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Review

Cisplatin in cancer therapy: Molecular mechanisms of action

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ABSTRACT

Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum (II), is a well-known chemotherapeutic drug. It has been used for treatment of numerous human cancers including bladder, head and neck, lung, ovarian, and testicular cancers. It is effective against various types of cancers, including carcinomas, germ cell tumors, lymphomas, and sarcomas. Its mode of action has been linked to its ability to crosslink with the purine bases on the DNA; interfering with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells. However, because of drug resistance and numerous undesirable side effects such as severe kidney problems, allergic reactions, decrease immunity to infections, gastrointestinal disorders, hemorrhage, and hearing loss especially in younger patients, other platinum-containing anti-cancer drugs such as carboplatin, oxaliplatin and others, have also been used. Furthermore, combination therapies of cisplatin with other drugs have been highly considered to overcome drug-resistance and reduce toxicity. This comprehensive review highlights the physicochemical properties of cisplatin and related platinum-based drugs, and discusses its uses (either alone or in combination with other drugs) for the treatment of various human cancers. A special attention is paid to its molecular mechanisms of action, and its undesirable side effects.

Contents

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1. Introduction

Cisplatin (CAS no. 15663-27-1, MF-$Cl_2H_6N_2Pt$; NCF-119875), cisplatinum, also called *cis*-diamminedichloroplatinum(II), is a metallic (platinum) coordination compound with a square planar geometry (The chemical book database, 2014). It is a white or deep yellow to yellow–orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimanide and *N*,*N*-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the *trans*-isomer (IARC, 1981; Akron, 2009). Cisplatin has a molecular weight of 301.1 g/mol, a density of 3.74 g/cm^3, a melting point of 270 °C, a log K_{ow} of −2.19 and a water solubility of 2.53 g/L at 25 °C (HSDB, 2014).

Cisplatin was first synthesized by M. Peyrone in 1844 and its chemical structure was first elucidated by Alfred Werner in 1893. However, the compound did not gain scientific investigations until the 1960s when the initial observations of Rosenberg et al. (1965) at Michigan State University pointed out that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in *Escherichia coli* created much interest in the possible use of these products in cancer chemotherapy. Since the identification of cis-dichlorodiammineplatinum (II) (cisplatin, r) as the agent responsible for this activity, considerable interest has been generated in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer.

Cisplatin has been especially interesting since it has shown anticancer activity in a variety of tumors including cancers of the ovaries, testes, and solid tumors of the head and neck. It was discovered to have cytotoxic properties in the 1960s, and by the end of the 1970s it had earned a place as the key ingredient in the systemic treatment of germ cell cancers. Among many chemotherapy drugs that are widely used for cancer, cisplatin is one of the most compelling ones. It was the first FDA-approved platinum compound for cancer treatment in 1978 (Kelland, 2007). This has led to interest in platinum (II)—and other metal—containing compounds as potential anticancer drugs (Frezza et al., 2010).

Cisplatin is clinically proven to combat different types of cancers including sarcomas, cancers of soft tissue, bones, muscles, and blood vessels. Although such cancers have recently received better prognosis and therefore have become less life threatening (Desoize and Madoulet, 2002), significant challenges remain with regard to their cure. Also, because of drug resistance and considerable side effects, combination therapy of cisplatin with other cancer drugs has been applied as novel therapeutic strategies for many human cancers. In this research, we aim to provide a comprehensive review of the physicochemical properties of cisplatin and related platinum-based drugs, to discuss its uses (either alone or in combination with other drugs) for the treatment of various human cancers, to examine its molecular mechanisms of action, and to discuss it potential side effects.

2. Cisplatin and other platinum-containing drugs

Since the early seminal work in the preclinical and clinical development of cisplatin, several thousand analogs have been synthesized and tested for properties that would enhance its therapeutic index. About 13 of these analogs have been evaluated in clinical trials, but only one (carboplatin) has provided definite advantage over cisplatin and achieved worldwide approval. Nine platinum analogs are currently in clinical trials around the world ormaplatin (tetraplatin), oxaliplatin, DWA2114R, enloplatin, lobaplatin, CI-973 (NK-121), 254-S, JM-216, and liposome-entrapped cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum (II) (LNDDP)] (Weiss and Christian, 1993). Fig. 1 presents the chemical structures of cisplatin and four of its analogs including carboplatin, oxaliplatin, ormaplatin and enloplatin.

From the molecular perspective, cisplatin represents a perfect example of how a small alteration in chemical structure can significantly affect biological activity in target cell (Goodsell, 2006). As illustrated in Fig. 2, cisplatin, carboplatin and oxaliplatin are composed of doubly charged platinum ion surrounded by four ligands, with the amine ligands on the left forming stronger interactions with the platinum ion, and the chloride ligands or carboxylate compounds on the right forming leaving groups allowing the platinum ion to form bonds with DNA bases (Goodsell, 2006).

Carboplatin or Cis diammine (1,1-cyclobutanecarboxylato) platinum (II) is a chemotherapeutic drug used for cancers of ovaries, lung, head and neck. In terms of its structure, carboplatin differs from cisplatin in that it has a bidentate dicarboxylate (CBDCA) ligand in place of the two chloride ligands, which are the leaving groups in cisplatin (Figs. 1 and 2). It exhibits lower reactivity and slower DNA binding kinetics, although it forms the same reaction products in vitro at equivalent doses with cisplatin. Unlike cisplatin, carboplatin may be susceptible to alternative mechanisms. Some studies show that cisplatin and carboplatin cause different morphological changes in MCF-7 cell lines while exerting their cytotoxic behavior (Natarajan et al., 1999). The diminished reactivity limits protein–carboplatin complexes, which are excreted. The lower excretion rate of carboplatin means that more is retained in the body, and hence its effects are longer lasting (a retention half-life of 30 h for carboplatin, compared to 1.5–3.6 h in the case of cisplatin).