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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.

Contents

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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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.

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