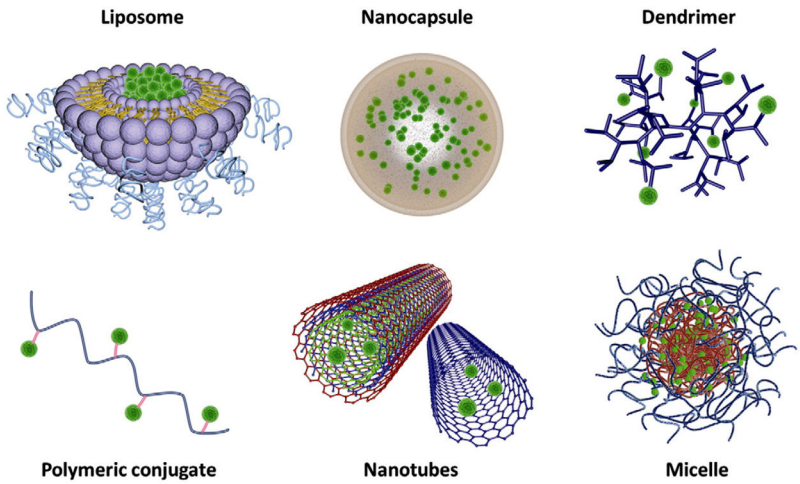


Fig. 2.

Various therapeutic macromolecular carriers for platinum drug delivery currently under preclinical and clinical development.

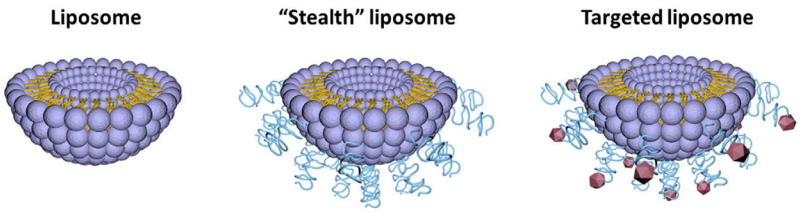


Fig. 3.

Schematic illustration of conventional, 'stealth' and targeted liposomal platforms for platinum drug delivery. Liposomes can be made 'stealth' by incorporation of PEG-conjugated phospholipids or by incorporation of PEG containing polymers such as Pluronics. Further conjugation of a targeting ligand can be achieved by using a functionalized PEG chain.

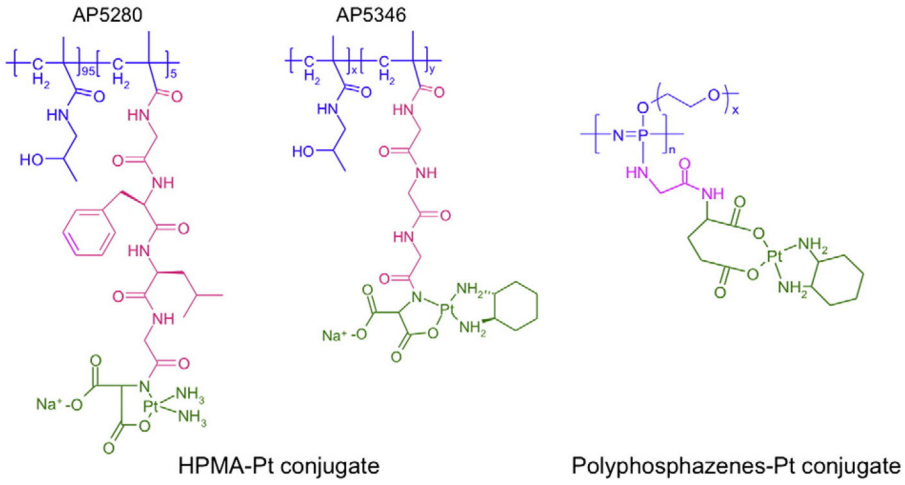


Fig. 4.
Chemical structures of polymer–platinum conjugates.

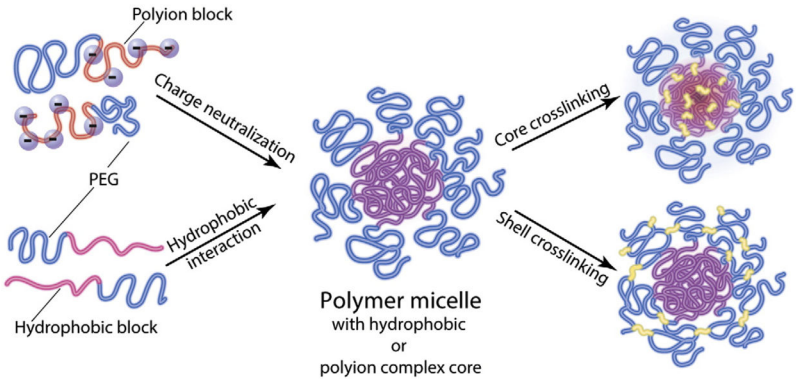


Fig. 5.

Schematic illustration of polymer micelle platforms for platinum drug delivery.

Table 1

Platinum complexes in current clinical use.

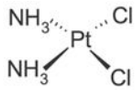
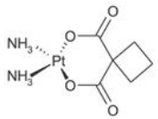
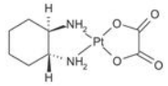
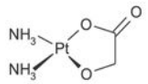
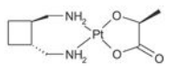
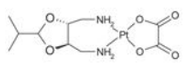
Complex	Brand names/ Synonyms	Year approved	Structure	Non-leaving ligands, A_2 (number of ligands)	Leaving ligands, X_2 (number of ligands)	Market status	Clinical use
Cisplatin	Abiplatin® Platinex® Platiblastin® Platosin® Briplatin® Randa® Cisplamerck® Platinol®	1979		Ammine (2)	Chloride (2)	Worldwide	Metastatic testicular and ovarian tumors, advanced bladder cancer
Carboplatin	Carbomerck® Paraplatin®	1989		Ammine (2)	1,1-Cyclobutanedicarboxylate (1)	Worldwide	Advanced ovarian carcinoma
Oxaliplatin	Dacotin® Eloxatin®	2002		1,2-Cyclohexanediammine (1)	Oxalate (1)	Worldwide	Metastatic colorectal cancer
Nedaplatin	Aqupla®	1996		Ammine (2)	Glycolate (1)	Japan	Small and non-small cell lung cancer, head and neck tumors, oesophageal and bladder tumors, cervix carcinomas
Lobaplatin	Miboplatin	2004		1,2-Cyclo-butanedimethanamine (1)	2-Hydroxy-propanoate (1)	China	Breast, testicular, ovarian, small cell lung and gastric carcinomas, chronic myeloid leukemia
Heptaplatin (SKI2053R)	Sunpla Eptaplatin	2005		2-(1-methyl ethyl)-1, 3-dioxolane-4,5-dimeth anamine (1)	2-Dioatopropanoate (1)	South Korea	Gastric cancer

Table 2

Platinum complexes in clinical evaluation.

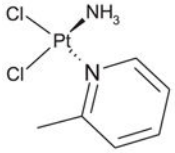
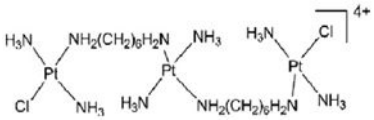
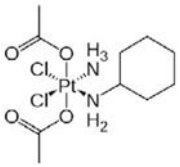
Complex	Synonyms	Structure	Regulatory status	Clinical use
Picoplatin	JM473		Phase II	Metastatic colorectal cancer
	NX473		Phase II	Metastatic castration-resistant prostate cancer
	ZD0473			
	AMD0473		Phase II	Refractory or resistant ovarian cancer
	Amminedichloro (2-methylpyridine)platinum(II)		Phase III	Refractory or progressed SCLC
BBR3464	Triplatin tetranitrate		Phase II	Gastric and oesophageal adenocarcinoma
Satraplatin	JM216		Phase II	Metastatic castrate-refractory prostate cancer
	BMY 45594			
	BMS 182751 (OC-6-43)-bis(acetato)		Phase II	Metastatic androgen-independent prostate cancer
	amminedichlorocyclohexylamine platinum(IV)			

Table 3

Proteins that specifically recognize cisplatin-damaged DNA (modified from Jung and Lippard [58]).

Protein	Function
[a] XPA	[b] NER: damage recognition protein
[a] XPC	[b] NER: damage recognition protein
RPA	[b] NER: damage recognition protein
hMSH2	[c] MMR: damage recognition protein
hMUTSα	[c] MMR: damage recognition protein
Ku80	[d] DNA-PK: DNA-binding subunit
HMGB1	Non-histone chromatin protein and extracellular signaling protein
SSRP1	Chromatin modulator
hUBF	rRNA transcription factor
tsHMG	Testis-specific HMG protein
TBP	Transcription initiation factor
p53	Tumor suppressor protein
PARP-1	Poly(ADP-ribose) polymerase
YB-1	Y-box binding transcription factor

[a] XP—xeroderma pigmentosum group.

[b] NER—nucleotide excision repair.

[c] MMR—mismatch repair.

[d] DNA-PK—DNA-dependent protein kinase.

Table 4

Platinum complexes which entered clinical trials but were not given marketing approval (compiled from Lebwohl and Canetta [21], Jakupec et al. [19] and Wheate et al. [28]).

Entered clinical trials in	Compound	Abandonment stage	Limiting toxicity
1970s	PAD (NSC 170898)	Phase I	Insufficient solubility
	Platinum uracil blue (PUB)	Phase I	Cardiac toxicity
	MBA	Phase I	Severe hypersensitivity
	JM-20 (SHP)	Phase I	Severe allergic reactions
	JM-74 (PHM)	Phase II	Nephrotoxicity, inferior activity
	Neo-SHP	Phase I	Severe allergic reactions
	Neo-PHM	Phase II	Nephrotoxicity, inferior activity
	BOP	Phase I	Insufficient solubility
1980s	Iproplatin (JM-9)	Phase III	Low activity
	JM-82 (DACCP)	Phase II	Chemical instability, low activity
	JM-11	Phase I	Poor pharmacokinetics
	Spiroplatin (TNO-6)	Phase II	Nephrotoxicity
	PYP	Phase I	Nephrotoxicity and myelosuppression
	JM-40	Phase I	Nephrotoxicity
	PHIC	Phase I	Difficulties in synthesis
	CI-973 (NK-121)	Phase II	Lack of activity
	DWA2114R (Miboplatin)	Phase III	No advantage over cisplatin
	Enloplatin	Phase II	Nephrotoxicity
	Zeniplatin	Phase II	Nephrotoxicity
1990s	Ormaplatin (Tetraplatin)	Phase I	Neurotoxicity
	Cycloplatam	Phase II	Hematological toxicity
	JM-216 (Satraplatin)	Phase III	Low activity
	ZD0473 (AMD473)	Phase I	Unknown
	TRK-710	Phase I	Unknown
	BBR3464 (Triplatin)	Phase II	Poor response rates

Table 5

Macromolecular platinum drug delivery systems in clinical trials.

Formulation	Incorporated drug	Carrier	Approx. size	Clinical phase	Indication
Lipoplatin	Cisplatin	Liposome	110 nm	Phase III	NSCLC, breast cancer, gastric cancer
SPI-77	Cisplatin	Liposome	110 nm	Phase II	Advanced NSCLC, refractory ovarian cancer
Aroplatin (L-NDDP)	NDDP	Liposome	1 μm	Phase II	Refractory colorectal cancer, malignant pleural mesothelioma
Lipoxal	Oxaliplatin	Liposome	250 nm	Phase I	Advanced gastrointestinal cancer
MBP-426	Oxaliplatin	Liposome	100 nm	Phase II	Gastric, gastroesophageal, esophageal adenocarcinomas
ProLindac (AP5346)	DACHPt	HPMA-Pt conjugate	25 kDa	Phase II	Advanced ovarian cancer
NC-6004 (Nanoplatin)	Cisplatin	Micelle	30 nm	Phase II	Advanced or metastatic pancreatic cancer
NC-4016	DACHPt	Micelle	30 nm	Phase I	Various solid tumors