This manuscript presents a review of the literature about nephrotoxicity of platinum derivatives, which are commonly used in paediatric oncology, such as cisplatin and carboplatin. It shows the incidence, pathomechanisms, risk factors, type and clinical features of the disorders. It presents differences in nephrotoxic effects of particular drugs, and describes possibilities of early detection and monitoring of clinical course and therapy. It emphasises the role of nephroprotective treatment. Hypomagnesiaemia and decreased glomerular filtration rate (GFR) are the most common clinical manifestations of cisplatin and carboplatin nephrotoxicity. The assessment of kidney function during active antineoplastic treatment and after termination of the therapy is one of the key diagnostic elements permitting the prompt diagnosis of the side-effects of the therapy. The awareness of the risk factors predisposing to drug-induced nephrotoxicity influences its incidence and permits the application of suitable procedures aimed at kidney protection.

Key words: neoplasms of childhood, antineoplastic treatment, nephrotoxicity, platinum derivatives.

Nephrotoxicity of platinum derivatives in children – a review of the literature

Joanna Stefanowicz1, Radosław Owczuk1, Ewa Iżycka-Świeszewska1, Katarzyna Rückemann-Dziurdzińska1, Anna Balcerska1

1Department of Paediatric, Haematology, Oncology and Endocrinology, Medical University of Gdansk
2Department of Anaesthesiology and Intensive Therapy, Medical University of Gdansk
3Department of Pathomorphology, Medical University of Gdansk
4Department of Pathophysiology, Medical University of Gdansk

Introduction

Cancer and antineoplastic treatment are interrelated with the risk of injuring various tissues and organs, kidneys included. Nephrotoxicity is the major side-effect of numerous antineoplastic agents used in paediatric oncology. Chemotherapy may cause direct damage to various structures of the kidney (glomeruli, tubules, vessels) or indirect injury resulting from hypoperfusion, haemolytic-uraemic syndrome and tumour lysis syndrome [1]. More to the point, drug interactions may increase the serum concentrations of antineoplastic agents and thus intensify their nephrotoxicity through reductions in the rates of metabolic processes in the liver or reductions in renal clearance. The severity of the clinical course in kidney impairment consequent to cytostatics may range from subclinical dysfunction to life-threatening conditions. The signs and symptoms of nephrotoxicity depend on the site and the degree of kidney damage. Nephrotoxicity may present as an acute kidney injury, slowly progressing chronic renal disease or dysfunction of the renal tubules. These processes may or may not be reversible [2].

For years the issue of monitoring nephrotoxicity, particularly late-onset, has been controversial. It remains inconclusive how often and which parameters should be assessed in long-term cancer survivors. Numerous clinical studies published worldwide differ not only in the choice of parameters but also in the analysed groups of patients, which are considerably heterogeneous. These differences cause considerable difficulty in comparing the obtained results.

Among cytotoxic agents, cisplatin (CDDP), carboplatin (CBDCA), ifosfamide (IFO), cyclophosphamide (CTX) and methotrexate (MTX) have known nephrotoxic activity [1].

In paediatric oncology the alkylating agents CDDP and CBDCA are the two most commonly used platinum derivatives. One of the most important side-effects of their use is kidney damage.

Kidney susceptibility to platinum derivatives probably results from the role played by the kidneys as the major excretory organ for platinum. Kidneys accumulate more CDDP than any other organ, which can lead to necrosis of
the terminal section of the proximal tubule and apoptosis of the distal nephron [6].

Cisplatin

The mechanism of cisplatin nephrotoxicity

Cisplatin administration and exposure to kidney cells, especially the proximal tubule, are associated with the activation of multifactorial and multidimensional processes comprising the activation of signal transduction pathways, leading to the damage and cell death of the renal tubule epithelium, the activation of inflammatory reactions, and vascular and ischaemic injury to the kidney. Kidney impairment results from the dysfunction of transporting networks, apoptosis or mitochondrial damage. Cisplatin binds extensively to DNA, damaging the double-stranded DNA and producing genotoxic stress that eventually triggers apoptosis of the renal tubule cells [7]. Studying an animal (rat) model has provided evidence that proximal tubules (S3 section) are the main sites of injury, which becomes overt three days after the administration of the drug. The morphological changes predominantly involve the terminal section of the proximal tubules. They take the form of focal damage of the brush border, cellular oedema, condensation of the nuclear chromatin, focal necrosis, altered number and shape of the lysosomes and mitochondrial vacuolisation [8]. On day five, changes in the terminal part of the proximal section become prevalent. Here, they take the form of tubular necrosis, leading to atrophy of the nephrons together with intratubular disintegration. A partial regeneration of the terminal part is observed on day seven. It manifests by the enlargement of the lumen of the tubules, which become lined with a flattened epithelium. Additionally, the morphological changes are observed in the renal distal and collecting tubules. Even though morphological features of the tubular damage are well described and generally accepted, the mechanism of their formation remains unclear. Cisplatin may disturb the transport of organic cations. Human organic cation transporter 2 (hOCT2) is the transporter critical for cisplatin nephrotoxicity in isolated human proximal tubules. Organic cations such as cimetidine and verapamil (inhibitors of OCT2) protect the cells from the nephrotoxicity of CDDP [9, 10]. Cisplatin, after entering the cell, may react with various reactive groups and, after activation, interacts with numerous particles, often glutathione. Cisplatin nephrotoxicity depends on metabolic activity and, above all, on its influence on γ-glutamyl transpeptidase and cysteine-S-conjugate β-1-hydrolase. The metabolic pathways of the aforementioned enzymes generate the more toxic derivatives of CDDP in the cells of the renal tubules, i.e., thiol and haloalkanes [10]. Cisplatin concentration in the renal tubular epithelium is five times higher than the serum concentration [11]. The tubular cells are exposed to CDDP during its secretion into the urine. In individuals with a normal renal filtration rate, a maximal CDDP level is observed three hours after drug administration. Necrosis may be the direct effect of toxic damage or may be a secondary event after apoptosis.

The exposure of the renal tubule cells to CDDP particles activates signal transduction pathways involving reactive oxygen species, mitogen-activated protein kinase, p53 and the cytoprotective active protein p21, and promotes the death of the renal tubule epithelial cells. Cisplatin induces TNF-α production in the renal tubular cells, which triggers a robust inflammatory reaction and, in consequence, intensifies the impairment of the renal tubules and contributes to their death. Cisplatin may also interfere with renal blood perfusion, leading to ischaemic death of the tubular cells and, consequently, to decreased GFR and the development of acute renal insufficiency [12]. The death of the renal tubule cells through apoptosis and necrosis is the common basic manifestation of CDDP nephrotoxicity observed in histopathological examinations. Apoptosis resulting from CDDP exposure may be induced through the activation of the intrinsic (mitochondrial) pathway or, less commonly, through the activation of the extrinsic pathway based on death receptors (Fas, TNF-α receptors 1 and 2). The latter is activated by ligand (e.g., CDDP) binding, damage to the endoplasmic reticulum causing the activation of caspase 12, and activation of the caspase-independent pathway. Previous studies have shown that the production of TNF-α by renal parenchymal cells, rather than by bone marrow-derived infiltrating immune cells, is responsible for CDDP-induced nephrotoxicity [13]. Additionally, endoplasmic reticulum stress may trigger the activation of the pathways leading to apoptosis that is dependent on or independent of caspases [12].

Risk factors of cisplatin nephrotoxicity

Risk factors that increase kidney impairment after CDDP administration include previous or concomitant renal diseases, solitary kidney (nephrectomy), combined anticancer treatment with IFO and MTX, concurrent treatment with other nephrotoxic agents such as aminoglycosides and amphotericin B, the cumulative dose of CDDP (≥ 200 mg/m²), radiation impacting the kidney (renal radiation dose ≥ 15 Gy), diabetes mellitus, hypertension, dehydration and hypoalbuminaemia [2, 14, 15].

Clinical aspects of cisplatin nephrotoxicity

The nephrotoxic activity of CDDP may manifest itself as an acute kidney injury and chronic kidney disease. Kidney damage may affect glomeruli, proximal, distal and collecting tubules. Clinical manifestations of CDDP nephrotoxicity include decreased GFR, electrolyte disturbances, polyuria and, infrequently, the renal salt-wasting syndrome [1]. Hypomagnesaemia and decreased GFR are the most common clinical manifestations of CDDP nephrotoxicity [2]. The grading of CDDP nephrotoxicity first proposed by Skinner in 1998 is widely used in clinical practice [14]. The scale is based on GFR and serum magnesium concentration (Table 1).

Hypomagnesaemia is present in almost 90% of patients treated with CDDP. It can be detected at only three months from the beginning of therapy, after reaching a cumulative dose exceeding 300 mg/m² [16]. The disturbances in magnesium homeostasis related to CDDP treatment probably result from direct damage of the proximal and distal renal tubules [16]. Clinical and experimental studies have shown that CDDP interferes with magnesium transport, predominantly in the distal tubules [17-19]. Hypomagnesaemia
caused by CDDP administration may persist for a few years after the end of therapy [20–23] and, in 1/3 to 2/3 children, may become permanent [21, 24].

Hypocalcaemia is another common electrolyte disturbance related to CDDP treatment. It may be caused by various mechanisms, but even the CDDP-induced hypomagnesaemia itself may lead to hypocalcaemia. Hypocalcaemia resulting from hypomagnesaemia is the consequence of the inhibition of parathyroid hormone (PTH) secretion and reduced tissue sensitivity to PTH, as well as a direct effect of low serum magnesium concentration on calcium release from the bones. In addition, CDDP directly impairs the renal tubular cells, which are responsible for calcium reabsorption, leading to increased calcium loss in the urine. CDDP-related hypocalcaemia is resistant to equalisation with only calcium supplementation. The mechanism of hypocalcaemia secondary to hypomagnesaemia implies that normalisation of the calcium level may be achieved only through simultaneous magnesium and calcium substitution [20]. In addition to hypomagnesaemia and hypocalcaemia, patients may also present with hypoponataemia [25] and, very rarely, hypoponataemia (renal salt-wasting syndrome) [26, 27].

Renal impairment is the main side-effect leading to CDDP dose limitation. Therapeutic protocols recommend a 50% dose reduction if GFR drops under 60 ml/min/1.73 m². During antineoplastic treatment, it is mandatory to monitor the principal marker of the filtration activity of the kidney, i.e., GFR. GFR can be assessed using isotope methods (the gold standard for GFR assessment) or by the application of the Schwartz formula. Womer et al. reported a considerable inter-individual range of clinical manifestations of nephrotoxicity caused by CDDP therapy. They showed that after the administration of a 100 mg/m² dose of CDDP, eGFR decreases, on average, by 8% [28]. The magnitude of GFR decrease is directly correlated with the peak platinum concentration in serum and/or urine and with the duration of CDDP infusion [29]. Cases of acute renal failure caused by CDDP have been reported previously [30]. Approximately 30% of patients undergoing CDDP treatment present signs of renal glomerular dysfunction at the end of the therapy [31]. It remains the subject of intense discussion whether the observed decrease in GFR is reversible [31, 32]. Pettiš et al. published results of a study on a group of patients who had undergone antineoplastic therapy for a CNS tumour using protocols containing CDDP. After the end of the therapy, the patients were found to have significantly higher arterial blood pressure (15.4%), especially those who had received brain radiotherapy (highest risk of arterial hypertension), had lower GFR or had hypomagnesaemia. The dysfunction in glomerular filtration was, in a majority of cases, persistent, but it generally did not present signs of progression in long-term observation [31]. In contrast, in the report published by Skinner et al., after a year of clinical observation, renal filtration activity radically improved: the mean GFR (corrected for body surface area, BSA) was significantly higher than the GFR value measured at the moment of the termination of antineoplastic therapy (92 ± 10 ml/min/1.73 m² BSA) [14]. Similar observations were published by Brock and Gomez Campdera [21, 33]. Brock reported that 92% of children who had reduced GFR at the end of CDDP therapy, after a median of 2.5 years (range 1.5–7.0 years), presented at least some improvement in renal filtration activity (median GFR increase 22 ml/min/1.73 m² BSA), while 8% presented signs of chronic renal disease [21].

**Table 1. Grading of cisplatin (CDDP) nephrotoxicity in children [14]**

<table>
<thead>
<tr>
<th>Nephrotoxicity grade</th>
<th>GFR</th>
<th>Mg &lt; 2 years</th>
<th>Mg ≥ 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>0.75</td>
<td>0.70</td>
</tr>
<tr>
<td>1</td>
<td>60–89</td>
<td>0.60–0.74</td>
<td>0.55–0.69</td>
</tr>
<tr>
<td>2</td>
<td>40–59</td>
<td>0.50–0.59</td>
<td>0.45–0.54</td>
</tr>
<tr>
<td>3</td>
<td>20–39</td>
<td>no symptoms</td>
<td>no symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>but 0.40–0.49</td>
<td>but 0.35–0.44</td>
</tr>
<tr>
<td>4</td>
<td>&lt;20</td>
<td>tetany or</td>
<td>tetany or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>convulsion &lt;0.40</td>
<td>convulsion &lt;0.35</td>
</tr>
</tbody>
</table>

Total score (Ns) (sum of GFR + Mg)

0 no nephrotoxicity
1 mild nephrotoxicity
2–3 moderate nephrotoxicity
≥ 4 severe nephrotoxicity

GFR – glomerular filtration rate (ml min⁻¹ 1.73 m⁻²). Mg – serum magnesium concentration (mmol l⁻¹). Tetany is defined by clinical symptoms/signs (carpopedal spasm, Chvostek’s sign, Troussseau’s sign) with biochemistry: mode-rate or severe hypomagnesaemia ≤ 0.60 at < 2 years of age, ≤ 0.55 at ≥ 2 years.

Hypocalcaemia may also cause tetany. If hypomagnesaemia and hypocalcaemia co-exist in the presence of tetany, assume that hypomagnesaemia is the primary cause unless there are good reasons not to do so, and grade appropriately. A score of 4 in an individual aspect of grading (e.g., GFR) constitutes severe toxicity in that aspect.


Cytoprotective therapy to prevent the nephrotoxicity of platinum derivatives

Intensive hydration simultaneous to CDDP administration, osmotic diffusion, magnesium supplementation, increasing duration of infusion and dividing the dose of CDDP within the cycle all decrease the nephrotoxicity of this cytostatic agent [25]. Hydration and intravenous mannitol administration reduce the incidence of CDDP nephrotoxicity by decreasing the exposure of the renal tubular cells to the drug [34]. Cisplatin is less nephrotoxic when administered in a long infusion compared to a bolus [29]. This results from the fact that endogenous sulphhydrils present in renal tubules neutralise CDDP at lower concentrations but are less efficient at higher concentrations achieved by a CDDP bolus. Experimental studies on a rat model provided evidence that the accumulation and cytotoxicity effects of CDDP on renal glomeruli and tubules depend on urine osmolarity. Low urine osmolarity enhances the accumulation and cytotoxicity of CDDP, while iso- and hyperosmolar urine have protective effects. These findings legitimise the strategy of the simultaneous intravenous infusion of osmotically active substances such as mannitol along with intensive hydration with 0.9 g/l NaCl saline and the use of 3 g/l NaCl as a CDDP carrier [35, 36].

More to the point, hope has been placed in amifostine (Ethylol) application for reducing CDDP nephrotoxicity. The
main mechanism of its protective action is the removal of free radicals [37]. Additionally, amifostine breaks the binding of CDDP to DNA, binds metabolites of cytotoxic agents, reduces apoptosis and activates tumour-suppressor gene p53. A limited amount of evidence suggests that amifostine might decrease hypomagnesaemia [32]. Regrettably, the studies assessing amifostine efficacy in paediatric populations show that it has only slight nephroprotective activity or even none at all [38, 39].

N-acetylcysteine (NAC) is another agent considered to be CDDP-nephroprotective [40-42]. NAC inhibits apoptosis caused by CDDP by interfering with caspase signalling [43]. In clinical practice, NAC is administered intravenously as protection against CDDP and paracetamol toxicity in a phase II clinical trial currently underway to assess the treatment strategies for recurrent and resistant liver cancers (hepatoblastoma and hepatocellular carcinoma) [44]. Bassinger and Jones reported D-methionine as a protection against CDDP nephrotoxicity [45]. Some other antioxidants, such as selenium, vitamin C and E, and aminoguanidine, are believed to play a renoprotective role [46].

A liposomal formulation of CDDP, lipoplatin, has been intensely studied over the recent years. It is regarded as equally effective but much less nephrotoxic which has been confirmed in animal studies as well as in clinical trials in adult patients with advanced pancreatic cancer, non-small cell lung carcinoma, head and neck neoplasm and metastatic breast cancer [47, 48].

Carboplatin
The mechanism of carboplatin nephrotoxicity
After intravenous administration, most CBDCA is bound to plasma proteins, and only the free platinum causes cytotoxicity. Almost 90% of the administered dose is filtered through the kidneys [20]. Moreover, contrary to CDDP, CBDCA is not transformed into toxic metabolic compounds in renal tubule cells [10]. It is presumed that CBDCA is less nephrotoxic than CDDP because it is less reactive with the proteins of the renal tubules [20, 49].

Risk factors of carboplatin nephrotoxicity
Among the known CBDCA risk factors are the treatment of children who are older [50], single kidney, diabetes mellitus, hypertension [2], the cumulative dose of CBDCA [50] and simultaneous treatment with IFO and other nephrotoxins [2, 51]. Paradoxically, the risk of kidney insufficiency and renal tubulopathy development is higher in the case of CBDCA/IFO therapy than with CDDP/IFO therapy [32, 51].

Clinical characteristics of carboplatin nephrotoxicity
The nephrotoxic activity of CBDCA is, above all, characterised by decreased GFR and hypomagnesaemia. Acute renal failure after CBDCA has been reported in a few occasional cases [50-53]. In most of the clinical studies on CBDCA treatment in children, GFR values are reported to be within the norm or only slightly decreased [54]. Hypomagnesaemia is a rare finding [50, 55-57].

Cytoprotective therapy to prevent carboplatin nephrotoxicity
The administration of an exact, set dose of a cytostatic agent is the crucial factor that prevents the development of myelosuppression and nephrotoxicity. The major marker limiting the dose of CBDCA is the GFR value. The set dose of the cytostatic agent is calculated according to the formula proposed by Calvert et al., which takes into account the value of GFR and the area under the plasma concentration time curve (AUC): dose [mg] = target AUC (mg/ml/min) × (GFR (ml/min) + 25) [58]. Bearing in mind the atypical pharmacokinetics of CBDCA in children, Newell put forward a modification of the Calvert et al. formula: dose [mg] = AUC (mg/ml/min) × (GFR (ml/min) + 0.36 × body mass (kg)) [59]. Another equation proposed by Newell can be used to calculate the dose of CBDCA, but this requires measuring the isotopic GFR, which limits its clinical application [59]. In everyday oncological paediatric practice, other modifications of the Calvert formula have also been used [60-62]. The results of the study published by Thomas et al. provided evidence that the administration of a CBDCA dose estimated from GFR results in more stable drug exposure when compared to a dose of CBDCA estimated from BSA [63].

Late nephrotoxicity of platinum derivatives
The late nephrotoxicity related to the administration of platinum derivatives is not fully characterised. Skinner et al. published results of a prospective study on 63 children treated with platinum derivatives (27 CDDP, 24 CBDCA, 12 both drugs). They reviewed kidney function by measurements of GFR, serum calcium and magnesium concentrations and an estimation of the overall grade of nephrotoxicity at the moment of the termination of the antineoplastic therapy, 1 year and 10 years later. Over time, no significant changes in kidney function were observed in any of the analysed groups. After 10 years of observation, eGFR < 60 ml/min/1.73 m² was found in 11% of the patients, severe nephrotoxicity in 15% of cases and hypomagnesaemia requiring oral magnesium supplementation in 7% of patients with CDDP [54].

Assessment of the chemotherapy-related nephrotoxicity in a group of 651 paediatric patients treated for sarcoma was performed (median follow-up 2 years) in a large multicentre study carried out by the CWS group. The median cumulative doses of CDDP and CBDCA were 360 mg/m² and 1500 mg/m², respectively. The patients not treated with platinum derivates were considered the control group. Most of the patients, including the control group, received IFO treatment. Kidney function was assessed by creatinine and magnesium serum concentration levels and eGFR value. None of the patients exhibited a reduction in eGFR. After termination of the antineoplastic therapy, hypomagnesaemia (defined as serum magnesium concentration < 0.7 mmol/l) was found in 12.1% of patients treated with CDDP and in 15.6% of patients receiving CBDCA, vs. 4.5% of patients from the control group (p = 0.008). In all the groups, the incidence of hypomagnesaemia decreased with observation time, though the values of serum magnesium concentrations remained lower in patients treated with platinum derivatives throughout the study [55].
Cancer combination therapy with nephrotoxic agents

A combination therapy for cancer is correlated with the highest risk of nephrotoxicity. Combination of CDDP with ICE escalates kidney damage [32, 51, 64]. The prospective study of kidney function performed by Ferrari et al. on a group of 43 osteosarcoma patients receiving a combined therapy with IFO, CDDP and MTX showed that 21/43 patients had eGFR reduction. The combination therapy was further associated with glycosuria in 15/43 cases and proteinuria in 14/43 cases. Renal threshold TmP/GFR was < 1 mmol/l in 11 (52%) patients [65].

Nephrotoxicity of platinum derivatives in Wilms tumour patients

Children diagnosed with Wilms tumour are predisposed to kidney filtration disturbances. Daw et al. published results of a prospective study of 12 patients diagnosed with high-risk Wilms tumour and treated with ICE chemotherapy, nephrectomy and radiotherapy. GFR reduction (measured by technetium 99 m-DTPA clearance) was found to be the key disorder present in those patients. Nephrectomy was the leading cause of GFR impairment (average 38% reduction vs. 7% reduction after two cycles of ICE chemotherapy). Increased beta-microglobulin secretion without clinically overt dysfunction of the renal tubules was also present [66].

Summary

Kidney damage is a serious but rare side effect of anticancer treatment in children. Platinum derivatives are among the cytostatics with significant nephrotoxic potential. Cisplatin is the most nephrotoxic one. Cisplatin mainly reduces glomerular filtration rate and causes hypomagnesaemia. Evaluation of renal function is a very important diagnostic procedure during the active phase of the anti-neoplastic treatment as well as over the follow-up period. It allows early recognition of the therapy side effects. It should be noted that history of cancer constitutes a risk factor of a chronic renal disease development.

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Address for correspondence
Joanna Stefanowicz
Department of Paediatric, Haematology, Oncology and Endocrinology Medical University of Gdansk
Dębinki 7
80-952 Gdansk
e-mail: jstefanowicz@gumed.edu.pl
tel. +48 58 349 28 80ax +48 58 349 28 47