ORIGINAL ARTICLE

Hyponatremia Caused by Cyclophosphamide-containing Chemotherapy for Malignant Lymphoma Patients: A Single-center and Retrospective Study

Junji Hiraga[1], Yasuhiko Harada[1], Naruko Suzuki[1], Natsuko Uematsu[2], Yoshitoyo Kagami[1]

[1]Department of Hematology, Toyota Kosei Hospital, Toyota, Japan, [2]Department of Pharmacology, Toyota Kosei Hospital, Toyota, Japan

ABSTRACT

Objective: Cyclophosphamide (CPM) is a key chemotherapeutic drug for malignant lymphoma (ML). Hyponatremia caused by CPM is a rare but severe adverse event. We studied the incidence of hyponatremia among hospitalized patients treated with CPM for ML patients in a single-center and retrospective study. **Patients and Methods:** This study investigated a total of 832 cases (367 patients) of chemotherapy, including intravenous CPM administration during hospitalization in our institute with ML between April 2009 and December 2019. Median age was 67 years (range, 18–91 years), with 210 men (456 cases, 54.8%). Diffuse large B-cell lymphoma was the most common type of ML treated (60.2%). Hyponatremia severity was defined according to the Common Terminology Criteria for Adverse Events version 5.0. We analyzed variables known to be associated with hyponatremia. **Results:** Of the 761 cases without hyponatremia before CPM administration, 82 cases (10.8%) developed hyponatremia after CPM administration. High-dose CPM administrations correlated significantly with hyponatremia ($P < 0.001$). After analysis of other variables, the complication of vomiting ($P < 0.001$) and use of a selective serotonin reuptake inhibitor ($P < 0.001$) showed a significant correlation with hyponatremia. **Conclusion:** The incidence of hyponatremia after chemotherapy, including CPM was high, particularly with high-dose chemotherapy. After CPM administration, close monitoring is warranted to prevent hyponatremia.

Key words: Cyclophosphamide, hyponatremia, malignant lymphoma, syndrome of inappropriate secretion of antidiuretic hormone

INTRODUCTION

Hyponatremia is a common electrolyte abnormality in hospitalized patients, with a widely varying incidence of 15–45%.[1-4] Although this complication has been reported with various infectious diseases and cardiovascular events, many reports have also described hyponatremia in association with chemotherapy, particularly with platinum agents.[5-7]

The alkylating agent cyclophosphamide (CPM) is a key drug in the treatment of malignant lymphoma (ML). As adverse events, bone marrow suppression, infection, hemorrhagic cystitis, and secondary malignancies are well known.[8] Although the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[9,10] is known as a rare adverse event that induces severe hyponatremia, studies remain limited to a few case reports, and the incidence of this complication remains unclear.[11-15]

Here, we report the incidence of hyponatremia among hospitalized patients treated with CPM for ML patients in a single-center and retrospective study.

Address for correspondence:
Junji Hiraga, Department of Hematology, Toyota Kosei Hospital, 500-1, Ibobara, Josui-cho, Toyota City 470-0396, Japan. Tel: 81-565-43-5000; Fax: 81-565-43-5100.

PATIENTS AND METHODS

We retrospectively analyzed the clinical records of 367 patients (administration of 832 cases) with ML admitted to Toyota Kosei Hospital to receive chemotherapy that included CPM infusion between April 2009 and December 2019. All patients had undergone a measurement of serum sodium levels before and after chemotherapy. Median age was 67 years (range, 18–91 years), with 210 men (456 cases, 54.8%). Cases were divided into three groups according to the dose of CPM administered. CPM doses were <30 mg/kg/day in 691 cases (357 patients), with typical chemotherapy regimens, including CHOP therapy (CPM, doxorubicin [DXR], vincristine [VCR], and prednisolone), EPOCH therapy (etoposide [ETP], prednisolone, VCR, CPM, and DXR), or hyper-CVAD therapy (CPM, VCR, DXR, and dexamethasone). CPM doses were 30–49 mg/kg/day in 117 cases (46 patients), and the main treatment regimen was CHASE therapy (CPM, high-dose cytarabine, dexamethasone, and ETP). CPM doses were ≥50 mg/kg/day in 24 cases (24 patients), as pretreatment for autologous peripheral blood stem cell transplantation using LEED therapy (melphalan, CPM, ETP, and dexamethasone). Hyponatremia severity was defined according to the Common Terminology Criteria for Adverse Events version 5.0:[16] Grade 1,<130–135 mmol/L; Grade 2, 125–129 mmol/L and asymptomatic; Grade 3, 125–129 mmol/L symptoms or 120–124 mmol/L regardless of symptoms; Grade 4,<120 mmol/L, life-threatening consequences; or Grade 5, death. We analyzed variables known to be associated with hyponatremia, age, sex, pathologically diagnosed diffuse large B-cell lymphoma (DLBCL) and others, CPM dose, complications of elevated serum creatinine before treatment, vomiting as a complication, death within 3 months after treatment, administration of VCR, development of pneumonia before CPM, use of a selective serotonin reuptake inhibitor (SSRI), total daily amount of free water intravenous fluid, and total daily amount of sodium by intravenous drip infusion.[9,10] The Chi-square test and t-test were used to compare categorical variables and Fisher's exact test for comparison between two groups. Logistic regression analysis was used for multivariate analysis. Statistical analysis was performed using JMP version 11 software (SAS Institute, Cary, North Carolina, USA).

RESULTS

In all 832 cases, the most common pathological subtype of ML being treated was DLBCL (60.2%). With 71 cases (8.53%), the patients showed hyponatremia before CPM-containing chemotherapy, comprising Grade 1 in 56 cases, Grade 2 in 8 cases, Grade 3 in 6 cases, and Grade 4 in 1 case. After CPM-containing chemotherapy, serum sodium level normalized in 32 cases (45.1%).

Among the 761 cases without pretreatment hyponatremia, 82 (10.6%) developed hyponatremia after CPM administration [Table 1], comprising Grade 1 in 68 cases, Grade 2 in 9 cases, Grade 3 in 3 cases, and Grade 4 hyponatremia in 2 cases. In the subgroups based on CPM dose, hyponatremia occurred in 63 of 623 cases (10.1%) with CPM dose <30 mg/kg/day, 8 of 115 cases (7.0%) with CPM dose 30–49 mg/kg/day, and 11 of 23 cases (47.8%) with CPM dose ≥50 mg/kg/day. A significant correlation was identified between high-dose CPM and hyponatremia ($P < 0.001$). After analysis of other variables, the complication of vomiting ($P < 0.001$) and use of an SSRI ($P < 0.001$) showed a significant correlation with hyponatremia. No significant differences in age, sex, diagnosis, complications of elevated creatinine before treatment, death within 3 months after treatment, administration of VCR, complication of pneumonia before CPM, total daily amount of free water intravenous fluid, and total daily amount of sodium by drip infusion. Two patients who received high-dose CPM developed SIADH with grade 4 hyponatremia and required treatment in the intensive care unit. Three other cases were diagnosed with SIADH. When the multivariate analysis was performed using parameters showing significant correlations on univariate analyses, three variables displayed significant results: CPM dose ($P = 0.0115$); vomiting as a complication ($P = 0.0005$); and use of an SSRI ($P = 0.0004$).

DISCUSSION

In this study, 832 cases of chemotherapy, including intravenous CPM administration, were administered to hospitalized patients in our hospital. Hyponatremia was observed with 71 cases before treatment with CPM, and with 82 cases (10.8%) after treatment with CPM, and the total rate of hyponatremia development was 18.4%. This was comparable with findings from previous reports.[1-3] Several reports have described SIADH in ML patients and with the use of SSRIs.[9,10]

When the CPM dose was <30 mg/kg/day, 63 (10.1%) of 623 patients developed hyponatremia. Similar doses of CPM are usually administered as outpatient chemotherapy, and those patients may also develop hyponatremia, but most do not undergo follow-up of serum sodium levels after chemotherapy. The hyponatremia caused by this dose was mostly Grade 1 and asymptomatic. With outpatient chemotherapy, the use of drip infusion is transient, and this relatively limited use of a drip may induce fluid restriction without inducing SIADH.[10] Conversely, with doses ≥50 mg/kg/day, hyponatremia was observed in 11 of 23 patients (47.8%). Two of the five patients diagnosed with SIADH required treatment in the intensive care unit. Careful attention should be paid to serum sodium levels after high-dose CPM administration, particularly among patients with vomiting or use of SSRIs.

Table 1: Characteristics of patients without hyponatremia before CPM-containing chemotherapy

Hyponatremia	Yes	No	*P*-value
	82	679	
Sex			
Male	40	373	
Female	42	306	0.292
Age			
Median (range)	70 (26–87)	66 (18–91)	0.122
Diagnosis			
DLBCL	54	401	
Others	28	278	0.313
Amount of CPM			
<30 mg/kg/day	63	560	
30–49 mg/kg/day	8	107	
≥50 mg/kg/day	11	12	<0.001
Elevated serum creatinine before treatment			
Yes	7	59	
No	75	620	0.963
Vomiting			
Yes	18	34	
No	64	645	<0.001
Death within 3 months			
Yes	6	26	
No	76	653	0.151
VCR			
Yes	61	515	
No	21	164	0.858
Pneumonia			
Yes	1	16	
No	81	663	0.416
Use of SSRIs			
Yes	9	10	
No	73	669	<0.001
Total daily amount of free water intravenously (mL)			
Median (range)	1750 (600–4500)	1700 (400–5000)	0.126
Total daily amount of sodium(mmol/L)			
Median (range)	153.9 (60–487)	142.4 (60.9–510.3)	0.371

CPM: Cyclophosphamide. DLBCL: Diffuse large B-cell lymphoma. SSRI: Selective serotonin reuptake inhibitor

Some limitations need to be considered when interpreting the present results. Amounts of drinking water, food, urination, and sodium in urine were not investigated in all cases, and this may represent a limitation to the study. This reason may be why no significant difference was found in the total daily amount of free water administered intravenously or total daily amount of sodium administered by drip infusion. Similarly, as the present was a retrospective study, prospective studies may be required to assess the incidence of hyponatremia more accurately.

CONCLUSION

The incidence of hyponatremia after chemotherapy, including CPM, was high, at 10.8%. In particular, hyponatremia was

frequently identified with high-dose chemotherapy. When hyponatremia develops during CPM use, examination and treatment with SIADH in mind should be performed as soon as possible.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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