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Drug transporters of platinum-based anticancer agents and their clinical significance

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ABSTRACT

Platinum-based drugs are among the most active anticancer agents and are successfully used in a wide variety of human malignancies. However, acquired and/or intrinsic resistance still represent a major limitation. Lately, in particular mechanisms leading to impaired uptake and/or decreased cellular accumulation of platinum compounds have attracted attention. In this review, we focus on the role of active platinum uptake and efflux systems as determinants of platinum sensitivity and -resistance and their contribution to platinum pharmacokinetics (PK) and pharmacodynamics (PD). First, the three mostly used platinum-based anticancer agents as well as the most promising novel platinum compounds in development are put into clinical perspective. Next, we describe the presently known potential platinum transporters – with special emphasis on organic cation transporters (OCTs) – and discuss their role on clinical outcome (i.e. efficacy and adverse events) of platinum-based chemotherapy. In addition, transporter-mediated tumour resistance, the impact of potential platinum transporter-mediated drug–drug interactions, and the role of drug transporters in the renal elimination of platinum compounds are discussed.

1. Introduction

Platinum-based drugs are among the most active anticancer agents and are used as single agent or in combination with other cytotoxic agents and/or radiation therapy in the management of a broad spectrum of human malignancies, including testicular, ovarian, head and neck, colon, bladder, gastric, and lung cancer (Ardizzoni et al., 2007; Go and Adjei, 1999; Lebwohl and Canetta, 1998; McWhinney et al., 2009; Raymond et al., 1998; Rixe et al., 1996; Zhang et al., 2006). Although most patients initially respond well to platinum-based chemotherapy, a considerable number of patients eventually develop drug resistance and relapse (Kollmannsberger et al., 2006). In spite of many efforts to circumvent platinum resistance and to reduce the toxicity of platinum-containing anticancer regimens, the development of either severe side effects, including nephro-, neuro- and ototoxicity, or clinical resistance, are frequent reasons for treatment discontinuation (Giaccone, 2000; McWhinney et al., 2009).

Platinum resistance is considered multi-factorial and includes both mechanisms that limit the formation of platinum–DNA adducts as well as mechanisms that prevent cell death following drug-induced damage (Table 1) (Shahzad et al., 2009; Brabec and Kasparkova, 2005; Stordal et al., 2007; Borst et al., 2008). Actually, reduced cellular accumulation of platinum either by impaired uptake or increased efflux is often found in cells selected for cisplatin resistance, both *in vivo* and *in vitro*, and is generally considered as one of the most consistent characteristics of platinum resistant cells (Gately and Howell, 1993).

Previously, passive diffusion through the cellular lipid bilayer was considered to be the dominant process involved in drug uptake and distribution. However, more recently the concept of carrier mediated and active uptake of commonly prescribed drugs, has become rule rather than exception (Dobson et al., 2009). Compelling evidence for a more prominent role of carrier-mediated uptake is rapidly cumulating in the literature (Dobson and Kell, 2008). Facilitated or active transport systems, as well as passive diffusion, are both relevant for the cellular uptake of platinum drugs (Andrews et al., 1990; Gately and Howell, 1993; Johnson et al., 1998). In addition general drug uptake/efflux systems in the intestine, liver and kidney are increasingly found to be important and may have a major impact on drug disposition and response to platinum-based chemotherapy (Terada and Inui, 2007). Thus, (membrane) transporters of platinum compounds, including solute carriers (SLCs) and in particular organic cation transporters (OCTs) belonging to the SLC22 subfamily, may at least in part, predict the platinum sensitivity/resistance of the tumour, markedly affect critical pharmacokinetic (PK) parameters, and determine the severity of platinum-associated adverse events.

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Table 1
Major cellular mechanisms involved in platinum resistance.

Mechanisms limiting platinum–DNA adduct formation
I. Impaired transport leading to reduced platinum accumulation (this review)
(a) Decreased drug uptake (influx)
(b) Increased drug efflux
II. Inactivation of platinum compounds by sulfur-containing molecules like glutathione and metallothionein
Mechanisms preventing cell death following drug-induced damage
III. Increased repair of platinum–DNA adducts
IV. Increased platinum–DNA adduct tolerance
V. Failure to provoke apoptotic pathways

Here we discuss the involvement of drug transporters in platinum uptake, efflux, distribution and (renal) elimination as well as their potential effect on treatment efficacy, on critical PK parameters and on the severity of platinum-associated adverse events. Finally, we assess the clinical relevance of platinum transporter-mediated drug–drug interactions.

2. Platinum compounds in clinical use

To date, three platinum drugs have been approved for clinical use, i.e. cisplatin (1978), its less toxic analogue carboplatin (1989) and oxaliplatin (2002). Various new generation platinum compounds with different properties have been developed over the years (Kelland, 2007a,b; Shah and Dizon, 2009). Some of these are currently evaluated in clinical trials. Especially, those with an improved safety profile, those exhibiting antitumor activity against tumour types resistant to approved platinum-based drugs and those enabling another route of administration with concomitantly altered PK parameters, such as orally formulated platinum compounds, receive special attention. In addition, novel delivery mechanisms of established platinum drugs are explored with emphasis on improving their uptake in tumour cells. For instance, liposomal formulations, encapsulations in nanocapsules, or linking the platinum moiety to physiological proteins have been evaluated (de Jonge et al., 2010; Shah and Dizon, 2009; Stathopoulos, 2010).

2.1. Cisplatin

Cisplatin (Fig. 1) has been recognized for its antineoplastic activity since the 1960s and is the most widely used cytotoxic drug in the US (McWhinney et al., 2009). It is generally accepted that the major target of cisplatin is nuclear DNA and that its antitumor effect is largely dependent on the level of interstrand and/or intrastrand cross-links (Zwelling and Kohn, 1979). The platinum-induced lesions or DNA adducts activate various signal-transduction pathways involved in DNA replication and transcription, DNA-damage recognition and repair, interfere with essential steps in cell cycle progression and cause cell growth arrest, and finally trigger the induction of apoptosis (Siddik, 2003). The extent of adduct formation, the cellular response to these cytotoxic lesions, and especially the rate of cellular repair of the DNA lesions determine the cellular effect of cisplatin and the ultimate fate of the platinum-treated target cell, i.e. either repair of the DNA damage culminating in cell survival or irreversible activation of the apoptotic cell death program (Brabec and Kasparkova, 2005). The introduction of cisplatin-based chemotherapy in the mid-1970s has advanced the management of various types of cancer, including urologic, gynaecologic and paediatric tumours and significantly improved the treatment outcome of testicular germ cell tumours, with cure rates for the latter approaching 90–95% (Raghavan, 2003). This has come at the cost of toxicity to the kidneys, the nervous system and gastrointestinal tract (Yao et al., 2007). These (sometimes) severe side effects have prompted the search for less toxic platinum analogues.

2.2. Carboplatin

Carboplatin (Fig. 1) entered the clinic in the mid-1980s. Carboplatin is a more stable analogue of cisplatin with in some tumour types equivalent activity but to some extend milder side effects (Ardizzoni et al., 2007). While carboplatin and cisplatin induce the same types of platinum-DNA adducts a 20–40-fold higher concentration of carboplatin is required and the rate of adduct formation is about 10-fold slower for carboplatin. Carboplatin is currently part of the first-line combination therapy of ovarian and lung cancer (Ardizzoni et al., 2007), but is less active than the parent compound in other diseases. Notably, its cross-resistance with cisplatin limits its application in cisplatin-resistant malignancies.

2.3. Oxaliplatin

Oxaliplatin is a third-generation platinum compound with a large 1,2-diaminocyclohexane (DACH) carrier ligand and an oxalate-leaving group (Fig. 1). This particular platinum compound has a different spectrum of resistance as compared to that of cisplatin or carboplatin (Rixe et al., 1996), and, has proven activity against cisplatin- and carboplatin-insensitive tumour types (Mishima et al., 2002; Misset et al., 2000; Raymond et al., 2002). Oxaliplatin-induced cytotoxic platinum adducts are recognized and processed differently compared to those formed by cisplatin and carboplatin. This has been suggested to explain why oxaliplatin-induced lesions have a much bigger impact despite the fact that oxaliplatin forms significantly fewer DNA adducts compared to cisplatin (Raymond et al., 2002). *In vitro* DNA repair studies revealed that these distinct platinum DNA lesions are equally well removed by the nucleotide excision repair system. However, in contrast to the cisplatin-induced DNA lesions, the cytotoxic DNA adducts evoked by oxaliplatin are hardly recognized by the mismatch repair (MMR) system and accordingly it was found that oxaliplatin has substantial and proven activity in MMR-defective cell lines (Vaisman et al., 1998). It has been proposed that the binding of the MMR complex to Pt-DNA adducts initiates a signaling pathway leading to cell cycle arrest and/or apoptosis. Thus the MMR complex is implicated in the cytotoxic activity of cisplatin. Accordingly, defects in MMR are associated with a modest to moderate level of resistance to cisplatin. Evidently, MMR seems to be an integral part of cisplatin-induced cytotoxicity, but not of oxaliplatin explaining why MMR-deficient cells are still susceptible to the cytotoxic activity of oxaliplatin (reviewed by Raymond et al., 2002). Hence, oxaliplatin was found to be active in locally advanced and metastatic colon cancer (Fu et al., 2006), which is frequently characterized by defects in MMR genes, and in which cisplatin and carboplatin are essentially inactive (Raymond et al., 2002; Rixe et al., 1996). In addition, oxaliplatin has been used in clinical trials for a number of other GI- and non-GI cancers and has proven anticancer activities to e.g. ovarian, gastric and oesophageal cancer (Fu et al., 2006; Van Meerten et al., 2007). Oxaliplatin is frequently compromised by the development of a sensory and motor neuropathy (Mishima et al., 2002), but is markedly less nephrotoxic than cisplatin and less myelosuppressive than carboplatin.

2.4. Satraplatin

Satraplatin (JM216) (Fig. 1) is a platinum compound, originally developed as an orally applicable version of carboplatin (Choy et al., 2008). Once absorbed via the mucosa of the gastrointestinal tract, satraplatin is rapidly biotransformed to yield at least six complex metabolites, including its most active platinum(II) containing