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Case Report

Ifosfamide-Induced Fanconi's Syndrome

Lin-Kun Lee[1], Po-Min Chen[1,2], Cheng-Hwai Tzeng[1,2], Jin-Hwang Liu[1,2], Chueh-Chuan Yen[1,2]*

[1]*Division of Hematology and Oncology, Taipei Veterans General Hospital, Taipei, Taiwan*
[2]*School of Medicine, National Yang-Ming University, Taipei, Taiwan*

Abstract.

Ifosfamide is an alkylating antineoplastic prodrug used to treat many solid tumors. The metabolism of ifosfamide is via CYP450 3A4 and 2B6 and produces active ifosfamide mustard, the toxic metabolite acrolein and chloroacetaldehyde (CAA). Additionally, CAA is believed to induce proximal tubular dysfunction which results in Fanconi's syndrome. It is a condition not commonly encountered in adults receiving ifosfamide but relatively common in children. Herein, we have reported a 25-year-old woman with a history of synovial sarcoma with multiple lung metastasis and repetitive locoregional recurrence. She received chemotherapy with high dose ifosfamide as her antineoplastic treatment. Before her 4th cycle of chemotherapy, the patient's pre-chemotherapy evaluation revealed proteinuria, glucosuria, phosphateuria, hypophosphatemia and non-anion gap metabolic acidosis. The above conditions were consistent with Fanconi's syndrome. We treated her with electrolyte supplement and close monitoring of the noted laboratory abnormalities. Fortunately, the laboratory abnormality gradually resolved. Our case highlights the rare potential complication of ifosfamide, especially in patients who had received a high cumulive dose. To avoid this rare but potentially debilitating condition, patients whose cumulative ifosfamide dose reaches threshold should be closely monitored.

Keywords **:** Fanconi's syndrome, ifosfamide, chloroacetaldehyde (CAA)

病例報告

使用 Ifosfamide 誘發 Fanconi 氏症

李霖昆[1] 陳博明[1,2] 曾成槐[1,2] 劉俊煌[1,2] 顏厥全[1,2]*

[1] *台北榮民總醫院 血液腫瘤科*
[2] *國立陽明大學 醫學院*

中文摘要

Ifosfamide 是一種烷化劑型的抗惡性腫瘤的前驅藥物，可以用來治療多種固態腫瘤。Ifosfamide 代謝主要是依靠 CYP450 3A4 及 2B6，代謝後會產生活性的 ifosfamide mustard，及其毒性代謝物 acrolein 及 chloroacetaldehyde (CAA)。CAA 被認為會造成近端小管功能失調，進而引發 Fanconi 氏症。這種情形在成年人中是比較少見的，但在小孩子當中則是相對比較常見的。在此，我們報告了一位 25 歲女性，本身患有滑液膜惡性肉瘤合併多處肺轉移及反覆局部復發，他接受高劑量 ifosfamide 做為其抗癌治療，在第四個療程之前，化療前評估發現其有蛋白尿，糖尿，磷離子尿及非陰離子隙代謝性酸中毒。以上徵象指其患有 Fanconi 氏症，因此我們幫其補充失衡的電解質，並密切追蹤其異常的檢驗數

據。幸運的是，這些異常的檢驗數據慢慢的恢復正常。我們的案例焦點在 ifosfamide 可能造成的併發症，特別是在那些已經接受了高累積劑量的人。因此，對於那些已經接受 ifosfamide 且其累積劑量已達閾值者，密切追蹤是必需的，其目的是為了避免這個稀少但卻會使人衰弱的病症。

關鍵字: Fanconi 氏症、ifosfamide、chloroacetaldehyde (CAA)

INTRODUCTION

Nephrotoxicity is a rare but potentially dangerous adverse effect of numerous chemotherapeutic agents [1]. Ifosfamide is one of the numerous chemotherapeutic agents which can cause nephrotoxicity in varying severities. Fanconi's syndrome is characterized by proximal tubule dysfunction which can cause electrolyte imbalance leading to even more severe complication (ex. osteomalacia). Ifosfamide is an alkylating antineoplastic prodrug used to treat many solid tumors, including sarcomas [2]. It frequently induces Fanconi's syndrome in children, but rarely in adults [3]. We reported a case where the patient received high dose ifosfamide to treat synovial sarcoma. Fanconi's syndrome was diagnosed in this patient, and after successful treatment, the patient discharged with no further electrolyte imbalance.

CASE REPORT

A 25-year-old woman was admitted to the hospital with symptoms of mild shortness of breath and dry cough. She had a history of recurrent synovial sarcoma over the right inguinal area diagnosed 6 years earlier, which was treated with surgical excision and external beam radiotherapy. However, locoregional recurrence was diagnosed 2 months after the primary treatment. At that time, she was making regular clinic visits for follow-up of the recurrent tumor status. Surgical excision of the recurrent sarcoma was performed after follow-up for 18 months. However, repeated locoregional recurrence was diagnosed in the last 3 years. At this time, the patient's staging work-up revealed diffuse metastasis over both lungs with massive left side pleural effusion, together with locoregional recurrence involving the contralateral inguinal area. She received 2 cycles of high dose ifosfamide (3000 mg/m^2/day, a 5-day cycle for the 1st cycle, and a 4-day cycle for the 2nd cycle), and reassessed with chest computed tomography and pelvic magnetic resonance imaging. Both imaging devices revealed shrinkage of tumor size. Furthermore, the patient's symptoms of shortness of breath and dry cough had also improved. However, new mixed osteolytic and osteoblastic lesions were noted over the thoracic spine area. Another 2 courses of high dose ifosfamide was planned to be administered, with a total ifosfamide dose of 39 g/m^2. During the pre-chemotherapy evaluation of the patient's last chemotherapy, routine blood test (hemogram, creatinine, liver enzymes, sodium and potassium) revealed no significant abnormality. However, the routine urine test revealed prominent proteinuria (> 300 mg/dl). Further analysis revealed normal calcium, chloride, albumin and magnesium, moderate hypophosphatemia (1.5 mg/d/, nl 2.1~4.7 mg/dl). Further collection of urine over a 24-hour period revealed proteinuria (2g/day), slightly decreased tubular reabsorption of phosphorus (74%, NL > 90%), loss of glucose (256 mg/dl) and normal urine chloride, sodium, and potassium. After completion of chemotherapy, subsequent blood analysis revealed non-anion gap metabolic acidosis ($HCO3^-$ 19.3 mmol/L, nl 21~28 mmol/L), mild hyponatremia (131 mmol/L, nl 135~

***Corresponding author:** Chueh-Chuan Yen M.D.

*通訊作者：顏厥全醫師

Tel: +886-2-28712121 ext.2525

Fax: +886-2-28757762

E-mail: ccyen@vghtpe.gov.tw

147 mmol/L) and hypokalemia (3.1 mmol/L, nl 3.4~ 4.7 mmol/L).

For these abnormalities, we concluded that the patient suffered from ifosfamide induced tubular dysfunction. Hypokalemia and non-anion gap metabolic acidosis were also consistent with type II renal tubular dysfunction. Potassium and phosphorus supplement was also provided at the same time. The follow-up blood and urine test revealed normalization of the proteinuria, hypophosphatemia and hypokaemia. Thereafter, the patient was discharged following a 15-day hospital stay.

DISCUSSION

Ifosfamide requires metabolic activation to form the active cytotoxic agent, Ifosfamide mustard [4]. This metabolism occurs at CYP450 3A4 and 2B6, and the toxic metabolite, acrolein, which was considered to be the nephrotoxic, is also released [5,6]. A certain percentage of ifosfamide undergoes metabolism through an alternative pathway, and another toxic metabolite, chloroacetaldehyde (CAA) is produced and also considered to be nephrotoxic [7,8].

Fanconi's syndrome is a serious renal complication associated with ifosfamide, and relatively common in children (1.4-5%); however, fewer cases have been described in adults [3]. Fanconi's syndrome is characterized by proximal tubular dysfunction manifested by a loss of phosphate, bicarbonate, potassium, glucose, amino acids, and low molecular weight protein in the urine [9]. Ifosfamide-induced Fanconi's syndrome is often dose-related, especially when the total dose exceeds 45-60 g/m^2 in children [2,3].

Few case reports have described Fanconi's syndrome in adults. One group described a 54-year-old man suffering from both Fanconi's syndrome and diabetes insipidus after receiving 44 g/m^2 of ifosfamide [10]. The abnormal renal function, sodium, potassium, and phosphorus serum level returned to normal after the patient was supplemented with free water, potassium phosphate, potassium chloride and potassium citrate. The non-anion gap metabolic acidosis also resolved after sodium bicarbonate supplement. Another case study described a 20-year-old man who developed Fanconi's syndrome 3 months after initiating chemotherapy with ifosfamide, methotrexate and doxorubicin [11]. The urinary loss of phosphate led to hypophosphatemia, which thereafter induced osteomalacia. Phosphate supplement was required in this patient.

Although the mechanism of ifosfamide-induced Fanconi's syndrome remains unclear, current theories tend to attribute this phenomenon to the ifosfamide toxic metabolite, CAA [2]. After it is metabolized via CYP450 3A4 and 2B6, ifosfamide is converted to ifosfamide mustard and its toxic metabolite, acrolein and CAA [7,8]. Acrolein can be completely neutralized by MESNA, so its toxicity can therefore be prevented by MESNA. However, CAA has low reactivity to MESNA, which results in accumulation and toxicity to proximal tubules [2,12]. At subcellular levels, CAA may decrease the glutathione and adenosine triphosphate (ATP) levels by inhibiting the activity of V-ATPase and NA+/K+-ATPase [9,13]. Cellular endocytosis at the proximal tubule is a dependent process, so when the ATP level decreases, the reabsorption in the proximal tubule is correspondingly reduced. V-ATPase plays a crucial role in intracellular vesicle trafficking. By inhibiting V-ATPase, intracellular protein processing and endocytosis are both disturbed [13].

There is no established treatment for Fanconi's syndrome. However, N-acetylcysteine (NAC) was demonstrated to have certain benefit in animal models [14,15]. It has been shown that ifosfamide induced oxidative damage to the kidney by depleting glutathione levels with CAA [14,15]. Cells exposed to a large dose of ifosfamide or those that have lower concentrations of glutathione experience more toxicity [2]. NAC is an antidote, thereby working as a precursor and substrate to enhance the biosynthesis of glutathione, and may reduce the toxicity of CAA [15]. NAC

successfully prevented ifosfamide-induced nephrotoxicity in rats [14]. Further research in humans is required to determine whether NAC is an adequate antidote for ifosfamide-induced toxicity without compromising its antineoplastic activity.

In conclusion, this 25-year-old woman presented with proteinuira, hypophosphatemia, glucosuria, and non-anion gap metabolic acidosis after treatment with a total dose of 39 g/m^2 ifosfamide. Fanconi's syndrome was suspected. After 15 days hospital stay and treatment, the patient was discharged with complete recovery. No established treatment for ifosfamide-induced Fanconi's syndrome was demonstrated, and therapeutic options were limited. The mechanism of ifosfamide-induced Fanconi's syndrome was not fully elucidated in our patient, which made this case difficult to manage. Hence, among patients who receive ifosfamide, it would be beneficial to closely monitor renal function, and electrolyte and routine urine test are furthermore mandatory, particularly when the accumulated dose exceeds 45 g/m^2.

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