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Polymers with platinum drugs and other macromolecular metal complexes for cancer treatment

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ABSTRACT

Metal-based anticancer drugs, in particular platinum-drugs, have been investigated for the treatment of cancer for the last 40 years. A small set of platinum-based drugs have meanwhile received FDA approval for the treatment of various cancer. Cisplatin and its relatives are currently one of the most widely used anticancer drugs. The use is however associated with significant side effects and rising drug resistance. To combat these problems, drug delivery carriers have been developed to increase the protection of the drug and increase efficacy. Metal-based drugs represent a rather unique drug delivery challenge. Most anticancer drugs are either physically encapsulated into a polymer matrix or they can be conjugated to the polymer via a degradable linker. While both pathways are possible for metal-based drugs, the conjugation to the polymer can be carried via labile or permanent ligands. In addition, the prodrug strategy using the drug in the higher oxidation state is a common approach that has been widely tested for platinum drug. The delivery of platinum drugs is now a mature field and the various conjugation techniques have been combined with a range of drug carriers including dendrimers, micelles and solid polymer nanoparticles. Hybrids of macromolecular metal complexes with inorganic nanoparticles have been

Abbreviations: A2870, ovarian cancer cells; A2870cis, cisplatin resistant ovarian cancer cells; A549, lung cancer cells; ABRs, auditory brainstem responses; AUC, area under the curve; AuNP, gold nanoparticles; CDDP or cisplatin, cis-diamminedichloroplatinum(II); *Cis*-$(cha)_2Pt(NO_3)_2$, *cis*-bis(cyclohexylamine) dinitratoplatinum (II); CM-dex, carboxymethyl dextran; CP750, $[(mPEG_{750})(GlyPheLeu)_2Et]_3$ nanoparticles; CRC, colorectal cancer cells; DCA, dichloroacetate; DMF, dimethylformamide; DMPC, dimyristoyl phosphatidylcholine; DMPG, dimyristoyl phosphatidylgycerol; DMSO, dimethyl sulfoxide; DNA, deoxyribonucleic acid; DOPC, dioleoyl phosphatidylcholine; DOPS, dioleoyl phosphatidylserine; DPPG, dipalmitoyl phosphatidyl glycerol; EPR effect, enhanced permeability and retention effect; FA, folic acid; FDA, Food and Drug Administration; HeLa, human cervical; hGR, glutathione reductase; HNDDSs, hybrid nanomaterial-based drug delivery systems; HPMA, N-(2-Hydroxypropyl) methacrylamide; HSPC, phosphatidylchlorine; hTrxR, thioredoxin reductase; K_2PtCl_4, potassium tetrachloroplatinate; KP1019, *trans*-$[RuCl_4(indazole)_2]$indazoleH; L-NDDP, aroplatin; MARxTC, 1,1-di-tert-butyl 3-(x-((2,3-dimethylbut-2-enoyl)oxy)R)butane-1,1,3-tricarboxylate; MABTC, MARxTC, R = butyl, x = 4; MAETC, MARxTC, R = ethyl, x = 2; MAHTC, MARxTC, R = hexyl, x = 6; MCF-7, breast cancer cell line; mPEG 2000-DSPE, polyethylene glycol-distearoyl phosphatidtylethanolamine; mPEG, methoxy poly(ethylene glycol); mPEG-b-PCL-b-PLL, methoxyl-poly(ethylene glycol)-b-poly(ε-caprolactone)-b-poly(L-lysine); MRI, Magnetic Resonance Imaging; MWCNTs, multi-walled carbon nanotubes; NAMI-A, *trans*-$[RuCl_4(DMSO)(imidazole)]$imidazoleH; NDDP, Cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II); NDs, nano-diamonds; NMR, Nuclear Magnetic Resonance; NTs, nano-tubes; OSC-19, nude mice bearing; OVCAR3, ovarian cancer cell line; P(Asp), poly(L-aspartic acid); P(Glu), poly(L-glutamic acid); PAA, polyamidoamine.

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tested in recent years to combine the ability to deliver the drug with imaging properties. An emerging trend is the surface decoration of the polymeric nanoparticles with targeting ligands such as folates. The advanced state of this field is evident by the fact that some macromolecular platinum drugs even advanced to the clinic. While the delivery of platinum drugs has been well explored, the delivery of other metal-based drugs based on gold, ruthenium or cobalt is still in their infancy.

Contents

1. Metal-based anticancer drugs

Medicinal inorganic chemistry receives rising interests in the area of biomedical applications. Metals are not only part of vital processes in the body such as enzyme driven reactions, but can also be used a therapeutic and diagnostic agents. Application of metal containing compounds can range from MRI agent (e.g. Gd, Mn), radiopharmaceutical diagnostic and therapeutic agents (99Tc and 90Y), enzyme inhibitor to therapeutic agents (e.g. Li, Pt, Au, Bi) [1]. Platinum complexes are widely used for the treatment of cancer [2].

Cisplatin, *cis*-diamminedichloroplatinum(II) (CDDP), has been discovered in 1965 and obtained FDA approval in 1978 for cancer treatment. The immediate success in cancer treatment was overshadowed by significant side effects. Since then a frantic search has begun to design derivative with the same efficiency, but significantly reduced side effects. However, apart from cisplatin, very few platinum compounds have received worldwide approval for clinical use. Among the most effective platinum drugs studied, oxoplatin, satraplatin, tetraplatin, iproplatin, and ormaplatin appear to be potent anticancer agents and they are especially used to treat cisplatin resistant tumours [3,4].

Platinum drugs contain of two different types of ligands. One ligand, usually based on N, binds strongly to the Pt ion. Indeed, classic platinum complexes have at least one ligand based on N with the activity of the platinum drug increasing according to NR_3 (inactive, R = alkyl), $NHR_2 < NH_2R$, NH_3. The other ligand is the leaving group, which is typically chloride or carboxylate. This leaving group should be moderately bound to platinum. Highly labile ligands such as NO_3^- would result in high toxicity while strong ligands such as N_3^-, SCN^- or CN^- cause the platinum complex to be inactive.

The varying reactivities of these next generation platinum complexes are derived from different solubilities and the rate of hydrolysis of these agents. Platinum complexes have to be in fact activated by substituting the chloride or carboxylate ligands with water, a process which is facilitated by the low intracellular chloride concentration. The antitumor activity of platinum complexes is accredited to the reaction between the metal and predominantly the DNA. Purines are thought to be the major target for the reaction with platinum. These interactions cause the cell death. However, some cells develop resistance towards platinum drugs and do not respond to the therapy. A major disadvantage of platinum drugs is their deactivation caused by reaction with thiols. This occurs when the platinum drug travels in the blood stream and reach the target where thiols are abundant in peptides and proteins. In the cytoplasm, the activated aqua species preferentially reacts with species containing sulphur such as cysteine or methionine amino acids. These species include the tripeptide glutathione or metallothioneins. In some platinum-resistant cancer cells, glutathione and metallothionein levels are relatively high, so activated platinum is effectively 'mopped up' in the cytoplasm before DNA binding can occur, thereby causing resistance [3].

While cisplatin was the first platinum anticancer drug it has major drawbacks as outlined above. It is not only the resistance of some cell types against this drug but also

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