



Platinum-based anticancer drugs encapsulated liposome and polymeric micelle formulation in clinical trials

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Abstract

Platinum-based anticancer drugs are one of the most widely used drug classes in cancer therapy. Almost half of the chemotherapy regimens used today contains a platinum drug, such as cisplatin or carboplatin. However, the drug resistance and non-specific cytotoxicity ultimately limits broader application of these drugs. Improvement of drug targeting and delivery systems are effective approaches to mitigate these disadvantages. This review focuses on liposome and micelle-based formulations using in the delivery of platinum-based anticancer drugs in clinical trials.

Keywords: Anticancer agents, cisplatin, liposome-based formulations, micelle-based formulations

Introduction

Cancer is one of the most serious and widespread diseases in the modern ages, with predictions that the number of cancer patients will double by 2050 [1], leading to a dramatic growth in demand for more effective cancer therapies. Today, platinum-based chemotherapy is a backbone of cancer treatment. Approximately 50% cancer patients who receive chemotherapeutic treatment are given using platinum-based anticancer drugs [2]. Platinum-based anticancer drugs can be applied in variety of cancers such as non-small and small cell breast, colorectal, lung, esophageal, gastric, cervical, ovarian and testicular cancers and melanoma, myelomas and lymphomas [3,4]. The most widely used platinum-based drug in cancer therapy is cisplatin, which was first described by Peyrone in 1845 [5], and approved by the US Food and Drug Administration (FDA) in 1978. The anti-neoplastic activity of cisplatin was reported by Barnett Rosenberg in 1960s, from which time it began being used in cancer therapy [6]. The use of cisplatin improves survival rate of treated cancer patients. For example, in testicular cancer therapy, the cure rate increases approximately tenfold with cisplatin compare to untreated groups [7]. The main mechanism of action of platinum-based chemotherapeutics is interaction with DNA and induction of apoptosis of tumor cells [8].

Although the platinum-based anticancer drugs are very potent, there are several significant shortcomings. These include their low solubility in water, unsuitability for oral administration, and short half-life in the body [9,10]. However,

the major disadvantage is their poor specificity, which is associated with severe side effects [11]. During the treatment there are often major systemic toxicities, such as neurotoxicity, nephrotoxicity and ototoxicity, which limit the administered dose of platinum drugs [12-15]. In addition, the intrinsic and acquired drug resistance is generated when tumors interact with sub-lethal doses of platinum-based drugs [4,16]. These two drawbacks restrict the efficacy of drugs. In order to deal with these issues, two major strategies could be implemented. One is to continue conducting research on developing better analogs of platinum drugs. Another is to apply bespoke drug delivery system to improve potency, while reduce side effects of currently used platinum drugs [17].

Review

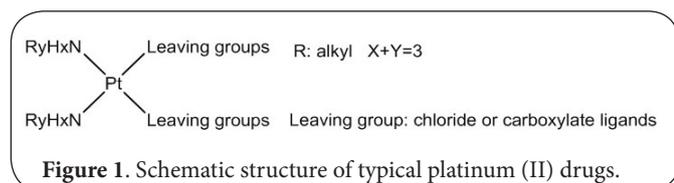
Platinum-based anticancer drugs

Since cisplatin was approved in 1978, thousands of platinum-based drugs have been developed with reduced toxicity and improved efficacy [18,19]. Among these products, 25 platinum drugs are in clinical trials, while several others have been already approved for use in humans, including carboplatin and oxaliplatin approved globally, as well as, nedaplatin approved in Japan, lobaplatin approved in China and heptaplatin (SK12053R) approved in Korea (Table 1) [20,21].

In general, platinum-based drugs have two different types of ligands attached to a central platinum cation (Figure 1). One type is amine or amine carrier ligands that strongly bind to the

Table 1. Six representative platinum-base anticancer drugs in the current clinical trials.

	Cisplatin	Carboplatin	Oxaliplatin	Nedaplatin	Lobaplatin	Heptaplatin
Structure						
Year of approval and Market status	1979 Worldwide	1989 Worldwide	2002 Worldwide	1996 Japan	2004 China	2005 Korea
Clinical use	Lung, ovarian, testicular, breast and brain cancer, sarcomas, lymphomas	Advanced ovarian carcinoma, head and neck, and lung cancer	Metastatic colorectal cancer, advanced gastric and ovarian cancer	Small and non-small cell lung cancer, head and neck cancer, esophageal, bladder, ovary and cervix cancer	Breast, testicular, small cell lung, gastric and ovarian cancer, chronic myeloid leukemia	Gastric cancer



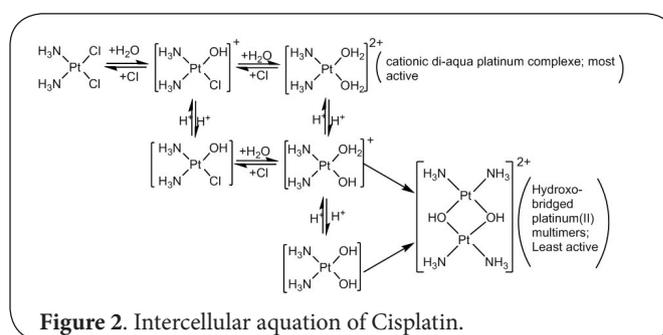
platinum ion. The activity of platinum drugs which have at least one ligand based on nitrogen is decreasing in following the order with NH_xR_y (R is alkyl, $X+Y=3$): $NH_3 > NH_2R > NHR_2 > NR_3$. Another type of ligands is labile chloride or carboxylate ligands, also termed leaving groups that allow the platinum ion to form bonds with DNA bases. The stronger ligands lead to less active platinum drugs, whereas the high toxicity of platinum complex is caused by highly unstable ligands such as NO_3^- [22,23].

Although the mechanism of action of platinum agents in cancer is still not completely understood, there are three major steps associated with these drugs action: i) cellular uptake of drugs; ii) drug interaction with DNA; and interference with transcription and replication mechanisms iii) the Pt-DNA lesion which induce the death of cell by activating signal transduction pathways [21,24].

The efficiency of uptake is directly associated with the efficacy of platinum drugs. Initially, passive diffusion was suggested as main pathway of platinum drugs transport [21,25]. Recently, studies revealed that various cellular transporters play a significant role in the uptake of platinum drugs [21]. For example, the copper transporter CTR1 and CTR2 are considered as a major gateway for platinum drugs access into the cell; however, the exact mechanism remains ambiguous [26-28]. In ovarian cancer cell lines, acquired cisplatin resistance was shown to increase when the cell decreased the expression of CTR1 [29]. Furthermore, the organic cation transporters (OCTs) have been proven to facilitate the transport of platinum drugs, such as oxaliplatin, into cells [30]. Therefore, passive, active

and facilitated transport mechanisms all have effects on the uptake of platinum complexes [21].

Once platinum complexes have entered into the cell, activation (via an aquation process) occurs (Figure 2) [21,24]. The leaving group is replaced by water molecules to form mono- and di-aqua platinum complexes, which are the most active forms of the drug. Hydroxo-bridged platinum(II) multimers the least active forms are generated (Figure 2) [31].



For example, after cisplatin enters into a cell, lower intracellular chloride concentrations (3-20 mM), in comparison to extracellular chloride concentration (100 mM), favours formation of the cationic aqua of platinum complexes [24]. This process has two significant implications: i) activated drugs are entrapped in the cell; and ii) the activated/aquated platinum complexes have the ability to bind to intracellular targets (DNA, RNA and proteins) [32]. The toxicity of platinum-based drugs is associated with the rate of exchange of water molecules with leaving groups. More severe systemic toxicity is caused by compounds that undergo more rapid aquation in the blood. Although toxicity could be minimized by the lower aquation, the activity of anticancer would also be reduced [33].

The cytotoxicity of platinum-based drugs is induced by the activated/aquated platinum species binding to intracel-

lular targets: predominantly DNA [34]. The activated/aquated platinum species are able to react with purine bases of DNA at nucleophilic centers. The N7 position of guanosine and adenosine residues is the most frequent binding site [24]. This binding causes a change of DNA structure, thus, the DNA duplex then unwinds, bends and destabilizes [35]. Two types of cross-links are formed in Pt-DNA adducts: intrastrand cross-links (more common), and interstrand cross-links as the platinum center has two liable sites that can react with the same, or two different, strands of DNA, respectively [24,36]. The effect of intrastrand cross-links is stronger than that of interstrand cross-links [37]. When DNA from patients who were treated with cisplatin was analyzed, interstrand cross-links accounted only for only a few percent of all Pt-DNA adducts [21,38].

After cellular machinery recognizes DNA adducts, three concurrent potential pathways can be induced: i) repairing, ii) bypassing affected DNA fragment and iii) apoptosis. It is believed the inhibition of transcription is the most likely to induce cell apoptosis in the presence of platinum drugs. The program of cell apoptosis is evoked if the DNA lesion cannot be repaired by cells [24]. However, the complete mechanism is still not clear as novel facts related to this mechanism are continuously discovered. For example, it was demonstrated that the death receptor CD95 was redistributed into membrane lipid rafts of human colon cell lines upon cisplatin action, and it caused sensitization to CD9-mediated apoptosis [39].

Although platinum-based drugs can induce cancer cell death, there have been only two new platinum-based drugs entering clinical trials in last ten years [4].

Drug delivery system for platinum-based anticancer drugs

Targeted therapy has the potential to reduce the damage of normal cells and retard the evolution of drug resistance [17,40]. Several tumor targeting delivery systems have been investigated [40,41].

Drug delivery systems can be separated into two categories: active and passive [17]. Active drug delivery systems exploit fact that there are the differences between tumors and normal tissues, and the interactions between anticancer drugs and the tumor cells containing the specific quantity or functionality of biomolecular entities [17]. In an active drug targeting and delivery system, the targeting moiety can be bound to the pharmacophore, and the specific binding affinity of this moiety can guide pharmacophore towards the targeting tumor tissues via transporter-based, antigen-based or receptor-based conjugates [42]. In active drug delivery systems, estrogens, carbohydrates, bisphosphonates, peptides and proteins, and cucubiturils are usually used as targeting ligands for platinum-based anticancer drugs.

Passive drug delivery systems are usually based on the enhanced permeability and retention (EPR) effect in neoplastic tissues [43]. Since the vasculature in tumor tissue is

often twisted and disorganized, there are more fenestrations and open junctions (size 200 nm~1.2 μ m) compared with vasculature in normal tissues [44]. Most nanoparticles (with the dimensions up to a few hundred nanometers) can cross fenestrations and reach tumor tissue. Furthermore, excess fluid from the solid tumor tissue is hardly to be removed as the functional lymphatic network is deficient. Therefore, the solid tumor tissues, in contrast to healthy tissue, can accumulate the large nanoparticles (100-300 nm) and retain them for a relatively long time [44]. Most types of solid tumor have EPR effects, and therefore tumor tissue concentrations can be enhanced 10~30-fold compared with that in other tissues. Passive drug delivery in tumor tissues and longer drug retention are key benefits of the EPR effect. In passive drug delivery, the carrier usually contains donor groups which could coordinate with the platinum moiety for platinum antitumor drugs [17]. Nanoparticles, such as liposomes and polymeric micelles, are suitable carriers for use in passive drug delivery systems that exploit the EPR effect [46,47].

Liposomes

Liposomes were recognized as potential drug delivery systems in 1965 [48] (Figure 3) are spherical vesicles, with aqueous inner core surrounded by concentric bilayers of phospholipids [49]. Liposomes are biocompatible, and they have abilities to loading hydrophilic or hydrophobic drugs in their internal water compartment and membrane, respectively. Liposomal formulations can be easily modified to match the pharmacokinetic profile of encapsulated drugs, with properties as size and charge easily altered. For targeted delivery of anticancer agents, liposomes can be designed to accumulate in the cancer tissue. For example, Doxil is the first approved liposomal antitumor drug by the US Food and

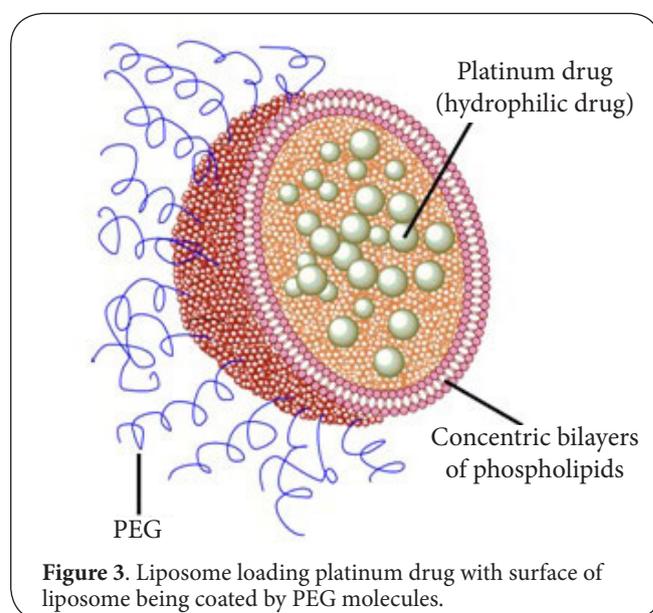


Figure 3. Liposome loading platinum drug with surface of liposome being coated by PEG molecules.

Drug Administration, FDA. Doxil is a doxorubicin encapsulated by a PEGylated liposomal formulation. Importantly, the EPR effect was first observed and proved in human, and through the passive drug delivery system, Doxil was accumulated in tumor tissues [50]. Then, platinum-based anticancer drugs encapsulated by liposomes have been investigated. So far, there are six types of liposomal platinum anticancer drugs in clinical trials (Table 2).

Lipoplatin

Lipoplatin™ is a liposomal formulation built from methoxy polyethylene glycol-distearoyl phosphatidyl-thanolamine, soy phosphatidylcholine, cholesterol and dipalmitoyl phosphatidyl glycerol (DPPG) containing cisplatin [51]. The ratio between cisplatin and total lipid content is approximately 1:10, and the average diameter of Lipoplatin vesicles is 110nm [52]. In order to keep liposomes more stable in body fluids and avoid immune responses against them, polyethylene glycol (PEG) was introduced onto the phospholipid bilayer surface. The uptake, accumulation and retention of Lipoplatin in tumor tissues are improved in comparison to the parent drug [53]. Upon encapsulation in PEGylated liposomes, the solubility of cisplatin is improved threefold and the circulation time prolonged almost 20-fold [17].

In pre-clinical studies in mice and rats nephrotoxicity and side effects were reduced with Lipoplatin compared to free cisplatin, with concomitant improvement in anticancer activity observed in prostate LNCaP human tumor xenograft and breast MCF-7 models [54,55]. Moreover, study on healthy dogs showed that the drug dose that could be safely injected was above 150 mg/m², which was twice the level tolerated for free cisplatin [56]. Pre-clinical studies of Lipoplatin showed that, the ability of antitumor was stronger against non-small cell lung cancer (NSCLC), and for normal cells, the Lipoplatin showed a much lower toxicity [57]. Some clinical trials of Lipoplatin have entered Phase III. Several clinical studies have shown that Lipoplatin could not only improve the efficacy of cisplatin compare to pure cisplatin, but also reduce systemic

toxicities such as myelotoxicity, ototoxicity, peripheral neuropathy and renal toxicity [58]. The accumulation of platinum drugs in solid tumors was up to 200-fold higher than that in adjacent normal tissues [51]. When Lipoplatin was used with other anticancer drugs such as paclitaxel or gemcitabine, the efficacy of treatment was similar or higher than that of cisplatin and the systemic toxicities were substantially reduced [52,59]. For example, one clinical study showed that twice as many patients survived when using Lipoplatin combined with paclitaxel compared with those using cisplatin combined with paclitaxel [60]. Lipoplatin also shows positive results in some Phase II and III trials for head and neck cancer, breast cancer, gastric cancer, and pancreatic cancer [51].

SPI-077

SPI-077 is a long-circulating and sterically stabilized cisplatin encapsulated by liposomes. SPI-077 is composed of all neutral lipids (the molar ratio of hydrogenated soy phosphatidylcholine, cholesterol and DSPE-PEG2000 is 51 : 44 : 5), and the cisplatin to total lipid ration is 1:70, and the size is 110 nm [61]. SPI-077 has a long blood circulation time. It is estimated that the half-life of SPI-077 is around 16 hours in mice, while half-life of cisplatin is about 0.24 hours. Furthermore the plasma concentration-time curve (AUC) was 60 times greater with SPI-077 compared to cisplatin, the amount of platinum accumulated in kidneys 4-fold lower, while the platinum AUC in tumor was 28 times higher [62]. In C26 and Lewis lung tumor xenograft models, the toleration and effectiveness were also enhanced by using SPI-077 compared with free cisplatin [62]. Despite superior pharmacokinetic profile of SPI-077 in preclinical experiments, enhancement of drug efficacy over cisplatin was not observed in several pre-clinical experiments including A-375 melanoma, M-109 lung carcinoma and J-6456 lymphoma in mouse [63]. Moreover, it has been shown that liposomes of SPI-077 were able to release 10% of cisplatin. The cytotoxic activity of SPI-077 was also reduced *in vitro* compared with cisplatin [64]. This poor performance might be related to extremely slow release of drug from liposomes

Table 2. Liposomal formulated platinum-based drugs in clinical trials.

Liposomal formulation	Platinum-based drugs	Liposome	Status	Drug-lipid weight ratio	MTD (mg/m ²)	References
Lipoplatin	Cisplatin	HSPC/DPPG/DSPE-PEG2000	Phase II/III	1:10	300	51~60
SPI-077	Cisplatin	HSPC/cholesterol/DSPE-PEG2000	Phase II	1:70	420	61 ~ 69
LiPlaCis	Cisplatin	DSPC/DSPG/DSPE-PEG2000	Phase I	--	--	70
Lipoxal	Oxaliplatin	HSPC/DPPG/DSPE-PEG2000	Phase I	--	300	71, 72
Aroplatin	NDDP	DMPC/DMPG	Phase II	1:15	312.5	73 ~ 79
MBP-426	Oxaliplatin	TF-PEG-liposomes	Phase I/II	--	226	80~ 82

MTD: Maximum tolerated dose; HSPC: Hydrogenated soy phosphatidylcholine; DPPG: 1,2-dipalmitoyl-sn-glycero-3-phospho-(1'-rac-glycerol). DSPE-PEG2000: 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-{methoxy(polyethylene glycol)-2000}. DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine. DSPG: 1,2-distearoyl-sn-glycero-3-phospho-(1'-rac-glycerol). DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine. DMPG: 1,2-dimyristoyl-sn-glycero-3-phospho-(1'-rac-glycerol). PEG: poly(ethylene glycol). NDDP: cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II)

at the cancer locus [64]. In a Phase I experiment, patients were administered with a 420 mg/m² dose of SPI-077 [65], and long circulation time of drug was observed. SPI-077 was tolerated in human bodies in a dose range from 40 to 420 mg/m², and patients suffered only from mild side effects: muscle weakness, mild anemia and mild gastrointestinal toxicity. However, in several Phase II trials, most of patients who had advanced non-small-cell lung cancer, platinum-sensitive recurrence of ovarian cancer or head and neck cancer did not generate a strong response to SPI-077 [66-68]. Some preclinical studies and Phase II studies showed extremely slow release of cisplatin from SPI-077, leading to the low therapeutic efficacy. SPI-077 was subsequently removed from clinical studies [69].

LiPlaCis

LiPlaCis is a cisplatin drug encapsulated by liposomal formulation which is composed of 1,2-disteryl-sn-glycero-3-phosphocholine, 1,2-disteryl-sn-glycero-3-{phosphor-rac-(1-glycerol)} (sodium salt) and 1,2-disteryl-sn-glycero-3-phosphoethanolamine-N-{methoxy(polyethylene glycol)-2000} (ammonium salt). Disodium hydrogen phosphate, sodium chloride, and sucrose are added as stabilizers. As with SPI-077, it is believed that it is difficult for cisplatin to cross a lipid membrane. It has been demonstrated that liposomes of LiPlaCis are degraded by secretory phospholipase A₂ at tumor site to release cisplatin [70]. Unfortunately, severe renal toxicity and an acute infusion reaction were observed in patients in Phase I study. Thus LiPlaCis clinical studies were halted [49].

Lipoxal

Lipoxal is liposomal formulations of oxaliplatin [71]. In a Phase I study, a dose range from 100 mg/m² to 250 mg/m² did not induce any obvious side effects. At doses of 300 mg/m²~350 mg/m², nausea, mild myelotoxicity and grade 2-3 peripheral neuropathy were observed [72]. Oxaliplatin minimized many side effects such as gastrointestinal tract toxicity and myelotoxicity while maintaining anticancer potency. The cellular uptake of oxaliplatin remarkably improved when administered as Lipoxal in comparison to pure oxaliplatin [71]. Further study on Lipoxal can be expected in near future.

Aroplatin

Aroplatin (L-NDDP) is a liposome encapsulating a cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum II, (NDDP an oxaliplatin derivative). This is first liposomal formulation loading new cisplatin analog in the clinic [49]. Multi-lamellar liposomes were formed from 1,2-dimyristoyl-sn-glycero-3-phospho-(1'-rac)glycerol (DMPG) and 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) lipids in acidified saline solution, and then NDDP were encapsulated by these liposomes to form Aroplatin [73].

In pre-clinical study, there were significant differences in the biodistribution between Aroplatin and NDDP. Major organs such as lymph nodes and liver accumulated platinum

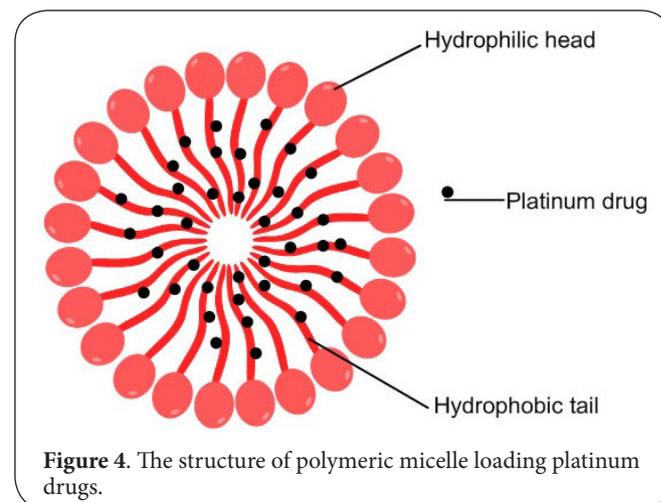
after patient treatment with Aroplatin [74,75]. In toxicity test, Aroplatin did not show the nephrotoxicity, but myelosuppression was observed. Diffuse hemorrhagic syndrome was also caused by Aroplatin in canine models [76]. However, stronger anticancer activities were observed for liver and spleen metastases in mice when treated with Aroplatin [77]. Importantly, Aroplatin did not share cross-resistance with cisplatin [17]. In a Phase I study, patients who received an intravenous administration every 4 weeks showed that 312.5 mg/m² was the maximum tolerated dose (MTD) of Aroplatin. The myelosuppression occurred when the dose of Aroplatin was close to MTD [78,79]. In Phase II study, Aroplatin was tested in refractory metastatic colorectal cancer to produce the partial response (5.6%), the stable disease (16.7%) and the development of disease progression (77.8%) in patients. In general, the response was modest. Aroplatin was also well tolerated, nearly half patients were able to receive Aroplatin in high dose (375 mg/m²) [79]. Although Aroplatin demonstrated promising efficacy and safety profile, there is no report of any ongoing Phase III study.

MBP-426

MBP-426 is a transferrin (TF)-conjugated N-glutaryl phosphatidylethanolamine liposomal formulation encapsulating oxaliplatin. The TF receptor is overexpressed in several types of cancers [17]. The retention time of oxaliplatin was prolonged in tumor tissues (Colin 26 tumor) while reduced in blood, when tested in mice model. MBP-426 was more effective to suppress the growth of tumor cells compared with pure oxaliplatin [80]. In Phase I study, the dose of 226 mg/m² MBP-426 was safe when injected every three weeks. Dose-limiting toxicities were thrombocytopenia at the dose of 400 mg/m² [81]. Thus, 226 mg/m² of MBP-426 is recommended for the Phase II study, which is ongoing [21,82].

Polymeric micelles

Polymeric micelles (Figure 4) are formed by amphiphilic block



copolymers [83], and including inner core (hydrophobic) and outer shell segments (hydrophilic) [84]. The loading, stability, and releasing of drugs are associated with inner core while the behavior of pharmacokinetics is controlled by the outer shell. The anticancer drugs such as cisplatin could be incorporated into the inner core of polymeric micelles [17]. Incorporation of the drug into micelles increases its stability. Nowadays, there are two types of polymeric micelles containing platinum-based anticancer complexes in clinical trials: NC-6004 and NC-4016 (Table 3).

NC-6004

NC-6004 (Figure 5) is a cisplatin encapsulated by polymeric micelles (30 nm), composed of block copolymer containing PEG (outer shell) and poly(glutamic acid) (pGlu) (inner core) coordinated with cis-diammineplatinum moieties [85].

In pre-clinical study, the blood retention profile of NC-6004 was longer than free cisplatin, and the tumor AUC of NC-6004 was 3.6 times higher than that of cisplatin [86]. There was no obvious differences in suppression of human gastric cancer (cell line MKN-45) in a murine model when NC-6004 (5 mg/kg of CDDP) was compared with cisplatin. Pre-clinical studies showed that neurotoxicity was minimized by injecting NC-6004 compared with cisplatin [87]. In a Phase I clinical study of NC-6004, the dosage from 10 mg/m² to 120 mg/m² was

injected one time every three weeks. When the dose was up to 120 mg/m², nephrotoxicity was not observed. Therefore, 120 mg/m² was recommend as the maximal tolerated dose for further clinical studies. Unfortunately, NC-6004 induced more frequently hypersensitivity reaction in comparison to free drug [88]. Nanocarrier, a biotechnology company, has recently initiated a Phase II/ III study on NC-6004 [89].

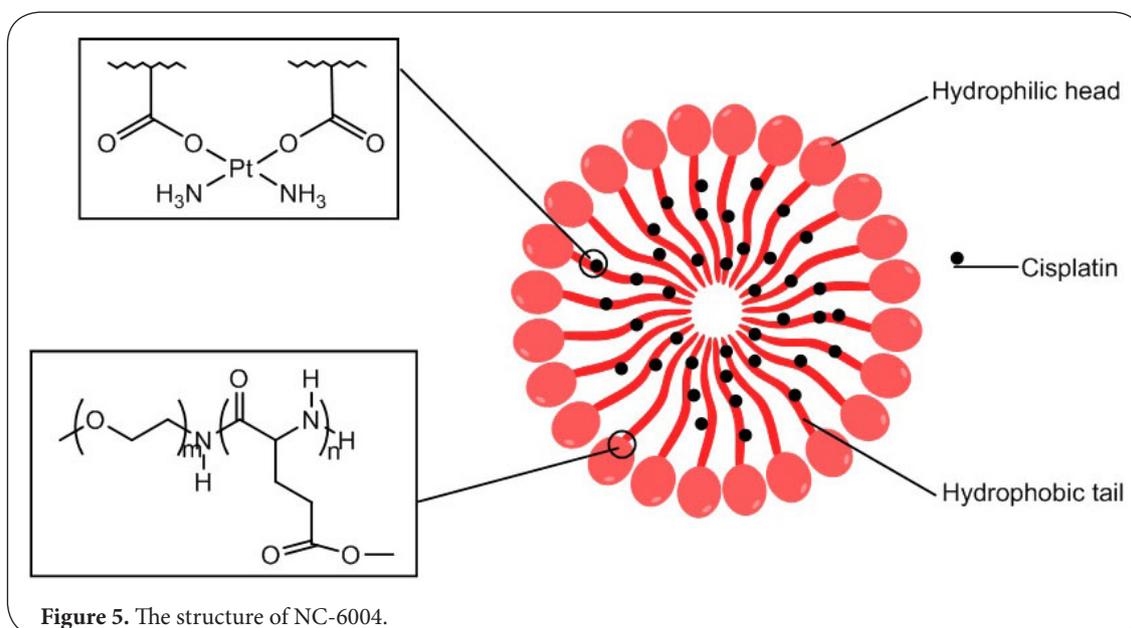
NC-4016

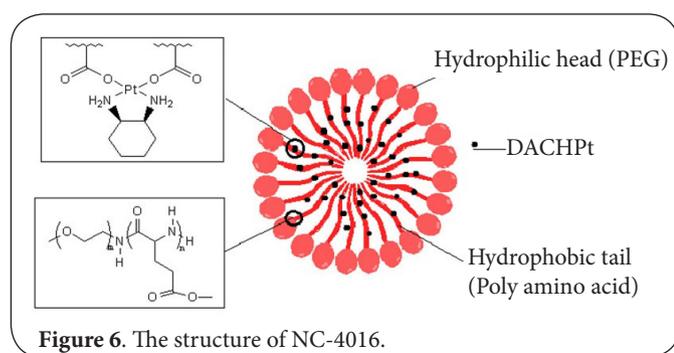
NC-4016 (Figure 6) is a polymeric micelle loading DACHPt. The structure of NC-4016 is similar to that of NC-6004, in that it is composed of outer shell, which is comprised by hydrophilic PEG chain, and a pGlu inner core that coordinates dichloro-1,2-diaminocyclohexane-platinum (II) (DACHPt, an active oxaliplatin element) [90]. Nanocarrier has begun conducting a Phase I clinical study in US [89].

In distilled water, DACHPt was not released from NC-4016. However, it could be released in media including chloride ions, and NC-4016 was more stable in phosphate buffered saline than NC-6004. Moreover, compared with oxaliplatin, the cytotoxicity of NC-4016 was lower, a longer blood circulation and higher relative tumor targeting than pure oxaliplatin. Furthermore, NC-4016 has potent anticancer activity against both primary solid and metastatic tumors [84]. In pre-clinical studies, NC-4016 inhibited tumor growth in an orthotopic

Table 3. Polymeric micelles containing platinum-based drugs in clinical trials.

Micelle formulation	Platinum based drugs	Micelles	Status	MTD (mg/m ²)	References
NC-6004	cisplatin	Poly(ethyleneglycol)- β -poly(glutamic acid)	Phase I/II/III	120	85~ 89
NC-4016	DACHPt	Poly(ethyleneglycol)- β -poly(glutamic acid)	Phase I		84,89~92





cirrhus gastric cancer and metastatic lymph nodes [91]. Moreover, in a mouse model with human carcinoma cell line KB, NC-4016 showed superior antitumor ability than free Oxaliplatin. Acute cold hypersensitivity, which is frequently occurred by using Oxaliplatin, was not observed in rats that received NC-4016 [92].

Remarks and perspective

There is no therapeutic regime that can totally cure cancer patients without any side effect, as anticancer drugs can not discriminate between healthy and tumor cells. Besides this lack of specificity, anticancer agents also suffer from diminishing efficacy. Cancer cells can develop mechanisms that can avoid apoptosis caused by cisplatin interactions with DNA. Thus, to overcome problem with poor performance of cisplatin, many analogs have been generated, including carboplatin, oxaliplatin, nedaplatin, heptaplatin and lobplatin. However, all of these platinum-based antitumor drugs have their shortcomings. For example, although the toxicity of carboplatin to normal cells is weaker than cisplatin, its anticancer efficacy also decreases.

In order to enhance efficacy of platinum-based drugs and reduce toxicity, more efficient drug targeting and delivery system are being examined. One of the most promising delivery systems includes liposomes-based targeting delivery exploiting the EPR effect. There are six liposomal platinum-based antitumor drugs that entered to the clinical trials. While some of them showed significant potential to reduce the systemic toxicity, avoid resistance and enhance the efficacy of these platinum-based drugs, other demonstrated poor performance. For example, SPI-077 was not able to release enough free platinum drug in certain time to produce desired anticancer effect. On the other hand, LiPlaCis was discontinued from the trials due to its excessive toxicity. Fortunately, liposomal platinum drugs formulations, such as lipoplatin and lipoxal showed very promising efficacy profiles and practical toxicity.

Most current research focuses on liposomes that encapsulate cisplatin, oxaliplatin, carboplatin, nedaplatin, heptaplatin or lobaplatin. The liposomal formulation itself can be also modified. In addition, analogously to MBP-426, tumor targeting moieties can be incorporated on the liposomes to further improve selectivity of the delivery system. Liposomes

covered by antibodies are becoming attractive choice for tumor targeting delivery systems.

Nanomedicine is one of the most rapidly developing fields in anticancer therapy and polymer-based delivery system for anticancer agents are a rapidly growing area of research. There are two platinum-based anticancer drugs encapsulated in polymeric micelles in the clinical trials (NC-6004 and NC-4016). These two polymeric carriers reduce toxicity of platinum drugs compared with free drugs, while their antitumor efficacy was maintained. In the future other platinum-based anticancer drugs such as carboplatin, nedaplatin, heptaplatin or lobaplatin could be encapsulated by polymeric micelles. Further improvement can be also achieved by combination of more than one anticancer agent in liposomes/micelles delivery system. Combination therapies on their own showed very promising outcomes; incorporation into them additional delivery system might further improve anticancer potency and reduce general toxicity of the therapeutics.

Conclusion

While some of these drugs did not meet expectations, others showed improved potency and reduced adverse effects in human. However, it is expected that further research and development is required to produce formulation that can reach the market. Thus, the formulation of liposomes and polymeric micelles could be modified by incorporation of cancer targeting moieties or modification of physicochemical properties of delivery system (e.g., size, charge). In addition, different platinum-based drugs could be encapsulated by liposomes and polymeric micelles. Finally, combination therapy can be applied. Hopefully, this optimization process can be performed in the near future leading to a better treatment of cancers.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	ZH	MAC	ZMZ
Research concept and design	✓	--	✓
Collection and/or assembly of data	✓	--	✓
Data analysis and interpretation	--	--	--
Writing the article	✓	--	✓
Critical revision of the article	--	✓	✓
Final approval of article	--	✓	✓
Statistical analysis	--	--	--

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