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Review Article

Coordination compounds in cancer: Past, present and perspectives

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ABSTRACT

Metal-based coordination compounds have been used throughout the history of human medicine to treat various diseases, including cancer. Since the discovery of cisplatin in 1965, a great number of metal coordination complexes, such as platinum, ruthenium, gold or copper have been designed, synthesized and tested in order to develop clinically effective and safe drugs. Currently, many reviews cover applications of cytostatic metal complexes pointing out the most promising examples of platinum- and non-platinum-based compounds in preclinical and clinical trials. However, recent comprehensive reviews covering chemical and biological aspects of metal-based coordination compounds in cancer therapy are still rare. In this review we wish to provide an overview of the coordination chemistry of current and novel cytostatic compounds, including an outline of their design and rationale of synthesis, and summarize bio-chemical reactivity and physicochemical properties of candidate metal complexes.

Introduction

Cancer is nowadays one of the leading causes of death in the developed world. Biologically, cancer represents a vastly heterogenic group of diseases sharing several common traits. One of these hallmarks is sustained proliferation, resulting in uncontrolled tumour growth (Hanahan and Weinberg, 2011). An extensive research has been done to characterize antiproliferative effect of various classes of compounds, ranging from naturally occurring molecules and their derivatives, to organometallic and inorganic compounds and their application in cancer therapy. The fortuitous discovery of the cytotoxic properties of cisplatin (diamminedichloroplatinum (II)) in 1965, opened new avenue for the application of metal complexes in cancer therapy (Arnesano et al., 2011) (Fig. 1). The antiproliferative effect of cisplatin and other compounds, however, induces adverse effects on normal tissues,

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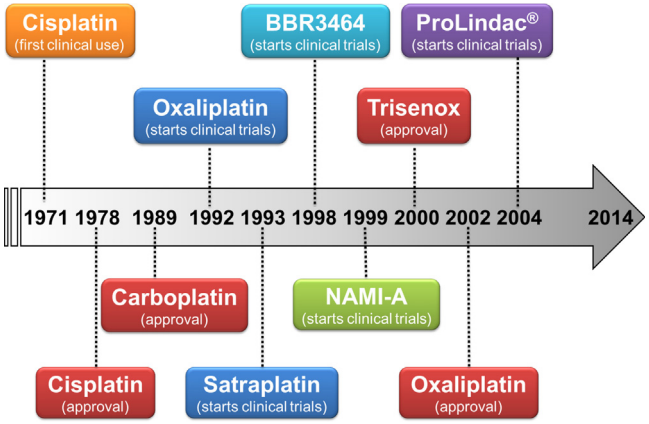

Fig. 1 – Historical overview of the cytotoxic metal and metalloid complexes that have been approved or entered the clinical practice.

decreasing therapeutic effectivity. Moreover, in many cancers, tumour cells may acquire resistance to the metal-based cytotoxic therapy resulting in virtually incurable relapsing disease (Desoize, 2004).

In the last 15 years, a great effort has been dedicated to the development of more effective and less toxic drugs. Various new trans-platinum(II) and platinum(IV) complexes have been synthesized, and some of them have been selected for clinical trials (Kelland et al., 1999), but with varying effectivity and safety. Therefore, less toxic metals, such as ruthenium, gold or copper were introduced as promising candidates for effective and safe therapy (Tiekink, 2002; Clarke, 2002; Marzano et al., 2009; Nobili et al., 2010). Various reviews have been published on the use of metal complexes as anticancer agents, with the intent to give an overview of the proposed approaches concerning the application of these systems in clinical practice (Tiekink, 2002; Boulikas et al., 2007; Milacic et al., 2008; Bruijnincx and Sadler, 2008; Todd and Lippard, 2009; Vilmar and Sørensen, 2009; Esteban-Fernández et al., 2010; Tisato et al., 2010; Wang and von Recum, 2011; Beija et al., 2012; Babu et al., 2013; Maldonado et al., 2013; Sukumar et al., 2013; Cao-Milán and Liz-Marzán, 2014; Mjos and Orvig, 2014; Muhammad and Guo, 2014; Petrelli et al., 2014). However, the majority of the available reviews point out the most relevant examples of platinum- or non-platinum-based compounds, eventually focusing on one particular metal ion or making a compendium on two or more metal ions. The aim of this review is to bridge a gap by summarizing on historical background, novel trends in synthesis of new metal complexes with antiproliferative effects and to describe their chemical reactivity, pharmacokinetic properties and interactions in the biological and biomedical context.

Platinum-based complexes

Platinum(II) complexes

Cisplatin and transplatin

Diamminedichloroplatinum(II) is a complex with square planar geometry and two possible *cis* and *trans* geometrical isomers, cisplatin and transplatin (Fig. 2).

Cisplatin has been a first-line therapy in many cancers and nowadays is used either alone or in combination with other compounds in many cancers, *e.g.* testicular, ovarian or bladder cancers or leukaemias. Due to low chemical stability of cisplatin, the direct intravenous administration is preferred over the other forms. In the blood stream, cisplatin rapidly interacts with plasma proteins such as human serum albumin (HSA), haemoglobin (Hb) or transferrin (Tf) (Rudnev et al., 2005) and 24 h after administration, 95% of cisplatin is bound to plasma proteins (Sooriyaarachchi et al., 2011). Cisplatin is widely distributed into body fluids and tissues, reaching the highest concentrations in kidneys (0.4–2.9 μg/g), liver (0.5–3.7 μg/g wet weight), and prostate (1.6–3.6 μg/g). Minor concentration levels can be found in muscles, bladder, testes, pancreas, and spleen (Stewart et al., 1982). Penetrance of cisplatin into tumour tissue differs in different cancers. However, the concentration of cisplatin and its analogues positively correlates with reduction of tumour mass and clinical parameters, such as recurrence free and overall survival, *e.g.* in non-small-cell lung cancer (Kim et al., 2012).

Cisplatin enters the cells either passively by a simple diffusion or by active protein-mediated transport systems, *e.g.* human organic cation transporter (hOCT2) and the copper transport protein (Ctr1) (Ishida et al., 2002; Song et al., 2004; Burger et al., 2010). In cytoplasm, cisplatin is hydrolysed and one of the two chloride ligands is displaced by a water molecule to form the $[PtCl(H_2O)(NH_3)_2]^+$ species, allowing for the binding of the platinum ion to DNA bases, especially in the N7 position of guanine and adenine and the N3 of cytosine, forming the monofunctional adduct $[PtCl(DNA)(NH_3)_2]^+$. The second chloride ligand can be displaced by a water molecule to

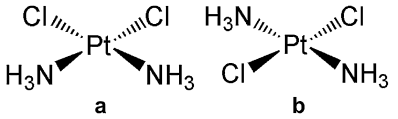

Fig. 2 – Structures of the *cis* (a) and *trans* (b) isomers of diamminedichloroplatinum(II), the cisplatin and transplatin, respectively.