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Development of anticancer agents: wizardry with osmium

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Teaser: The drawbacks of currently used cancer chemotherapeutics have led to the development of novel anticancer agents with alternative modes of action. Compounds featuring an osmium center are a promising class of new therapeutics with widely tunable activity.

Platinum compounds are one of the pillars of modern cancer chemotherapy. The apparent disadvantages of existing chemotherapeutics have led to the development of novel anticancer agents with alternative modes of action. Many complexes of the heavy metal osmium (Os) are potent growth inhibitors of human cancer cells and are active *in vivo*, often superior or comparable to cisplatin, as the benchmark metal-based anticancer agent, or clinically tested ruthenium (Ru) drug candidates. Depending on the choice of ligand system, osmium compounds exhibit diverse modes of action, including redox activation, DNA targeting or inhibition of protein kinases. In this review, we highlight recent advances in the development of osmium anticancer drug candidates and give insight into their cellular mechanisms of action.

Introduction

The field of inorganic medicinal chemistry has boomed in recent years following the hallmark discovery of the anticancer activity of DNA-targeting cisplatin and later its analogs carboplatin and oxaliplatin. Nowadays, these platinum-based drugs are routinely used in approximately 50% of cancer therapy regimens [1]. However, similar to many other chemotherapeutics, their therapeutic efficacy is limited by the emergence of drug resistance and severe adverse effects [2]. This has provided great impetus for investigations of metal complexes with higher selectivity and enhanced efficacy, thus creating a new paradigm in the field of anticancer drug discovery. Consequently, the antitumor properties of different metal complexes based on gold, gallium, titanium, arsenic, iron, ruthenium and osmium have been evaluated [3–5]. These metal ions display different chemical properties in terms of oxidation state, redox potential, rate of hydrolysis or ligand exchange and binding preferences to biomolecules. Prominent examples of nonplatinum anticancer complexes are ruthenium and gallium coordination compounds and titanocenes [3,6], all of which have been evaluated in clinical trials. Moreover, arsenic trioxide (Trisenox®) was approved by the US Food and Drug Administration (FDA) in 2000 for the treatment of relapsed acute promyelocytic leukemia [7].

The group-8 metals iron, ruthenium and osmium, have found particular interest in metal-based anticancer drug development. The most promising iron compounds are the ferrocenyl derivatives of tamoxifen, which target hormone receptors in breast cancer cells [8,9]. Ruthenium is represented by several biologically active compounds and imidazolium *trans*-[tetrachlorido(dimethylsulfoxide)(1*H*-imidazole)ruthenate(III)] (NAMI-A), indazolium *trans*-[tetrachloridobis(1*H*-indazole)ruthenate(III)] (KP1019) and sodium *trans*-[tetrachloridobis(1*H*-indazole)ruthenate(III)] (KP1339) (Figure 1) have been tested in clinical trials. In preclinical tests, NAMI-A showed strong efficacy towards solid tumor metastases, whereas the indazole complexes KP1019 and KP1339 demonstrated excellent activity in several primary tumor models. Ru(III) complexes are considered as prodrugs that can be activated by reduction to Ru(II) species *in vivo* and binding to plasma proteins is considered important in their modes of action. Ruthenium complexes in oxidation state 2+ are more labile and can bind more rapidly to biomolecules [10]. Organometallic half-sandwich Ru(II)-arene complexes have also revealed their potential as tumor-inhibiting agents. Two representative examples of these organometallic compounds are [Ru(η^6-*p*-cymene)(PTA)Cl_2] PTA = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (RAPTA-C) and [Ru(η^6-biphenyl)Ru(en)Cl]$^+$ (RM175; en = ethylenediamine). Whereas the ethylenediamine complex displayed *in vitro* anticancer activity similar to that of cisplatin and was more active in cisplatin-resistant *in vivo* models, the RAPTA complexes inhibited metastasis *in vivo*, whereas were inactive *in vitro* [5,11].

Despite extensive research devoted to iron and ruthenium complexes during the past two decades, studies on biologically active osmium complexes are scarce. However, osmium offers several features distinct from ruthenium, including the preference for higher oxidation states, slower ligand exchange kinetics, stronger π-back-donation from lower oxidation states and markedly stronger spin-orbit coupling. Therefore, osmium complexes are considered interesting alternatives to ruthenium-based anticancer agents because of their relative inertness and sufficient stability under physiological conditions. Various synthetic approaches and ligand systems have been investigated, often to design structural analogs of well-established ruthenium compounds. This resulted in a structurally diverse library of osmium complexes, including mononuclear coordination complexes, multinuclear clusters and organoosmium compounds with a wide variety of chemical and biological properties [12–16]. In this