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Cisplatin Toxicity in Children with Malignancy

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Platinum' derivates are antineoplastic agents widely adopted for their efficacy for the treatment of many pediatric cancers. The use of cisplatin has positively influenced the results of the cure of different childhood malignancies. However, cisplatin-based treatments are limited by the risk of severe and progressive toxicities, such as oto- or nephrotoxicity, that can be more serious in very young children expecially when high cumulative doses and/or radiotherapy is administered. A correct knowledge of the cisplatin' pharmacological features might be of interest for clinicians in order to manage its potential toxicities. Based on the positive trend in the cure of children with cancer, it is crucial that all children receiving cisplatin-based chemotherapy have and appropriate and long-term follow-up to improve their quality of life.

Keywords: Cisplatin; Children; Nephrotoxicity; Neurotoxicity; Myelotoxicity; Ototoxicity.

The use of the cisplatin in the chemo-treatment of pediatric malignancies has contributed to positively impact on the chances of cure of children affected by tumor [1]. Regrettably, the cisplatin use can be limited by different toxicities that can include otological, neurological, nephrological, hematological toxicity, and emesis [2,3]. These potential toxicities can negatively impact on the adherence to the treatment and on the health status of children cured for their cancer.

The purpose of the present manuscript is to describe the main pharmacological and clinical features of cisplatin with a focus on its pharmacokinetic profile and toxic effects in order to promote the development of appropriate strategies for preventing them.

Pharmacokinetics

In the early 70s, cisplatin was among the first platinum compounds available for the clinical practice and since that time it continues to play a fundamental role in the current chemotherapy [4,5].

Cisplatin (cis-diamminedichloroplatinum II) structure contains a platinum atom surrounded by two ammonia groups and two chloride leaving groups in the cis-position (Figure 1). It is intracellulary activated by a replacement reaction in which the cisplatin' chloride ligands are replaced by water molecules with consequent platinum cations that can covalently bind with the purine DNA bases obtaining intra-strand and inter-strand cross-links [6].

The cisplatin' antineoplastic effects is mediated by the generation of cisplatin-DNA

adducts (N-7 adducts at d(GpC) and d(ApG)) able to block the DNA, RNA and protein synthesis, on the basis of the proliferative index of cancer cells [5,7].

The drug is characterized by a high binding affinity with plasma proteins: following the intra-venous administration of the cisplatin almost 90% bind with the plasmatic proteins. This binding of the platinum appears to significantly influence its pharmacokinetic profile and activity as only the unbound drug can have antineoplastic activity. The protein-bound platinum can persist in plasma for a long time and detected in urine for many hours or days up to 4 days [8,9]. On the contrary, the unbound drug appears to have a rapid metabolism with a brief half-life of less than 1 hour. In the pediatric population, the total and unbound platinum have very different half-lives ranging from 44 for total drug to 1.3 hours for unbound drug [10]. In addition, about 90% of the platinum is excreted by the kidney via glomerular filtration and tubular secretion and the remaining 10% by biliary excretion

Both the unbound cisplatin and the total platinum, which consists of bound and unbound platinum, can be measurable in serum, although only the ultra-filtrable platinum is related to the antitumor and toxic effects of the drug.

Ototoxicity

Up to 60% of children treated with cisplatin-based chemotherapy can be at risk of developing irreversible bilateral hearing loss [1,11-14]. The otological toxicity may develop when a high dosage of cisplatin is given intraperitoneally or intravenously. However, a single low dose of drug can be nevertheless ototoxic when infused retrograde into the common carotid artery due to the drug first-pass into the vertebral artery that provides blood to the cochlea [14,16].

Sensory cells of the inner ear are protected by a blood labyrinth barrier very similar to the blood-brain barrier. However, the platinum has been found in the cochlea tissues even in presence of a blood labyrinth barrier intact making the passage mechanism unclear [14,17].

This barrier can be evaded with the intrusion of the cisplatin directly into the cochlea or temporarily opening the barrier through the use of loop diuretics [18,19]. Alternatively, the combination of noise and cisplatin injection can favorite the passage of platinum into the cochlea [20]. The blood labyrinth barrier and the stria vascularis can be damaged by the noise exposure; also the cochlea can become more vulnerable due to the induction of the oxidative stress and the concomitant reduction of the antioxidant enzyme levels [18,20].

The damaged cochlear hair cells degenerate first at the base of the cochlea and then gradually towards the apex if the exposure to the drug is repeated over time [14,21]. At the level of the mitochondria of cochlear cells, alkylation of cisplatin is able to determine the mitochondrial production of factors favoring apoptosis and high levels of reactive oxygen species (ROS) with the consequence of activating caspases, thus triggering cell death. Moreover, the high toxic levels of ROS increase and amplify the degeneration following the damage of proteins and lipids and facilitating the exhaustion of the antioxidant agents of the cell [22]. Moreover, some data attribute to p53 a potential role in the initial development of the hair cell death process induced by the cisplatin administration [23,24]. The upregulation of p53 and later the upregulation induction of caspase 8-9, cytochrome-c and Bax can speed up the apoptotic cell death [25].

Myelotoxicity

Cisplatin can induce reversible and dose-related myelotoxicity. Clinically, it is generally of a mild level and can involve all three hematopoietic lines. Data from the literature suggest that cisplatin might determine in mice CFU-S and CFU-C progressive and cumulative toxicity [26]. Previous studies have reported serious leucopenia or thrombocytopenia up to 5% to 6% of patients including episodes secondary to haemolysis and erythropoietic toxicity [27-29].

Nephrotoxicity

Over the years, many studies have tried to identify the molecular mechanisms that are the basis of nephrotoxic cisplatin damage, I conclude that the damage is linked to its accumulation in renal tubular cells with the consequence of causing a direct inflammation, stress and damage oxidative, and finally to activate a mechanism of apoptosis with tubular lesion and dysfunction [30,31].

Alterations from cisplatin damage are found mainly in the epithelial cells that are located in the S3 segment of the proximal tubule; this site

is particularly damaged for the reason that in this renal site the concentration of cisplatin is about five times greater than the serum concentration. Furthermore, the OCT2 organic cation transporter is also involved in renal cisplatin damage, which is essential for active absorption in renal tubular cells. In fact, by administering cimetidine, which is an OCT2 substrate, the absorption of cisplatin and the consequent nephrotoxicity is reduced. As confirmation of the role of OCT2, Filipski et al. showed that the presence of a non-synonymous single-nucleotide polymorphism (SNP) in the OCT2 gene SLC22A2 (rs316019) is able to reduce its nephrotoxicity in patients receiving cisplatin [32,33].

Other studies on molecular pathogenesis have hypothesized that the nephrotoxicity of cisplatin may be due to the splitting of a cisplatin-glutathione conjugated with gamma-glutamyl transpeptidase (GGT) at the level of the luminal surface of the proximal renal tubules. GGT performs its function by initiating the catalysis of drugs conjugated with glutathione to mercapturic acids, some of which can be severely nephrotoxic [34].

Once penetrated into the tubular cells, cisplatin acts to damage nuclear DNA and especially mitochondria, leading to activation of both mitochondrial and non-mitochondrial pathways in apoptosis and necrosis processes. Mitochondria are particularly vulnerable to injury, due to the lack of any efficient DNA repair mechanism; their abundant presence in the proximal tubule may be at the basis of the vulnerability of this specific renal site to cisplatin damage [35]. In cisplatin-induced renal cell death processes, both the intrinsic mitochondria pathway and the endoplasmic reticulum stress pathway and extrinsic activation of TNF or Fas receptors are involved, although significant interactions between the two pathways are reported.

Furthermore, cisplatin is able to increase the renal expression of TNF-a, which in turn can induce apoptotic mechanisms, increase ROS production, promote the activation of pro-inflammatory cytokines and chemokines, thus performing a key role in the pathogenesis of cisplatin-induced renal damage.

The production of pro-inflammatory cytokines induces and amplifies an inflammatory response, with the infiltration of macrophages and lymphocytes, with the consequence of inducing severe interstitial fibrosis [36].

The study of the various mechanisms of cisplatin-induced toxicity has led to propose various potentially protective agents. For example, amifostine, vitamin C and E, allopurinol, melatonin, ebselen, erdosteine ??seem able to act against oxidative stress damage; erythropoietin and amifostine may play a cytoprotective and antiapoptotic role. Salicylates have been shown to reduce renal inflammation in cisplatin toxicity models as fibrates appear to prevent cisplatin nephrotoxicity in animal studies. However, of all these agents only a few have been applied in human studies [37,38].

Cisplatin can cause acute renal failure due to degeneration, necrosis, desquamation of epithelial cells of the proximal, distal tubules and collecting ducts, without evident glomerular morphological changes. Furthermore, tubular necrosis with dilated cystic tubules and interstitial fibrosis is observed in patients receiving long-term cisplatin treatment [38]. The tubular lesion appears before acute renal failure and haemodynamic dysfunction processes. The consequent reduction of mitochondria and ATPase activity and the coexistent reduction of the expression of solute, co-transporter and aquaphorin transporters at the level of the water channel determine a reduction of the tubular reabsorption capacity of sodium and water, thus increasing the water and sodium excreted. Patients may present with polyuria, reduction of urinary osmolarity after 24 and 48 hours from the infusion of cisplatin, although the glomerular filtration rate remains stable (GFR). Subsequently, also the GFR can be reduced and in the patients increases the urinary excretion of electrolytes such as sodium, potassium, magnesium, calcium, glucose and small amounts of proteins, with potential orthostatic hypotension. However, these alterations are often transient and renal function is usually restored 2-4 or more weeks after cisplatin treatment [39,40].

Cisplatin-induced renal damage is mainly acute damage, but may also result in several clinical pictures such as isolated hypomagnesemia (especially in patients receiving prolonged cisplatin treatment), Fanconi-like syndrome, hypocalcemia, renal salt wasting and reduced capacity of renal

concentration, hyperuricemia, distal tubular acidosis, thrombotic-based microangiopathy, transient proteinuria, erythropoietin deficiency [41].

In children receiving platinum-based chemotherapy nephrotoxicity, nephron toxicity, GFR reduction, hypocalcemia, hypomagnesaemia, hypopotassemia can occur. However, data on the long-term results of renal cisplatin damage in children are not conclusive, as chronic kidney damage often appears in adulthood [42,43].

Data on children reported that the risk of cisplatin nephrotoxicity is higher in older children (generally older than 10 years) compared to young children as well as the reduction in GFR was less frequent in children when they received a lower dose of cisplatin at 40 mg / m2 / dose [44].

Furthermore, the infusion rate of cisplatin in children appears to significantly influence the severity of renal damage: long-term cisplatin infusions appear to be less nephrotoxic than repetitive and intermittent bolus administrations [43].

Hyper-hydration with isotonic saline was the most frequently adopted strategy for reducing the incidence of renal cisplatin damage. Recent clinical guidelines have also established that the addition of diuretics, such as mannitol and furosemide, does not seem to offer greater nephroprotection than the use of hydration alone [41,45,46]. Hypomagnesemia itself may lead to an increased risk of cisplatin nephrotoxicity; therefore the continuous integration of magnesium (both during the administration of the cisplatin and between one cycle and another) must be part of the routine regimen [47].

In addition, other potentially nephrotoxic agents (such as iphosphamide, antibiotics, intravenous radiographic contrast) can contribute to increased renal damage and therefore should be avoided when patients are receiving cisplatin treatment [48].

Neurotoxicity

The neuropathy related to cisplatin administration is cumulative and dose-dependent. Up to approximately 50% of patients treated with cumulative doses of cisplatin greater than 300 or 600 mg / m2 may be present [49].

Clinical manifestations can be moderate to severe, with signs and symptoms of peripheral lesions, such as numbness, loss of vibration and sense of position, painful tingling and paresthesia, loss of taste, tremor, ataxia. Symptoms generally improve gradually after cisplatin withdrawal and very rarely neuropathy can become permanent [50].

Some researchers attribute to thiol compounds (such as amifostine, glutathione and melanocortin) a potential protective role against the development of cisplatin neurotoxicity [6]. Glutathione, although further studies are needed on its safety, appears to reduce the incidence of cisplatin neurotoxicity without interfering with the antineoplastic effect of the chemotherapy drug [51].

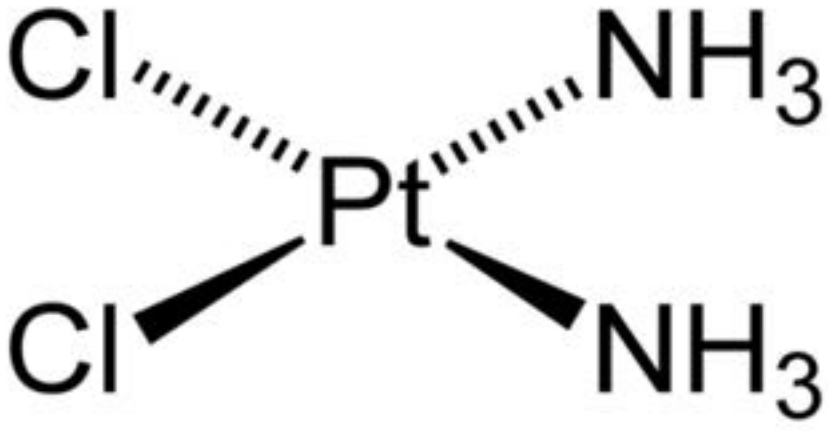

Fig. 1. Cisplatin chemical structure

The concentration of cisplatin in the DRG reduces the reserves of vitamin E, thus reducing resistance to oxidative stress; Pace et al. has shown that supplementing with vitamin E given before and after treatment with cisplatin may have a neuroprotective effect [52].

A deleterious interaction was described when cisplatin treatment was combined with cranial irradiation with the appearance of acute neurological symptoms of different severity such as coma, paralysis of multiple cranial nerves, quadriparesis, convulsions. Furthermore, the hyperhydration used to administer cisplatin can accentuate neurological disorders; therefore, caution should be exercised when treatment with cisplatin is planned in children with brain tumors. This treatment with cisplatin should be carefully considered, given the risk of significant hearing loss and acute neurological deterioration later [53].

Nausea and vomiting

Cisplatin frequently has nausea and vomiting as side effects. Vomiting caused by cisplatin may be early (= 24 hours after treatment) or delayed (> 24 hours after treatment). The use of 5-hydroxytryptamine (5-HT3) receptor antagonists has allowed to control and significantly reduce acute cisplatin-related emesis [34].

Risk factors

Studies on cisplatin toxicity have allowed us to identify various risk factors for children. Among the main reports were the cumulative dose of cisplatin, concomitant therapies with nephrotoxic or ototoxic drugs, a young age, suffering from tumors of the central nervous system (CNS) and receiving CNS radiation [54-58].

Age. Young children are at greater risk of developing cisplatin ototoxicity. Children under the age of 5 have a risk up to 21 times greater than developing a moderate / severe high frequency hearing loss compared to patients aged 15 to 20 [59]. This increased risk appears to be related to immaturity of cochlea cells or to a different pharmacokinetic of cisplatin in young children.

Radiation. The severity of hearing loss due to platinum compounds can be increased by previous craniospinal or concomitant radiotherapy treatments. This hearing loss can also occur when patients receive low cumulative platinum doses [60-62].

Cumulative dose. Increasing the cumulative dose of cisplatin increases the risk of ototoxicity. When the cumulative dose> 400 mg / m2 is exceeded, there is a significant risk of developing moderate to severe ototoxicity [59].

Nephro- and ototoxic drugs

Concomitant administration of aminoglycosides, bleomycin and loop-inhibitor diuretics may increase the risk of cisplatin-related ototoxicity [63].

Interpatient variability. The ability of renal excretion and protein binding by cisplatin appear to be determinant factors of interpatient variability. This variability, unlike adults, is very wide especially in very young children where the immaturity of the physiological processes responsible for the metabolism of the drug determines a slower elimination of platinum with a large volume of distribution [64-66]. Among the factors that can increase platinum ototoxicity, polymorphisms of the megalin gene have also been reported [67]. Megalin is a multiligand endocytotic receptor involved in the transport of cisplatin or cisplatin adducts. This receptor is found highly expressed in proximal renal tubular cells and in marginal cells of the vascular stria of the inner ear. Furthermore, the cumulative risk of developing ototoxicity appears to increase if other factors such as renal failure or intravenous bolus administration are present.

CONCLUSIONS

Cisplatin, since its discovery, is an important drug in the treatment of children with cancer. However, its widespread use is limited by several toxic effects that can negatively affect patients' quality of life due to the risk of toxicity of the auditory and nervous system, as well as kidney function and bone marrow.

In order to prevent toxicity and improve the quality of care of patients with pediatric cancer, an adequate knowledge of the pharmacokinetic and toxicological characteristics of platinum is recommended.

In particular, children, due to the physiological immaturity of metabolic systems, are more at risk of developing serious negative effects such as ototoxicity that can have a negative impact

on learning, on language acquisition and academic performance. Therefore, particular attention must be paid to the nefrologic and otological follow-up of these young patients to protect them from the disabling effects of potentially curative treatments.

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