

TOXIC EFFECTS OF METALLOPHARMACEUTICALS

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TOKSIČNI EFEKTI METALOFARMACEUTIKA

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Received / Priljubljen: 27. 09. 2016.

Accepted / Prihvaćen: 08. 10. 2016.

ABSTRACT

Discovery of the metallopharmaceutical cisplatin and its use in antitumour therapy has initiated the rational design and screening of metal-based anticancer agents as potential chemotherapeutics. In addition to the achievements of cisplatin and its therapeutic analogues, there are significant drawbacks to its use: resistance and toxicity. Over the past four decades, numerous transition metal complexes have been synthesized and investigated *in vitro* and *in vivo*. The most studied metals among these complexes are platinum and ruthenium. The key features of these investigations is to find novel metal complexes that could potentially exert less toxicity and equal or higher antitumour potency and to overcome other pharmacological deficiencies. Ru complexes have a different mode of action than cisplatin does, some of which are under clinical trials for treating metastatic or cisplatin-resistant tumours. This review consists of the current knowledge, published and unpublished, related to the toxicity of metallopharmaceuticals, and special attention is given to platinum [Pt(II) and Pt(IV)] and ruthenium [Ru(II) and Ru(III)] complexes.

Key words: antitumor therapy, metallopharmaceuticals, platinum complexes, ruthenium complexes, toxicity

SAŽETAK

Otkrićem cisplatine, metalofarmaceutika kojima se postigao ogroman uspeh u terapiji tumora započeo je proces racionalnog dizajna i ispitivanja agenasa na bazi metala kao potencijalnih citostatika za hemijoterapiju. Pored navedenog uspeha cisplatina i njeni terapijski analozi ispoljili su značajne nedostatke: pojava rezistentnosti i toksičnost. U poslednjih četiri decenije veliki broj kompleksa prelaznih metala je sintetisan i ispitivan *in vitro* i *in vivo*. Najviše proučavani prelazni metali su platina i rutenijum. Ključni cilj ovih istraživanja ogleda se u izvođenju novog metalofarmaceutika sa smanjenom toksičnošću, istim ili jačim antitumorskim dejstvom i prevaziđenim ostalim farmakološkim nedostacima. Kompleksi rutenijuma poseduju drugačiji mehanizam dejstva u poređenju sa cisplatinom a neki se ispituju u kliničkim studijama za lečenje metastaza tumora koji su rezistentni prema cisplatinu. Ova revija opisuje trenutna (publikovana i ne publikovana) saznanja koja se odnose na toksičnost metalofarmaceutika, pri čemu je posebna pažnja posvećena kompleksima platine [Pt(II) i Pt(IV)] i rutenijuma [Ru(II) i Ru(III)].

Ključne reči: antitumorska terapija, metalofarmaceutici, kompleksi platine, kompleksi rutenijuma, toksičnost



The wide use of metallopharmaceuticals in contemporary oncology dates to the discovery of cisplatin by Rosenberg and coworkers in 1965 (1). This discovery opened the gate to the unexplored world of metal-based chemotherapeutic agents, which have different pharmacokinetic, pharmacodynamic and pharmacological mechanisms of action than do conventional organic drugs (2). Today, there

are many successful metallopharmaceuticals that are primarily used in clinical trials not just to treat cancer but to fight a range of diseases, including parasitic and bacterial infections (3). Over the past several decades, several cisplatin analogues have been screened as potential antitumour agents, but of these, only two (carboplatin and oxaliplatin) have entered worldwide clinical use (4). The clinical use of



these agents is severely limited by their toxic side effects. In addition to platinum, special attention over the past several decades was paid to many ruthenium complexes because of their potential low toxicity. Numerous ruthenium complexes have been evaluated for clinical applications, particularly in the treatment of cancer due, in part, to the fact that Ru(II) and Ru(III) complexes exhibit a similar spectrum of kinetics for their ligand substitution reactions as Pt(II) complexes do (5). The representative group of cytotoxic Ru compounds are Ru(II) arene complexes, which were developed primarily by Dyson and coauthors (5) and Sadler and coauthors (6), although none of these compounds has yet entered clinical trials.

Toxicities

There are growing interests in designing new metallopharmaceuticals that are capable of overcoming the problems of clinically used drugs while maintaining their efficacy. The main goal is to reduce systemic toxicity and increasing the spectrum of activity. The toxicities associated with metallopharmaceuticals such as platinum and ruthenium complexes range from mild to severe. The most common and serious toxicities of these complexes are nephrotoxicity, neurotoxicity, ototoxicity and vascular toxicity (7,8).

Nephrotoxicity

Nephrotoxicity is associated with cisplatin treatment but is rare with the later-generation analogues carboplatin or oxaliplatin (9,10). Because cisplatin nephrotoxicity is stereospecific to the cis and not the trans isomer, the platinum atom is not the proximate nephrotoxicant. It is likely that a metabolite of cisplatin, possibly an aquated and/or hydroxylated complex, mediates the nephrotoxicity of cisplatin (11). The nephrotoxic effect of cisplatin appears to be related to its preferential uptake by the proximal tubular cells of the inner cortex and outer medulla, especially in the S3 segment. Other segments of the renal tubule also accumulate cisplatin, although to a lesser extent, and their damage may contribute to clinical nephrotoxicity (12). The persistent reduction (20% to 30%) in glomerular filtration found in long-term follow studies indicates that these cisplatin-induced changes are irreversible (13,14). Some investigators have reported that the severity of persistent renal impairment is correlated with the dose of cisplatin applied (14,15).

Based on current research, it is known that ruthenium complexes also show toxic effect on kidneys. However, a study by Kersten and coworkers suggested that compared to cisplatin, proteinuria was significantly lower after the administration of any of three ruthenium coordination complexes (KP418, KP692, KP1019) in rats (16).

Peripheral neuropathy (neurotoxicity)

The peripheral neuropathy was observed in patients with testicular cancer, and this is mainly attributed to cis-

platin. The primary target of cisplatin-induced damage in the central nervous system is the dorsal root ganglion of the spinal cord (17). The most frequent clinical signs of neurotoxicity are paraesthesia, dysesthesia, disturbances of position, vibratory sensations and relative sparing of motor units, which disappear in most cases after chemotherapy (18). Carboplatin is significantly less neurotoxic than cisplatin in conventional doses, but high doses of carboplatin are associated with sensory ataxia soon after treatment (19). In contrast, oxaliplatin neuropathy has a wide spectrum, ranging from an acute sensory neuropathy immediately following treatment to a chronic, dose-limiting neuropathy that usually takes several weeks of treatment to appear (20). Motor dysfunctions were associated with low serum levels of magnesium and can be managed by treatment with calcium gluconate or magnesium sulfate before and following treatment (21). Additionally, vitamin E has been shown to decrease sensory neuropathy in patients treated with cisplatin (22). Because there are almost no previous studies, to the best of our knowledge, that investigate the neurotoxicity of ruthenium complexes, it is important that future experimental research provide information about this type of toxicity.

Ototoxicity

The incidence of ototoxicity established by audiometric techniques is approximately 20% to 40% (17,22,23). Higher bolus doses of metallopharmaceuticals, especially cisplatin, have been shown to be more ototoxic and nephrotoxic than repeated infusion at lower doses in adults. Conversely, prolonged infusions in children are less nephrotoxic than bolus doses are (24,25). Cisplatin-induced ototoxicity depends on more than the dose, as there are marked interindividual variations in toxicity in patients receiving similar cumulative doses of this agent. Other factors are considered important, and it has been hypothesized that genetic variation may be a key component in determining a patient's susceptibility to the effects of cisplatin (23). Ototoxicity is probably caused by cisplatin damage to the secretory mechanism of the organ of Corti and manifests as high-frequency hearing loss and tinnitus (26). Ototoxicity observed with platinum complexes may be acute or delayed and irreversible, and no preventive treatments are available (27). In the literature, there is no clear evidence about the ototoxicity of ruthenium complexes, which was expected because as mentioned above, these complexes are not yet in clinical use.

Vascular toxicity

Vascular toxicity occurs in approximately 3% to 49% of patients, and one of the most common manifestations after treatment with metallopharmaceuticals is Raynaud's syndrome, a clinical consequence of small-vessel disease (28,29). Studies that used provocative testing suggested that even asymptomatic patients might exhibit a



vasospastic response to cold stimuli (29). Literature data suggest that it is a possible delayed onset, with a median time of 10 months after chemotherapy (30). Ruthenium complexes are still not approved for clinical use, so there are no reports about vascular toxicity to these metallopharmaceuticals.

The toxicities of metallopharmaceuticals are probably a result of the increased production of reactive oxygen species. In the literature data, there is evidence to support a role of metallopharmaceutical induced oxidative stress in each of these adverse effects (31,32). Both *in vitro* and *in vivo*, cisplatin has been shown to increase oxidative stress by increasing the levels of different free radicals (31,33). Additionally, some of the examined ruthenium complexes lead to increased cellular oxidative stress and promote cell death *via* apoptosis (34).

CONCLUSION

A vast number of metallopharmaceuticals has been evaluated as antitumour agents, but only a very small fraction has shown sufficient promise during preclinical evaluation to enter human clinical trials. It is believed that ruthenium complexes will demonstrate significant clinical advantages over the current platinum complexes (36). Considering the toxic potential of metallopharmaceuticals, further experimental studies and careful clinical monitoring during treatment are necessary to overcome this problem. Thus, efforts should be focused on designing more selective metallopharmaceuticals that possess the ability to overcome resistance and toxic side effects.

Oxidative stress is probably one of the molecular mechanisms in the development of toxicity induced by the administration of platinum or ruthenium complexes. Understanding the individual differences of metallopharmaceuticals and the potential for redox effects to manifest as toxicities is increasingly valuable, not only for existing therapies but also for tailoring clinical metal complex development. In addition to the design and screening of new metallopharmaceuticals, extensive efforts should be directed towards investigating their molecular mechanisms of action.

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