Coordination Chemistry Reviews 284 (2015) 286–297

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Effect of chirality in platinum drugs

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Contents

ARTICLE INFO

Article history:
Received 19 May 2014
Received in revised form 16 July 2014
Accepted 17 July 2014
Available online 27 July 2014

Keywords:
Antitumor drugs
Chirality effect
Platinum-DNA
Non-covalent interactions
Mutagenicity and antitumor activity

ABSTRACT

Biological targets, such as proteins and nucleic acids, are chiral, therefore stereoisomers of chiral molecules interact with these targets differently and, indeed, the antitumor drug oxaliplatin contains only one enantiomer (*R*,*R*) of its 1,2-cyclohexanediamine (DACH) ligand. In this review article we illustrate the effect of chirality in platinum drugs in relation to different aspects spanning from cytotoxicity to mutagenicity, from differences in the reaction with DNA and processing of DNA lesions to gene expression and proteomic profile, to conclude with a section on the use of platinum compounds with chiral amines to investigate non-covalent interactions in adducts of platinum drugs with nucleotides and DNA. Unlike the deep understanding of the interactions at a molecular level which has allowed us to interpret the different antitumor activity and mutagenicity of DACH enantiomers and to propose an explanation for the particularly high efficacy of cisplatin toward the testis tumor, it is noted that "omics" investigations are still scanty and a reassessment of chirality effects, through molecular profiling technologies, would be timely as well as appropriate.

1. Introduction

Cisplatin (**1**, *cis*-[$PtCl_2(NH_3)_2$]) is one of the most commonly used anticancer agents, and is integrated in a large number (>50%) of chemotherapy regimens [1]. The extraordinary and long-term research activity focusing on metal-based anticancer compounds was inspired by the great efficacy of cisplatin in testicular cancer, where cure rates over 80% are obtained [2]. The hope was to repeat that clinical success in other solid tumors. To leave nothing unexplored, compounds of metals other than platinum, were also investigated. Such an impressive research effort has been sustained by the great versatility of metals and metal compounds, whose properties can be variously modulated depending upon the metal itself, its oxidation state, number and type(s) of ligands, and coordination geometry of the complex.

This big research investment has led to the introduction in worldwide clinical use of two more platinum drugs, carboplatin and oxaliplatin, approved by FDA in 1989 and 2002, respectively (Fig. 1) [3]. Carboplatin has the same indications of cisplatin, but a different toxicity profile. In contrast, oxaliplatin has a spectrum

Abbreviations: cisplatin, *cis*-[$PtCl_2(NH_3)_2$]; BIP, 2,2′-bipiperidine; CL, 1,2-GG intrastrand cross-link; CP-GG, cross-link given by cisplatin; CNS, central nervous system; DAB, 2,3-diaminobutane; DACH, diaminocyclohexane; DMC, dimethylcantharidine; EN, ethylenediamine; G, guanine base; GI, growth inhibition; GMP, guanosine monophosphate; HH, head-to-head; HT, head-to-tail; HMGB1, high mobility group box protein 1; NCI, National Cancer Institute; NER, nucleotide excision repair; oxaliplatin, l-OHP, [Pt(oxalate)(*R*,*R*-1,2-DACH)]; *cis*-OHP, [Pt(oxalate)(*R*,*S*-1,2-DACH)]; d-OHP, [Pt(oxalate)(*S*,*S*-1,2-DACH)]; OX-GG, cross-link given by oxaliplatin; rs, Spearman rank correlation coefficient.

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http://dx.doi.org/10.1016/j.ccr.2014.07.016
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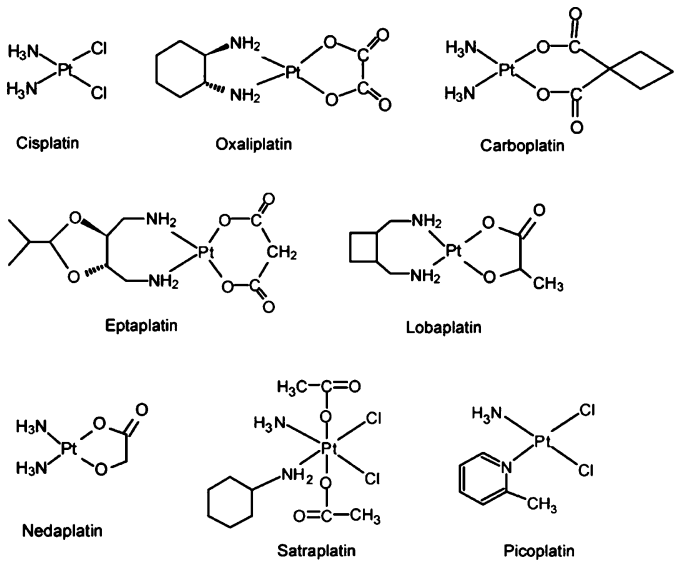

Fig. 1. Structural formulae of platinum drugs in clinical use or undergoing clinical trials.

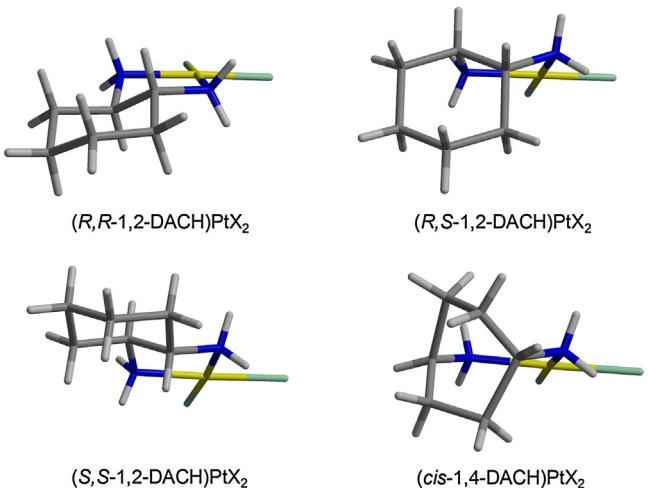

Fig. 2. Three-dimensional structures of various isomers of diaminocyclohexane (DACH) ligand able to *cis*-coordinate to a Pt center. Color codes: hydrogen, white; carbon, gray; nitrogen, blue; platinum, yellow; X atom, green. 3D representations were obtained with the program PC-MODEL (Serena Software).

of activity different from that of cisplatin. Indeed, oxaliplatin is indicated in the treatment of colorectal cancer, a malignancy quite refractory to cisplatin and carboplatin, while it has no effect in germ cell tumors or squamous cell carcinomas. Therefore, oxaliplatin satisfies the requirements for novel compounds with a spectrum of activity different from cisplatin. However, the impact of oxaliplatin on colorectal cancer is hardly comparable to that of cisplatin on germ cell tumors. Other platinum compounds are used regionally (Nedaplatin in Japan, Lobaplatin in China and Heptaplatin in Korea) or undergoing clinical trials with changing fortunes (*e.g.* Picoplatin and Satraplatin) (Fig. 1) [4–6], and many strategies are being developed to improve tumor targeting, so as to reduce toxicity [7–13], as well as to modify the DNA interaction properties [14,15] and/or the biological targets [16,17].

Oxaliplatin has gained increasing attention not only for its lack of cross-resistance with cisplatin [18–20] but also for its intrinsic chirality. The trans form of 1,2-diaminocyclohexane (1,2-DACH) can exist as *R*,*R* (*R*,*R*-DACH for short) and *S*, *S* (*S*,*S*-DACH for short) isomers. The *cis* form of 1,2-diaminocyclohexane (*R*,*S*-1,2-DACH), the *meso* form, is not chiral since it contains a plane of symmetry and has been much less investigated. Also non chiral is the *R*,*S* form of isomeric 1,4-diaminocyclohexane (*cis*-1,4-DACH) (Fig. 2).

Only the platinum complex with *R*,*R*-DACH has been approved for clinical use ([Pt(oxalate)(*R*,*R*-DACH)], oxaliplatin). When the two enantiomers interact with a protein or a double-helical DNA, which also have a chiral structure, there should be differences. Indeed, differences in antitumor activity were observed, although they were probably not large [21–25]. Differences in mutagenicity were also observed [26,27], usually the more active enantiomer (*R*,*R*) being the less mutagenic. This interesting observation inspired research programs aiming to identify the causes of these differences.

Since the antitumor effect of platinum compounds mainly results from their ability to damage DNA (by forming various types of covalent adducts which affect essential processes, such as replication and transcription, ultimately leading to cell death) [18,28–30], the mode of interaction with DNA has been the focus of several investigations aiming to highlight differences between cisplatin and oxaliplatin and between oxaliplatin and its *S*,*S*-enantiomer. As it will be shown in this review article, the deep research carried on in this field has not only lead to an explanation of the greater antitumor activity of oxaliplatin and greater mutagenicity of its *S*,*S*-enantiomer, but also given support to the prevailing hypothesis on the mechanism of action of platinum drugs.

Chiral ligands similar to DACH (that is having two chiral carbon centers in the chain bridging the two platinum-coordinating amine groups) have also been exploited as a tool to unravel non-covalent interactions in adducts of platinum drugs with nucleobases. These studies have led to some important acquisition about the multiple conformers that characterize platinum adducts with nucleotides and DNA and how these can be modulated by the size and chirality of the amine carrier ligand(s).

A fundamental contribution to the present understanding of cancer molecular and cellular biology comes from gene expression microarray technologies. Developed in the 1990s, DNA microarrays can monitor, simultaneously, RNA products of thousands of genes. Transcription profiling can provide unprecedented and comprehensive information on which genes are switched on (or off) when tumor cells grow, proliferate, differentiate, or respond to molecular signals as well as to therapeutic agents. Thus, the transcriptional profiling approach can represent a unique tool for investigating differences between antitumor drugs belonging to the same family such as cisplatin and oxaliplatin or oxaliplatin and its *S*,*S*-enantiomer.

Although scientists have initially focused on the characterization of platinum-DNA interaction [31], protein-bound platinum represents the most part of administered drug in the case of cisplatin, both in the extracellular medium (up to 98% of cisplatin interacts with albumin) [32] and into the cytoplasm [33], binding to S-donors being markedly favored [34]. Reactions occurring with cytosolic components are generally retained responsible for the broad spectrum of side effects [35], and contribute to resistance [36]. Consequently, the investigation of platinum interactions with biological molecules different from DNA is an important task of both toxicity- and resistance-oriented research programmes [37]. In addition, interaction of platinum drugs with the plasma membrane [38] or with regulatory proteins [39] (in addition or as an alternative to DNA damage) is also gaining consideration in relation to the cytotoxic effect of platinum compounds. Interestingly, antitumor platinum compounds that do not interact with cellular DNA have been recently reported [40]. In this context, the relevance of protein targets appears evident. Therefore, similarly to genomic investigations mentioned in the previous paragraph, also the basal