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Renal Salt Wasting in Patients Treated with High-Dose Cisplatin, Etoposide, and Mitomycin in Patients with Advanced Non-Small Cell Lung Cancer

Yong Koo Lee, M.D. and Dong Moon Shin, M.D.*

Department of Internal Medicine, Wonkwang University Medical College, Iri, Korea

Cisplatin has many toxic effects; emesis, impairment of renal function, myelosuppression, peripheral neuropathy, ototoxicity and renal tubular wasting.

We used MVP regimen (Mitomycin C, Vp-16, and Cisplatin) in advanced Non-Small Cell Lung Cancer (NSCLC).

Using hydration and prophylactic supplementation of sodium and potassium before and during chemotherapy, we have observed the development of hyponatremia in 48 courses (43%), hypokalemia in 23 courses and hypomagnesemia in 11 courses.

Some patients showed abnormalities of renal function in 16 courses.

All the electrolyte depletion and renal problem was corrected before next courses by hydration and replacement of the wasting.

Frequent measurement of serum cation and appropriate replacement are recommended when high dose Cisplatin containing regimen is used in chemotherapy of neoplasms.

Key Words: *Cisplatin Non-Small Cell Lung Cancer.*

INTRODUCTION

Cisplatin (CDDP) is a chemotherapeutic agent of proven value in the treatment of a number of solid tumors.

Nephrotoxicity and electrolyte depletion are dose-limiting toxicity of CDDP and discouraged attempts at dose escalation[1].

Initial reports of azotemia and acute renal failure were followed by reports of other renal disorders, including renal magnesium wasting, as a consequence of cisplation treatment.

Renal magnesium wasting is present in virtually all patients treated with Cisplatin, resulting in hypomagnesemia with associated hypokalemia and hypocalcemia[1].

We have observed the development of hypomagnesemia, hyponatremia and hypopotassemia in patients receiving Cisplatin as part of a combination chemotherapy protocol for NSCLC.

The use of Cisplatin is likely to increase, and the nephrotoxic effects are iatrogenic and thus some what preventable. We have had the opportunity to follow a number of patients with NSCLC who were treated with Cisplatin-containing regimen. This report describes the occurrence of nephrotoxicity and some electrolyte depletion in such a patient population.

MATERIAL AND METHODS

Fourty seven patients with advanced NSCLC were entered into the study from October 1987 to December 1988. One patient was not eligible because he had inadequately controlled brain metastasis. Among the 46 eligible patients, females were 17 (37%) and males 29 (63%).

Medium age was 56 years old (range 33-74). Thirty four patients belonged to Zubrod's performance status 1 and others were 2. The distribution

Address reprint requesests to: Dong Moon Shin, M.D., University of Texas M.D., Anderson Cancer Center Head, Neck and Thoracic Medical Oncology-Box 80, 1515 Holcombe Boulevard, Houston, Texas 77030

of patients by histologic diagnosis was; 39 adenocarcinoma, 3 squamous cell carcinoma, one large cell carcinoma, one adeno-and squamous cell carcinoma respectively, and 2 were unclassified carcinoma.

Before starting the chemotherapy, patients were hydrated with 1.2L of 5% dextrose with 0.45% sodium chloride. Mitomycin was given intravenously in distilled water at 0.5 mg/mL by intravenous push on day 1 after methylprednisone and antiemetics. Cisplatin was then given in 250 mL of 3% sodium chloride with 37.5 g Mannitol and 20 mEq Kcl intravenously for 3 hours on days 1 and 7. Etoposide was administered orally in two equally divided doses on days 3, 4 and 5. During & after completion of each courses of chemotherapy, we measured the serum level of Na, K and Mg until these began to normalize.

Also, we checked creatinine clearance, BUN and creatinine in three to four days interval.

RESULTS

The dose schedule of chemotherapy was revealed in Table 1. Among the total 93 courses, hyponatremia developed in 40 courses (43%), only one course showed severe hyponatremia ($Na < 125$ mEq/L) on dose level 0. Nineteen courses were moderate ($125 \leq Na \leq 130$ mEq/L) and 20 courses were mild ($131 \leq Na \leq 135$) hyponatremia. Hypokalemia was 23 courses. Severe hypokalemia was only 1 on dose level 0. Nine courses were moderate hypokalemia ($2.6 \leq K \leq 3.0$ mEq/L) and mild hypokalemia ($3.1 \leq K \leq 3.5$ mEq/L) was 13 courses. Hypomagnesemia was 11 courses; 5 were mild ($1.4 < Mg < 1.8$ mg/dl) and 6 were moderate ($0.9 < Mg < 1.3$ mg/dl). Above results are revealed in Table 2.

Table 1. Dose Schedule of Chemotherapy

Agent	Dose level (mg/m^2)				
	-3	-2	-1	0	1
Mitomycin, I.V. Day 1	3	4	6	8	10
Cisplatin, I.V. Days 1 and 7	60	60	80	100	100
Etoposide, PO Days 3, 4, and 5	40	50	60	80	100

Abbreviations: IV, intravenously; PO, per orally

According to the escalation of dose level, the frequency of electrolyte depletion increased. In this trial, no cumulative toxicity can be estimated, because all the electrolyte levls were normalized before the next administration of chemotherapeutics.

Some patients showed severe diarrhea, nausea and vomiting but, specific electrolyte depletion was not observed.

BUN/creatinine increased in 16 courses but almost recovered before the next course of chemotherapy.

And renal dysfunction did not always precede the electrolyte depletion in the majority. We had no specific measure to assist the cause-effect relationship.

DISCUSSION

The effect of combination chemotherapy containing CDDP has been well established in a number of solid tumors, including testicular cancer, ovarian cancer, lung cancer and head and neck cancer[2].

As a coordinate metal complex, Cisplatin may cause acute and chronic renal insufficiency and renal magnesium wasting[3]. There are many reports of electrolyte depletion using an usual dose of Cisplatin containing regimen and some cases showed fatal results[6]. Some reports describe the relationship between renal insufficiency and

Table 2. Serum Sodium, Potassium and Magnesium Level in NSCLC Treated by MVP Regimen

Dose level	Na (mEq/L)				Mg (mg/dl)				K (mEq/L)			
	>136	131-135	125-130	>125	>1.8	1.4-1.8	0.9-1.3	<0.9	>3.6	3.1-3.5	2.6-3.0	<2.5
+1	1/3	2/3	0/3	0/3	3/3	0/3	0/3	0/3	3/3	0/3	0/3	0/3
0	7/14	3/14	3/14	1/14	11/14	0/14	3/14	0/14	10/14	1/14	2/14	1/14
−1	21/37	9/37	7/37	0/37	34/37	2/37	1/37	0/37	28/37	6/37	3/37	0/37
−2	19/31	5/31	9/31	0/31	29/31	2/31	2/31	0/31	25/31	4/31	3/31	0/31
−3	7/8	1/8	0/8	0/8	7/8	1/8	0/8	0/8	5/8	2/8	1/8	0/8
Total	53/93	20/93	19/93	1/93	84/93	5/93	6/93	0/93	70/93	13/93	9/93	1/93

hypomagnesemia, hyponatremia and potassium depletion as a serial event[4,5]. To disclose the dynamics of electrolyte depletion, they investigated renal function abnormalities. To overcome the renal and nonrenal toxicities, someone used high dose Cisplatin in hypertonic saline and got a measurable effect. And they suggested several measures to prevent impairment of renal function and electrolyte imbalance. Nephrotoxicity has been considered to be the dose limiting toxicity of Cisplatin[7].

When some studies used the dose of Cisplatin less than 100-200 mg/m^2 body surface area with moderate hydration (3 L/d), mannitol and furosemide diuresis, an acceptible degree of nephrotoxicity has been reduced.

To overcome the dose limiting toxicity of Cisplatin, Robert[6] et al have administered high dose Cisplatin together with extensive hydration. And they reported that there was no statistically significant decrease in creatinine clearance or elevation of serum creatinine after three to four cycles of a combination chemotherapy regimen.

Their studies show that high dose Cisplatin (40 mg/m^2 Body surface area d for 5 days) can be administered without any increase in nephrotoxicity in previously untreated patients, using vigorous saline hydration and 3% saline as a vehicle for drug delivery.

Baum and associates reported a 44% incidence of renal toxicity with Cisplatin doses of 130 mg/m^2 body surface area in childhood cancer[8]. Schilsky and Anderson noted hypomagnesemia during Cisplatin therapy and demonstrated inappropriate urinary magnesium loss in the presence of low serum levels[9]. Monique et al studied the influence of hydration on Cisplatin kinetics and kidney function in patients treated with Cisplatin[10]. Groups of ten patients received 100 mg/m^2 Cispatin in isotonic or hypertonic saline by a 20-min infusion. According to their results, they suggest that the infusion of Cisplatin in hypertonic saline with salt hydration could exert a protective effect on the kidney.

Hypokalemia associated with hypomagnesemia is also considered an effect of magnesium deficiency. Although the mechanism remains unclear, the movement of magnesium and potassium appears tightly coupled in the intracellular compartment and, to some extent, in the extracellular compartment[11,12]. The rate of Cisplatin infusion has been manipulated in an attempt to minimize renal toxicity. Hill and associates[13] reported that azotemia occured significantly less often when infusion rate did not exceed 1 mg/kg body weight[13].

Cvitkovic and colleagues found that vigorous intravenous hydration before, during and immediately after the administration of Cisplatin to dogs reduced the incidence of azotemia and acute renal failure[14]. At this time, there is no complete measure on the avoidance of Cisplatin-induced nephrotoxicity and magnesium wasting. Careful evaluation of renal function before each course of Cisplatin and frequent serum measurements and replacement, of magnesium, sodium and potassium are recommended.

In our experience, the incidence and severity of Cisplatin nephrotoxicity and consequent electrolyte depletions are reduced by liberal intravenous hydration during and for 4-6 hours after Cisplatin administration. But some others point out that avoidance of othe nephrotoxic drugs, such as aminoglycosides, and keeping off rapid Cisplatin infusion are also important.

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