**INTRODUCTION**

The severity of antineoplastic drug-induced nephrotoxicity is variable, ranging from subclinical impairment of renal function to life-threatening disease. Nephrotoxicity may be acute and reversible in children treated for malignant disease, but it has the potential to cause chronic and irreversible damage. Even in children with subclinical toxicity only, the potential for morbidity in later life is a serious concern, and this indicates the importance of reduction of the frequency and severity of nephrotoxicity. There are many potential causes of acute and chronic renal impairment in patients receiving treatment for cancer. Chemotherapy, supportive treatment with drugs such as carboplatin and ifosfamide may be implicated in causing nephrotoxicity, especially in children. Risk factors for nephrotoxicity include the cumulative dose, dehydration, hypoalbuminemia, and concurrent use of nephrotoxic drugs. The adverse effects of these drugs may also be more common in pediatric patients than in adults, but it is unclear why a young age is a risk factor and further research is required regarding the mechanism of antineoplastic drug-induced nephrotoxicity in children.
as aminoglycoside antibiotics, surgery, immature transporter function, and wasting by antineoplastic drugs may all cause nephrotoxicity. Among such drugs, cisplatin and ifosfamide are particularly associated with nephrotoxicity.

Mammalian nephrons consist of a glomerulus, proximal tubule, loop of Henle, and distal tubule draining into a collecting duct. The proximal nephron includes the proximal tubule and the loop of Henle, and the distal nephron comprises the distal tubule and collecting duct. Glomerular filtration leads to formation of an ultrafiltrate, which then enters the proximal nephron where it is progressively modified by tubular reabsorption and secretion of electrolytes, amino acids, glucose, uric acid and other small molecules such as β2-microglobulin. Tubular secretion eliminates endogenous and exogenous toxic substances, and subsequent acidification and concentration of the ultrafiltrate occur in the distal nephron with formation of urine. Cisplatin nephrotoxicity mainly affects the S3 segment of the proximal tubule in the outer medulla, while ifosfamide nephrotoxicity appears to affect all of the nephron segments. The mechanisms of cisplatin- and ifosfamide-induced nephrotoxicity in children are not completely clear, and an improved understanding could lead to novel renoprotective interventions.

Cisplatin and carboplatin metabolism

Cisplatin

Organic cation transporters (OCTs) have been implicated in cisplatin uptake based on the higher toxicity in Madin-Darby canine kidney (MDCK) cells following application of cisplatin to the basolateral side compared to the apical side (Ludwig et al., 2004). These results suggest that cisplatin-induced tubular cell injury may be related to basolateral organic cation transport, and this is supported by the partial prevention of cisplatin-induced cytotoxicity by cimetidine, an OCT inhibitor. In addition, Ciarimboli et al. (2005) reported that OCT2, which is mainly expressed in the kidney, is the critical OCT responsible for cisplatin uptake in the kidney. In contrast, cisplatin does not interact with OCT1, which is mainly expressed in the liver. Therefore, expression of OCTs in different tissues might account for the organ-specific toxicity of cisplatin, and it is also of note that less nephrotoxic analogs of cisplatin such as carboplatin and oxaliplatin do not interact with OCT2 (Ciarimboli et al., 2005).

After entry into cells, cisplatin may react with various molecules. In the kidney, it has been suggested that the nephrotoxicity of cisplatin may depend on metabolic activation via a pathway including γ-glutamyl transpeptidase and cysteine-S-conjugate β-lyase. The major site of renal injury is the S3 segment of the outer medulla. The cisplatin concentration in tubular epithelial cells is five times in excess of that found in plasma (Finkel et al., 2007). The plasma decay curve for platinum showed a biphasic pattern with a terminal t1/2 of 58.5-73 hr, with clearance mainly in the urine with 15-75% as the unchanged drug (Li et al., 2007).

Carboplatin

Carboplatin is a second-generation platinum agent that has similar efficacy and less nephrotoxicity compared with cisplatin when each drug is given in combination with other agents in treatment of pediatric organ cancer. After intravenous administration, most carboplatin is bound to protein and only free platinum causes cytotoxicity. Approximately 70% of the administered dose is cleared through the kidneys, with 32% of the dose excreted as unchanged carboplatin within 24 hr after administration (Li et al., 2007; Koeller et al., 1986). Dose adjustment is required in patients with renal dysfunction. Calvert’s formula (carboplatin dose in milligrams = A target area under the concentration curve (AUC) × (glomerular filtration rate (GFR) + 25)) is widely used for carboplatin dosing based on the GFR. AUC of 5-7 mg/ml·min is recommended for the formula. GFR is set to zero for patients with end-stage renal disease.

Mechanisms of cisplatin nephrotoxicity

An overview of the pathophysiological events in cisplatin nephrotoxicity is shown in Fig. 1. Exposure of tubular cells to cisplatin activates molecules and signaling pathways that promote cell death, including reactive oxygen species (ROS), the mitogen-activated protein kinase (MAPK) pathway, and P53 or cytoprotective p21. Cisplatin induces tumor necrosis factor-α (TNF-α) production in tubular cells, which results in a robust inflammatory response and further contributes to tubular cell injury and death. Cisplatin may also induce injury in the renal vasculature, leading to ischemic tubular cell death and a decreased GFR, and resulting in acute renal failure (Pabla and Dong, 2008).

Renal tubular cell death via apoptosis and necrosis is a common histopathological feature of cisplatin nephrotoxicity. Apoptosis of renal tubular cells has been a recent focus in mechanistic investigation of cisplatin nephrotoxicity. Cisplatin activates both the intrinsic mitochondrial pathway and extrinsic death receptors in apoptosis, including Fas and TNF-α receptor (TNFR) 1 and 2. Recent studies have shown that TNF-α is produced mainly from resident kidney cells, rather than infiltrating immune cells, and may trigger tubular cell death directly via TNFR1 as well as indirectly through an inflammato-
Nephrotoxicity induced by cisplatin and ifosfamide in children

Cisplatin nephrotoxicity

Fig. 1. Overview of pathophysiological events in cisplatin nephrotoxicity. ROS: reactive oxygen species, MAPK: mitogen-activated protein kinase, TNF-α: tumor necrosis factor α, GFR: glomerular filtration rate.

Clinical findings in cisplatin and carboplatin nephrotoxicity

Cisplatin

Cumulative dose, dehydration, hypoalbuminemia, and concurrent use of nephrotoxic drugs have been suggested as risk factors for cisplatin nephrotoxicity. The mean cumulative dose of cisplatin precipitating persistent hypomagnesemia in 10 of 22 pediatric patients (age 1 to 15 years old) treated with various cisplatin-containing chemotherapy regimens was 500 mg/m² (Ariceta et al., 1997). Increased magnesuria and a decreased serum magnesium level were detected soon after administration of cisplatin in all 22 patients. In a study of 18 patients followed for a mean of 2.3 years after discontinuation of cisplatin, chronic hypomagnesemia accompanied by moderately elevated serum creatinine levels was detected in 6 patients, chronic hypocaliuria in 5 patients, and hypokalemia in 1 patient.

A 20-40% reduction of GFR following treatment with cisplatin is common, with a significant elevation of urinary β2-microglobulin during the first week of each cycle with a subsequent decline during the next cycle. Significant increases in urinary excretion of albumin and IgG have been found on day 9 of the first chemotherapy cycle (Daugaard et al., 1988), and a mean reduction in GFR of 8% per cycle was shown in measurement of renal function in 22 pediatric patients (age 1.3 to 10 years old) receiving cisplatin 100 mg/m² every 21 to 28 days for neuroblastoma or malignant germ cell tumors (Womer et al., 1985).

Carboplatin

A mean reduction of GFR of 22 ml/min/1.73 m² was found in 23 pediatric patients (age 0.4 to 15 years old) receiving a median cumulative dose of carboplatin of 2,590 mg/m², with a mean reduction of 0.17 mmol in the serum magnesium level following treatment. These changes occurred mainly during the first month following carboplatin administration and post-treatment changes in GFR and serum magnesium did not markedly improve or worsen in 24-month follow-up (English et al., 1999). Acute renal failure occurred in 4 of 16 pediatric patients (age 16 months to 14 years old) receiving carboplatin 1,000 mg/m², melphalan 180 mg/m², vincristine 1.5 mg/m², and etoposide 250 mg/m² prior to autologous bone marrow transplantation, and an increase in serum creati-
nine was noted within 24 hr of chemotherapy in 4 of the 16 patients. Three of the 4 patients with acute renal failure required dialysis. GFR was reduced by a mean of 24% in 10 patients evaluated 7 months after transplantation (Corbett et al., 1992).

Ifosfamide metabolism
Ifosfamide is transformed to its active metabolites primarily by hepatic enzymes such as cytochrome P450. Urinary excretion of ifosfamide occurs predominantly as inactive metabolites and acrolein, with unchanged ifosfamide accounting for 20% of the administered dose (Li et al., 2007). Ifosfamide exerts its antineoplastic effect only when hydroxylated to its active alkylating metabolites, ifosfamide mustard and acrolein, and acrolein is responsible for hemorrhagic cystitis in ifosfamide therapy. Introduction of the uroprotective thiol compound MESNA (sodium 2-mercaptoethanesulfonate) has virtually eliminated urotoxicity. In addition to hydroxylation, the oxazaphosphorine ring of ifosfamide undergoes side chain dealkylation (about 50%) that results in formation of non-toxic 2- and 3-dechloroethylifosfamide and equimolar amounts of chloracetaldehyde, which is thought to be responsible for ifosfamide nephrotoxicity.

Mechanisms of ifosfamide nephrotoxicity
The pathophysiological mechanisms of ifosfamide nephrotoxicity remain to be elucidated. Depletion of adenosine triphosphate (ATP) by binding of toxic metabolites to mitochondrial DNA or blockage of cell regeneration by binding to nuclear DNA have been proposed, and recently Patzer et al. (2006) reported that the ifosfamide metabolites chloracetaldehyde, 4-hydroperoxylifosfamide and ifosfamide mustard are able to inhibit sodium-dependent phosphate co-transport in kidney cells. The ifosfamide mustard effect occurs via internalization and reduction of de novo synthesis of the type IIa sodium-dependent phosphate transporter (NaPi-IIa).

Clinical findings of ifosfamide nephrotoxicity
A cumulative dose exceeding 45 g/m², an age younger than 3 years old, previous or concurrent cisplatin treatment, and unilateral nephrectomy are the most important risk factors for ifosfamide nephrotoxicity (Loebstein et al., 1999; Skinner et al., 2003). Ifosfamide may cause chronic glomerular, proximal or distal tubular toxicity with a wide range of severity. The main features of ifosfamide nephrotoxicity are shown in Table 1 (Skinner, 2003; Kintzel et al., 2001; Skinner et al., 2000; Rossi et al., 1999). An incidence of 1.4 to 30% has been report-

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**Fig. 2.** Cisplatin activates both the intrinsic mitochondrial pathway and extrinsic death receptors in apoptosis, such as the tumor necrosis factor-α receptor. In addition, endoplasmic reticulum stress may be induced. Activation of these pathways leads to caspase-dependent or -independent apoptosis. ER: endoplasmic reticulum, AIF: apoptosis induced factor.
ed for significant chronic glomerular toxicity in children, and chronic proximal tubular toxicity is very common, ranging from subclinical glycosuria in about 90% of children to hypophosphatemic rickets and/or proximal renal tubular acidosis in over 25%. Urinary excretion of amino acids showed a marked increase in 28% of patients. Fanconi syndrome occurs in 1 to 7% of children receiving repeated doses of ifosfamide and impairment of renal phosphate reabsorption is found in 20 to 30%. An apparent reduction in urinary concentrating ability may occur in up to 30% of children, but severe distal tubular toxicity is rare. Chronic tubular dysfunction persisting over a period of 5 years has been found in 47% (7 of 16) and 25% (4 of 16) of pediatric patients with severe and moderate ifosfamide nephrotoxicity, respectively (Loebstein et al., 1999).

Ifosfamide/Carboplatin(or Cisplatin)/Etoposide (ICE) combination therapy and hypouricemia

Background

We experienced a 14-year-old Japanese girl with recurrent Wilms’ tumor who developed hypouricemia (< 2.0 mg/dl) and Fanconi syndrome soon after ICE administration of ICE therapy for 7 months. Based on this case, we retrospectively examined the incidence of hypouricemia and clinical findings in pediatric patients treated with an ICE regimen.

Patients and methods

Twenty-eight pediatric patients were enrolled in the study, including 25 with a solid tumor (20 with a brain tumor, 2 with Wilms’ tumor, 2 with osteosarcoma, and 1 with rhabdomyosarcoma), 2 with Hodgkin disease, and 1 with non-Hodgkin disease. The median age was 8 years old (range: 1 to 19 years old) and the median follow-up period was 14 months (range: 2 to 54 months). Hypouricemia was defined as a serum level of uric acid < 2.0 mg/dl for over 1 week. Statistical analyses were performed using a non-parametric Mann-Whitney U-test or chi-square test as appropriate. Calculations were performed using Statview 5.0 (Abacus Concepts, Berkeley, CA, USA). The level of significance was 0.05. Data are expressed as means ± S.D.

RESULTS

The 28 subjects were divided into those with hypouricemia (group H, n = 20, 71.4%) and those with normal serum levels of uric acid (group N, n = 8, 28.6%). The mean lowest levels of serum uric acid were 0.9 ± 0.4 and 3.2 ± 0.8 mg/dl in groups H and N, respectively, and these levels were significantly different (p < 0.01). Cumulative doses of ifosfamide and carboplatin or cisplatin did not differ significantly between the two groups. The incidences of hypomagnesemia, hypophosphatemia, hypocalcineemia, hypokalemia, glucosuria, and proteinuria were higher in group H compared to group N, but there were no significant differences (Table 2). There was a significant correlation (p < 0.05) between the lowest uric acid level in serum and peripheral white blood cell count (Fig. 3), but hypouricemia persisted despite recovery of the peripheral white blood cell count (> 1,500 /mm²) (data not shown).

We also compared clinical findings and serum levels of uric acid in a remission subgroup (n = 17) and a non-remission subgroup (n = 3) in subjects in group H. There were no significant differences between these subgroups, but the duration of hypouricemia was longer in the non-remission subgroup (117 ± 35 days) compared with the remission subgroup (41 ± 19 days). The cumulative doses of ifosfamide and carboplatin in the non-remission subgroup (35.0 ± 7.5 g/m² and 4.0 ± 2.1 g/m², respectively) were higher than those in the remission subgroup (22.1 ± 9.9 g/m² and 2.5 ± 1.2 g/m², respectively) (Table 3).

Table 1. Clinical features of ifosfamidenehrotoxicity

<table>
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<tr>
<th>Glomerular toxicity (1.4-30%)</th>
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<tr>
<td>Acute renal failure</td>
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<td>Chronic renal failure (CRF)</td>
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<th>Proximal tubular toxicity</th>
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<tr>
<td>Aminoaciduria (28%)</td>
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<td>Glycosuria (90%)</td>
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<tr>
<td>Low molecular weight proteinuria (β2MG, α1MG, et al.)</td>
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<tr>
<td>Fanconi syndrome (1-7%)</td>
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<tr>
<td>Hypophosphatemia and hypophosphatemic rickets (HR)</td>
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<tr>
<td>Proximal renal tubular acidosis (RTA)</td>
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<td>Hypokalemia</td>
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<tr>
<td>Impairment of phosphate reabsorption (20-30%)</td>
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<tr>
<td>Calciuria, magnesuria, natriuria (rarely)</td>
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<th>Distal tubular toxicity</th>
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<tr>
<td>Subclinical impairment of urinary concentration (30%)</td>
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<tr>
<td>Distal RTA</td>
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<td>Nephrogenicdiabetes insipidus</td>
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Renal toxicity

<table>
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<tr>
<th>Proteinuria</th>
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<tr>
<td>Hypertension</td>
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<td>Growth failure (related CRF, HR, and/or RTA)</td>
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( ) indicates the incidence rate.
was no significant difference in the incidence of electrolyte abnormalities and glycosuria between the subgroups (data not shown).

**DISCUSSION**

Hypouricemia has been recognized frequently in pediatric patients treated with an ICE regimen, in addition to electrolyte abnormalities and glycosuria, probably due to renal tubular dysfunction. There was a significant difference of the lowest serum level of urate between groups H and N, although cumulative dose of antineoplastic drugs and the age did not differ significantly between two groups. The exact reason is obscure, but these findings might be explained by different tubular function of uptake and/or excretion of these drugs, or by different metabolizable function between two groups.

The duration of hypouricemia was longer in the non-
remission subgroup of patients, which suggests that hypouricemia may be a predictive marker for prognosis of malignant disease and efficacy of drugs such as ifosfamide, carboplatin and cisplatin. A large scale prospective study in both adult and pediatric patients is required to determine if these findings are specifically characteristic of pediatric patients.

In conclusion, nephrotoxicity induced by antineoplastic drugs may be more common in pediatric patients than adults, but it is unclear why a young age is a risk factor and further research is required, including examination of transporter function in pediatric patients (Loebstein et al., 1999; Skinner et al., 2003).

ACKNOWLEDGMENT

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REFERENCES


Table 3. Clinical features in the non-remission and remission subgroups

<table>
<thead>
<tr>
<th></th>
<th>Non-remission (n = 3)</th>
<th>Remission (n = 17)</th>
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<tbody>
<tr>
<td>Lowest serum level of uric acid (mg/dl)</td>
<td>0.9 ± 0.3</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Duration of hypouricemia (days)</td>
<td>117 ± 35</td>
<td>41 ± 19</td>
</tr>
<tr>
<td>Ifosfamide (g/m²)</td>
<td>35.0 ± 7.5</td>
<td>22.1 ± 9.9</td>
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<tr>
<td>Carboplatin (g/m²)</td>
<td>4.0 ± 2.1</td>
<td>2.5 ± 1.2 (n = 14)</td>
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Table 3. Nephrotoxicity induced by cisplatin and ifosfamide in children