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Anemia Is a Novel Predictive Factor for the Onset of Severe Chemotherapy-Induced Peripheral Neuropathy in Lymphoma Patients Receiving Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone Therapy

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Chemotherapy-induced peripheral neuropathy (CIPN) frequently occurs in lymphoma patients receiving R-CHOP, a drug combination therapy. Although severe CIPN may lead to reduction and/or discontinuation of the medication, predictive factors of CIPN have not been investigated sufficiently to date. We performed a retrospective exploratory research to determine associations between prevalence of severe CIPN and socio-demographic data, health characteristics, and medical conditions such as anemia at initial diagnosis. Forty patients (indolent lymphoma, $n=9$; diffuse large B-cell lymphoma; $n=31$) received R-CHOP therapy from September 2009 to July 2014. The median age of patients was 58 years (range = 27–76 years). Statistical analyses were applied to the patients, who were divided into two groups: mild CIPN (no symptoms or grade 1 according to the CTCAE version 3.0 program) and severe CIPN patients (grade 2 or higher). Forward stepwise logistic regression analyses were performed using the following variables: sex, BMI, BSA, hyperglycemia, malnutrition, and anemia. Severe CIPN occurred in seven patients (17.5%). Gender and anemia remained following the stepwise procedure, and anemia predicted severe CIPN significantly (OR = 19.45, 95% confidence interval = 1.52–171.12). Our study suggests that anemia at initial diagnosis could be a predictive factor of R-CHOP-induced CIPN.

Key words: Chemotherapy-induced peripheral neuropathy (CIPN); Anemia; R-CHOP; Diffuse large B-cell lymphoma (DLBCL)

INTRODUCTION

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) is the standard chemotherapy for diffuse large B-cell lymphoma (DLBCL), and this combination drug therapy is also frequently used for indolent lymphoma (IL)[1,2]. However, R-CHOP therapy induces some significant adverse events such as nausea, alopecia, myelosuppression, and neurological toxicity[1]. In particular, neurological toxicity, called chemotherapy-induced peripheral neuropathy (CIPN), occurs as an adverse reaction by vincristine (VCR) in approximately 50% of DLBCL patients receiving R-CHOP[1]. Furthermore, grade 3 CIPN prevents further administration of VCR[3]. Severe CIPN also affects gait and activities of daily living (ADL) and is followed by worsening performance status (PS). Once severe CIPN occurs, causative medication should be reduced and/or discontinued[4]. Therefore, these patients cannot obtain further therapeutic benefit from the chemotherapy.

Although many studies cover prevention of CIPN and its treatment, predictive factors of severe CIPN have not been sufficiently documented[5]. To develop treatment and prevention strategies for CIPN so as to continue chemotherapy, we must first accumulate evidence of predictive factors of severe CIPN.

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In the present study, we aimed to identify predictive factors of severe CIPN resulting from R-CHOP treatment. At initial diagnosis, we investigated associations between severe CIPN and sociodemographic data, health characteristics, and medical conditions. Hyperglycemia, renal dysfunction, hepatic dysfunction, anemia, malnutrition, and electrolyte abnormality (defined as "poor medical conditions") have been reported to be predictive factors of peripheral neuropathy or could influence nerve regeneration and neural transmission[6–10]. We hypothesize that these preexisting medical conditions contribute to R-CHOP-induced CIPN and hence their presence could predict the onset of severe CIPN.

MATERIALS AND METHODS

Patients and Study Design

Forty patients, who were diagnosed with DLBCL or IL and received R-CHOP as first-line chemotherapy in Kobe University Hospital from September 2009 to July 2014, were included in this retrospective cohort study. Patients who received other chemotherapy regimens and received blood transfusions were excluded. To find predictive factors of severe CIPN, we evaluated medical conditions such as hyperglycemia, renal dysfunction, hepatic dysfunction, malnutrition, anemia, and electrolyte abnormality using laboratory data at initial diagnosis. This study was approved by the ethics committee of Kobe University Graduate School of Health Sciences. For this type of study, formal consent is not required.

Data Collection

All data were collected from patient medical records at Kobe University Hospital. We investigated sociodemographic and health characteristics [age, gender, body mass index (BMI)], body surface area (BSA), cancer clinical stage, PS, dose of VCR per cycle, and laboratory data at initial diagnosis.

Poor medical conditions were defined as hyperglycemia with blood glucose (Glu) ≥126 mg/dl according to the World Health Organization (WHO) criteria[11]; renal dysfunction with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 according to the Kidney Disease: Improving Global Outcomes criteria[12]; hepatic dysfunction with alanine transaminase (ALT) >30 IU according to the Japan Society of Hepatology Guideline for the Management of Hepatitis C Virus Infection Criteria[13]; malnutrition with serum albumin (Alb) <3.5 g/dl according to the criteria used in some studies[14,15]; anemia with hemoglobin (Hb) concentration <12.0 g/dl for females and <13.0 g/dl for males according to the WHO criteria[16]; and electrolyte abnormality with serum potassium (K) ≥5 or <3.5 mEq/L according to the American Heart Association criteria[17]. The presence or absence of each condition corresponded to the categorical variables used in this study.

Assessment of CIPN

Information on the severity of CIPN was evaluated during each cycle of chemotherapy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 program, and we adopted the highest grade of CIPN throughout the treatment. We regarded patients with no symptoms or grade 1 CIPN as mild CIPN cases, and patients with grade 2 or higher CIPN as severe CIPN ones.

Statistical Analysis

To describe characteristics of the variables, medians for continuous variables and frequencies and percentages for categorical variables were computed. To compare the two groups (mild CIPN vs. severe CIPN patients), Student's *t*-test was used for normally distributed continuous variables, the Wilcoxon rank sum test for nonnormally distributed continuous variables, and the chi-square test for categorical variables.

Subsequently, the forward stepwise logistic regression model was performed to find predictive factors of severe CIPN. In this model, factors with ≤0.2 in univariate analysis were used as independent variables. A value of $p<0.05$ was defined as statistically significant for all analyses. All statistical analyses were conducted using JMP v11.0 software (SAS Institute, Japan).

RESULTS

Characteristics of patient with mild and severe CIPN are shown in Table 1. Thirty-one of 40 patients (77.5%) were diagnosed with DLBCL, and 9 (22.5%) with IL (follicular lymphoma, $n=7$; mantle cell lymphoma; $n=2$). The median age of the patients was 58 years, and 24 of these patients (60%) were male. During the treatment, seven patients (17.5%) experienced grade 2 or higher CIPN that influenced their ADL in some way. Details of patient symptoms are shown in Table 2. There were no statistically significant differences in all demographic characteristics between mild and severe CIPN patients.

The frequency of poor medical conditions at initial diagnosis is shown in Table 3. Seven patients (17.5%) were identified with hyperglycemia, 5 patients (12.5%) with hepatic dysfunction, 12 patients (30%) with malnutrition, 16 patients (40%) with anemia, and only 4 patients (10%) with electrolyte abnormality. The results of the chi-square test showed that there were more patients with anemia in the severe CIPN group than in the mild CIPN group ($p<0.01$). The mean values of Hb concentrations

Table 1. Baseline Characteristics of the Patients

Variables	All Patients ($n=40$)	Mild CIPN Patients ($n=33$)	Severe CIPN Patients ($n=7$)	p
Median age (years ± SD)	55.38 ± 11.88	54.85 ± 2.08	57.86 ± 4.53	0.63
Gender				0.06
Male (%)	24 (60)	22 (66.7)	2 (28.6)	
Female (%)	16 (40)	11 (33.3)	5 (71.4)	
BMI (kg/m^2 ± SD)	22.88 ± 4.35	23.21 ± 0.76	21.28 ± 1.64	0.17
BSA (m^2 ± SD)	1.67 ± 0.18	1.69 ± 0.03	1.56 ± 0.07	0.10
Cancer type				0.56
DLBCL (%)	31 (77.5)	25 (75.8)	6 (85.7)	
Indolent lymphoma (%)	9 (22.5)	8 (24.2)	1 (14.3)	
Disease stage				0.53
Limited (I–II) (%)	15 (37.5)	11 (33.3)	4 (57.1)	
Advanced (III–IV) (%)	21 (52.5)	18 (54.5)	3 (42.9)	
Missing* (%)	4 (10.0)	4 (12.2)	0 (0)	
LDH ± SD	295.43 ± 154.45	303.34 ± 27.5	259.29 ± 58.78	0.21
Missing* (%)	1 (0.03)			
ECOG PS				1.00
0–1 (%)	24 (60.0)	20 (60.6)	4 (57.1)	
2–4 (%)	6 (15.0)	5 (15.1)	1 (14.3)	
Missing (%)	10 (25.0)	8 (24.3)	2 (28.6)	
Dose VCR per cycle (mg)	1.98 ± 0.10	1.98 ± 0.01	1.99 ± 0.04	0.71

CIPN, chemotherapy-induced peripheral neuropathy; BMI, body mass index; BSA, body surface area; DLBCL, diffuse large B-cell lymphoma; ECOG PS, performance status according to Eastern Collaborative Oncology Group; VCR, dose of vincristine.
*Some data were lacking on the medical records.

Table 2. Details of Severe Chemotherapy-Induced Peripheral Neuropathy (CIPN) Among Seven Patients

Patient	Grade	Onset Cycle	Place	ADL Restriction	Duration
1	3	2	Lower	Gait	Continued for 2 months after the end of treatment
2	3	2	Lower	Gait: need T-cane	Continued for 6 months after the end of treatment
3	2	3	Upper	Skilled movement (i.e., button up)	Recovery within 1 month after the end of treatment
4	2	5	Upper	Skilled movement (i.e., button up)	Recovery within 1 month after the end of treatment
5	2	5	Lower	Gait	Continued for 6 months after the end of treatment
6	2	2	Upper	Skilled movement (i.e., button up)	Recovery within 1 month after the end of treatment
7	2	2	Upper	Skilled movement (i.e., button up)	Recovery within 1 month after the end of treatment

Table 3. Frequency of Each Medical Condition at Baseline

Variables	All Patients ($n=40$)	Mild CIPN Patients ($n=33$)	Severe CIPN Patients ($n=7$)	p
Anemia (%)	16 (40)	10 (30.3)	6 (85.7)	<0.01
Malnutrition (%)	12 (30)	12 (36.7)	0 (0.0)	0.06
Hepatic dysfunction (%)	10 (25)	9 (27.3)	1 (14.3)	0.47
Hyperglycemia (%)	7 (17.5)	7 (21.2)	0 (0.0)	0.18
Renal dysfunction (%)	5 (12.5)	4 (12.1)	1 (14.3)	0.86
Electrolyte abnormality (%)	4 (10)	3 (9.1)	1 (14.3)	0.68

CIPN, chemotherapy-induced peripheral neuropathy.

at baseline were 13.13±1.66 and 11.64±0.96 g/dl in the mild CIPN group and the severe CIPN group, respectively. The prevalence of other medical conditions was not significantly different between the mild and severe CIPN groups. Regarding hyperglycemia, there were four patients with diabetes mellitus in this study. Two of them were included in the normal blood glucose group, in accordance with the results of the chi-square test, because their disease was medically well managed. Therefore, we included them in the hyperglycemia group and performed reanalysis. As a result, the prevalence of hyperglycemia increased to 14.29% in the severe CIPN group; however, this change did not affect the association of CIPN and hyperglycemia ($p=0.32$). All variables, such as gender, BMI, BSA, hyperglycemia, malnutrition, and anemia, satisfied the criteria of entry into the forward stepwise logistic regression model. Gender and anemia remained in the regression model following the stepwise procedure. The logistic regression analysis showed that anemia predicted severe CIPN in the R-CHOP treatment (odds ratio=19.45, 95% confidence interval=1.52–171.12).

DISCUSSION

Dose reduction of anticancer drugs due to symptoms of severe CIPN indicates that patients could not complete the planned chemotherapy regimen and receive enough therapeutic value. Therefore, it is necessary to predict and establish an effective management strategy for CIPN. However, few studies show valuable predictors to date[18]. In this study, we determined that anemia before the treatment was a novel predictive factor of severe CIPN in lymphoma patients receiving R-CHOP therapy, whereas no such relationship was observed for sociodemographic and health characteristics and other medical conditions. Anemia is a good predictor for the development of CIPN, because laboratory data (including blood test) for evaluating medical conditions are commonly examined before chemotherapy.

Glendenning et al. investigated the association between CIPN and age, medical information, and dose of anticancer drugs among testicular cancer patients and reported that age was a significant predictor of peripheral neuropathy[19]. However, our results differed from those in their study. The reason could be explained by the difference in age groups of participants between two studies. Patients in our study were older and the median age was 58 years, but the median age in their study was 30 years. Aging has been shown to affect the peripheral nervous system, particularly in elderly people (aged over 60 years)[20,21]. Our patients were generally of such an age that their peripheral nervous system appeared to have degenerated significantly. Therefore, age would be excluded as a predictor in our study.

Our results expand the evidence of CIPN induced by VCR. Kawakami et al. similarly examined whether the baseline laboratory data enabled prediction of severe CIPN among non-small lung cancer patients receiving paclitaxel plus carboplatin therapy (PC therapy)[22]. They reported that pack-year of smoking and low creatinine clearance level predicted severe CIPN in the treatment. They also argued that renal dysfunction affected metabolism and excretion of paclitaxel, probably followed by developing severe CIPN. However, our results could not support their findings, as VCR has different pharmacokinetics from paclitaxel or carboplatin because the former is metabolized in the liver and excreted with feces. Therefore, renal function does not significantly affect the pharmacokinetics of VCR[23].

Although anemia is a common medical condition among cancer patients, literature explaining the association between anemia and severe CIPN is not adequate. Penninx et al. showed that anemia was associated with disability and decreased muscle strength[24]. They also assumed that hypoxia in muscle tissue affected muscle strength, citing the experimental study in vivo by Dodd et al.[25]. Several publications also reported that anemia affected physical performance and quality of life and suggest that decreased oxygenation of tissues might cause these results[26,27]. The response to hypoxia varies according to the organ. For example, the brain and the heart can maintain oxygen homeostasis during anemia, but this homeostasis is affected by the peripheral tissues[28,29]. This peripheral tissue hypoxia is also involved in peripheral nerve system dysfunction and induces a reduction of overall protein synthesis in the cells and production of inflammatory cytokines[30,31]. Furthermore, protein synthesis disorders may inhibit nerve repair. In addition, sensory nerves are irritated by inflammatory cytokines that occur around the dorsal root ganglion after nerve damage[32,33]. Therefore, anemia-induced tissue hypoxia might affect the repair of peripheral nerve injured by VCR and subsequently lead to severe CIPN.

This report has some limitations. First, as this retrospective analysis was performed using a relatively small sample size (40 patients), these results might be influenced by random error. Second, we evaluated CIPN only depending on subjective judgment of the patients using the CTCAE version 3.0 program. Clinical research at the MD Anderson Cancer Center routinely used several objective assessment tools to evaluate CIPN and investigated various sensory disturbances[34]. More research is required with large sample sizes that include objective assessment tools such as the monofilament test for measuring the touch detection threshold as a superficial sensation[35] and the tuning fork test for measuring the vibration detection threshold as a deep sensation[36].

In conclusion, anemia, as a preexisting condition before treatment, was a useful predictive factor of severe CIPN in lymphoma patients receiving R-CHOP therapy. Despite some limitations described above, this result provides a starting point in the management and prevention of CIPN.

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