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Review

Photoactivated platinum-based anticancer drugs

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ABSTRACT

Following the serendipitous discovery of the anticancer drug, *cisplatin*, numerous platinum(II) complexes have been synthesized and some of them, such as *carboplatin, oxaliplatin, nedaplatin, heptaplatin* and *lobaplatin*, have been clinically approved either locally or worldwide. Since these drugs are structurally related to *cisplatin*, the unfortunate problems that are associated with *cisplatin* are more or less the same for them. To overcome these problems, octahedral, low-spin d^6 and coordinatively saturated Pt(IV) complexes have been examined because of their substitution inertness towards off-target biomolecules. Owing to the availability of bio-reducing agents, mainly proteins, in all cell types, Pt(IV) prodrugs can be reduced to their cytotoxic active Pt(II) analogues in both cancer and normal cells. However, prolonged hydrolysis and less stability against bio-reducing agents are problems still to be overcome. To address the passive activation of Pt(IV) prodrugs, the choice of photoactivated Pt(IV) prodrugs seems to be a promising chemotherapeutic strategy. Therefore, iodo-based photolabile Pt(IV) complexes which, upon light exposure, undergo photolytic reactions to give active Pt(II) species have been developed. Unfortunately, these complexes had to be later discarded because of their low stability in the dark. Eventually, azido-based complexes with enhanced stability in the dark were developed. The selective photoactivation of these photolabile azido-based Pt(IV) prodrugs has dramatically opened up new avenues of research aimed at overcoming the problems associated with chemotherapeutic drug delivery by incorporating different polymers, biological target molecules, permeation enhancers or nanoparticles. These photolabile complexes are the focus of the present review.

Contents

Abbreviations: Arg-Gly-Asp, Arginylglycylaspartic acid; FDA, Food and Drug Administration; DNA, Deoxyribonucleic acid; NCI, National Cancer Institute; SCLC, Small cell lung cancers; NSCLC, Non-small cell lung cancers; 5-FU, 5-Fluorouracil; OTCs, Organic cationic transporters; DACH, R,R-diaminocyclohexane; RNA, Ribonucleic acid; SHAB, Soft and hard acids and bases; PDT, Photodynamic therapy; ALA, 5-aminolevulinic acid; S_0, Singlet ground state; S_1, Singlet excited state; T_1, Triplet excited state; $^3O_2$, Triplet oxygen; ADME, Absorption, distribution, metabolism and excretion; QY, Quantum yield; ROS, Reactive oxygen species; E_p, Cathodic peak potentials; GSH, Glutathione; CT-DNA, Calf thymus-deoxyribonucleic acid; ds-DNA, Double-stranded DNA; LMCT, Ligand to metal charge transfer; 5′-GMP, Guanosine 5′-monophosphate; r_b, Number of moles of Pt attached per nucleotide of DNA; MA, Methylamine; Py, Pyridine; Tz, Thiazole; PBS, Phosphate buffer solution; 1-Melm, 1-Methylimidazole; EPR, Enhanced permeability and retention; CDs, Carbon dots; DLS, Dynamic light scattering; FA, Folic acid; FR, Foliate receptor; FRET, Fluorescent resonance energy transfer; G4K+B, Guanosine quartets potassium Borate; HSA, Human Serum Albumin; -b-PCL, block-poly(ε-caprolactone); mPEG, methoxypoly(ethylene glycol); NIR, Near Infrared radiation; PEG, Polyethylene glycol; PEI, Polyethylenimine; PLL, poly-L-lysin; Pt-DA, Platinum conjugated with dopamine; PU, Polyurethane; RGD, Arginylglycylaspartic acid; UCNPs, upconversion nanoparticles; MTD, Maximum tolerated dose; EMEM, Eagle's minimum essential medium.

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1. Introduction

Light is among the basic needs for our existence on Earth because of its seminal role in food, energy, vision, transit of information and, currently, as a diagnostic and therapeutic tool in clinical medicine [1]. Historically, the biological usage of light can be traced back to the Egyptians about 4000 years ago, when sunlight and plants were used for the treatment of vitiligo disease [2,3]. At the end of 19th century, Oscar Raab began a systematic study of the photosensitized reactions of dark inactive antimicrobial *acridine* and *eosine* dyes to kill microorganisms (paramecia) upon exposure to light [4]. In 1903, Tappeiner used light and eosin for the treatment of skin cancer [5]. It is believed, however, that phototherapy was first introduced by Finsen in the early 20th century for the treatment of skin tuberculars by means of heat-filtered light from a carbon arc lamp [6].

The theragnostic (therapeutic and diagnostic) use of light (UV, visible and IR) in clinical medicine is termed phototherapy. The therapeutic introduction of light into biological systems can be achieved either directly or indirectly. In the direct method, biological molecules like proteins, nucleic acid and other small molecules undergo various changes upon direct light irradiation, as illustrated by the treatment of vitamin D deficiency, neonatal jaundice, autoimmune system diseases and manic depression. In the indirect method, changes in biological systems are achieved by clinically administered photosensitive drugs [7]. In this latter context, transition-metal complexes are the most potent and active chemotherapeutic candidates owing to their many oxidation states, chelating properties, redox potentials and variable ground and excited electronic states. Since the fortunate discovery of *cisplatin* for the treatment of cancer by Rosenberg's group in 1969 [8], metal complexes are now being used widely as potent therapeutic agents in clinical medicines. Among these chemotherapeutics, platinum-based drugs are still the most effective. The platinum anticancer drugs of note are *cisplatin, carboplatin* and *oxaliplatin*, which have been approved by the FDA and are used transnationally for the treatment of various cancers [9–17]. Additionally, *nedaplatin* has been recommended by Japan for the treatment of both non-small and small lung cancers and for head, neck and esophagus tumors [18,19]. Furthermore, *heptaplatin* is being used in Korea for curing gastric tumors and, recently, China has approved *lobaplatin* for the treatment of human chronic granulocytic leukemia, inoperable breast tumor metastasis and small cell lung cancers [20,21].

Lamentably, the problems associated with Pt(II) antitumor drugs, such as the necessary intravenous administration, intrinsic cell resistance, low bioavailability, severe chronic kidney disease, neurological disorder and ototoxicity, are still major barriers to their clinical use. The labile nature of Pt(II) complexes is the key reason for most of these difficulties. Consequently, octahedral Pt (IV) complexes have been extensively investigated as they are low-spin d^6 complexes and are thus inert to substitution. Moreover, their redox and oral administration properties provide additional advantages to these drugs [22]. For their proper anticancer functioning, however, the Pt(IV) prodrugs need to be reduced to Pt(II) by different bio-reducing reagents, such as ascorbic acid, glutathione, cysteine and metallothionein in or outside the cytosol. Moreover, photoactivated-Pt(IV) complexes generally have an advantage over non-photoactivated Pt(IV) complexes owing to their selective activation in cancer cells. Since some Pt(IV) prodrugs have proved to be pharmacokinetically inert towards reduction, but this really depends on the nature of the molecules, especially the axial ligands present [23–25]. On the other hand, photosensitized Pt(II) complexes, which undergo intra-ligand transition upon light irradiation, need oxygen for their operating mechanisms inside the cell.

To mitigate the forgoing problems, an attractive strategy was recently designed to tailor Pt(IV) prodrugs, which involved the synthesis of photoactivated Pt(IV) antitumor complexes. These photoactivated anticancer drugs are usually triggered by focusing UV, blue or green light onto tumor cells to release their counterpart Pt(II) complexes thereby ensuring targeted accumulation and efficient cellular apoptosis [26–28]. However, insufficient light penetration into the biomass and unforeseen photodamage to tissue, DNA and proteins are still some of the problems to be overcome.

In this review, we discuss the present status and scope of clinically approved Pt(II) complexes, photosensitized Pt(II) complexes and the development of non-photoactivated and non-labile Pt(IV) complexes as prodrugs. The latter part of the review describes the recent research on the evolution of platinum-based anticancer drugs. Among all this research activity, platinum-based antitumor prodrugs that have been photoactivated provide the most important approach to address the problems known to be associated with platinum chemotherapy. We have especially tried to provide a comprehensive discussion on photoactivated prodrug strategies with a focus on the different generations of photolabile Pt(IV) complexes that have been developed over the past few years, their non-classical mechanisms of action, the characteristic features of ideal photoactivated prodrugs and the different strategies that have been explored for target specific delivery of photoactivated P(IV) complexes in chemotherapy.

2. Present scope of clinically approved Pt(II) complexes

Platinum-based drugs have had a profound impact in clinical medicine and are the mainstay of antineoplastic chemotherapy. Numerous platinum-based drugs have been synthesized over the years, but only a few of them have been clinically approved. Among these, *cisplatin* has enjoyed the most success and is used either alone or in combinatorial therapy. *Cisplatin* was first used for the treatment of cancer in humans in 1971 and obtained commercial approval in Canada in 1978 [29].

The clinical drug development of *cisplatin* was initiated by the National Cancer Institute (NCI) and the precious metal refining companies, Johnson Matthey (UK) and Engelhard Industries