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Expression of vincristin-induced peripheral neuropathy related to different administration methods

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Vincristine (VCR) is an important drug used in R-CHOP regimens for the treatment of non-Hodgkin's lymphoma. The purpose of this study was to examine whether the administration method affects the incidence of VCR-induced peripheral neuropathy. We investigated the ratio of VCR-induced peripheral neuropathy during rapid intravenous infusion and intravenous drip infusion. A total of 71 patients who had received six or more courses of R-CHOP from January, 2015 to December, 2016 at Komaki City Hospital and Ogaki Municipal Hospital were retrospectively investigated. Peripheral neuropathy was observed in 27/39 patients (69 %) and 24/32 (75 %) in rapid intravenous infusion and intravenous drip infusion of VCR, respectively (P = 0.79). Peripheral neuropathy was observed at a high frequency in this study. Additionally, there was no difference in frequency of peripheral neuropathy due to the difference in administration method. In both groups, the degree of peripheral neuropathy was grade 1 and grade 2 in most patients. However, in rapid intravenous infusion, grade 3 peripheral neuropathy was observed. Some cases required dose reduction and discontinuation in rapid intravenous infusion. In contrast, there were no discontinuing patients in the intravenous drip infusion. Therefore, it was suggested that intravenous drip infusion of VCR reduced serious peripheral neuropathy because the ratio requiring dose reduction and discontinuation was less than that in the rapid group. In conclusion, this study is informative as there are few reports focusing on the administration method of vincristine.

1. Introduction

Vincristine (VCR) is an important drug used for R-CHOP or R-CHOP-like regimens for the treatment of non-Hodgkin's lymphoma (Fisher et al. 1993; Coiffier et al. 2002). It is considered that VCR causes axonal degeneration by binding to microtubules of peripheral nerves and causes peripheral neuropathy. Peripheral neuropathy is a dose-limiting factor of VCR (Carbone et al. 1963; Jackson et al. 1981). Peripheral neuropathy of the VCR may interfere with walking and daily life, and may be severe in some cases. Moreover, peripheral neuropathy caused by VCR may affect quality of life. Thus, it is necessary to reduce or stop VCR depending on the degree of peripheral neuropathy. Previous studies reported that the relative dose intensity (RDI) of VCR affects the treatment of non-Hodgkin's lymphoma (Utsu et al. 2016). Peripheral neuropathy after VCR varies from early treatment to appearance by repeated treatment, but some studies reported that it is related to the total dose of VCR and the number of treatment courses (Ocean et al. 2004; Kanbayashi et al. 2010). Peripheral neuropathy has been reported to be affected by a single dose, total dose, increased blood concentration by combination of cytochrome P450 3A4 (CYP3A4) inhibitors (Ocean et al. 2004; Kanbayashi et al. 2010; Moriyama et al. 2012). Peripheral neuropathy may be associated with blood concentration of VCR, and the rise of VCR blood concentration may be dependent on the administration method of the drug. However, no studies have focused on the expression of peripheral neuropathy due to differences in the administration method of VCR. The VCR administration varies by facility, with rapid intravenous infusion and intravenous drip infusion. The treatment was administered slowly over 1 min (rapid intravenous infusion) at Komaki City Hospital. However, there are facilities that administer VCR in intravenous drip infusion for 15 to 30 min for the convenience of the medical staff. Since administration methods are not unified between each facility, it is necessary to consider the optimal VCR administration method. In this study, we investigated the expression of peripheral neuropathy in comparison between rapid intravenous infusion and intravenous drip infusion of VCR.

Table 1: Patient characteristics

	Rapid group (n = 39)	Drip group (n = 32)	P-value
Age, years (range)	68 (35-88)	68 (45-84)	0.428 [a]
Gender			0.479 [b]
Male	22	15	
Female	17	17	
Weight, kg	57.0 (36.8-79.3)	56.4 (31.8-76.7)	0.862 [a]
Body surface area, m^2	1.58 (1.21-1.85)	1.57 (1.17-1.95)	0.743 [a]
VCR dose, mg	1.60 (0.80-2.00)	2.00 (1.00-2.00)	<0.01 [a]
ARDI, %	76.4 (45.5-91.1)	98.7 (50.0-100.0)	<0.01 [a]
RDI-VCR, %	75.0 (45.0-100.0)	100.0 (50.0-100.0)	<0.01 [a]
CYP3A4 inhibitor			0.746 [b]
presence	5	5	
absence	34	27	
Lymphoma type, n (%)			0.070 [b]
Diffuse large B-cell lymphoma	33 (85)	22 (69)	
Follicular lymphoma	6 (15)	6 (19)	
Others	0	4 (13)	

VCR, vincristine; ARDI, average relative dose intensity; RDI, relative dose intensity.
[a] The Mann-Whitney U test. [b] Fisher's exact probability test.

2. Investigations and results

2.1. Patient characteristics

VCR was administered to 39 patients by rapid intravenous infusion (rapid group) and to 32 patients by intravenous drip infusion (drip group). Table 1 shows the patient's characteristics of the two groups. The drip group was significantly higher than the rapid group in the average dose of VCR, average relative dose intensity (ARDI), the RDI of VCR. There were no significant differences between the two groups with regard to age, sex, body weight, and body surface area.

2.2. The ratio and degree of express peripheral neuropathy

There was no significant difference in the ratio of patients with peripheral neuropathy between the rapid and drip groups. In both groups, the degree of peripheral neuropathy was grade 1 and grade 2 in most patients. However, in the rapid group, grade 3 peripheral neuropathy was observed (Table 2).

Table 2: Number, degree and cycle of express peripheral neuropathy

		Rapid group (n = 39)	Drip group (n = 32)	P-value
Peripheral neuropathy (%)		27 (69)	24 (75)	0.791 [a]
Grade (%)	1	19 (49)	20 (63)	0.140 [b]
	2	5 (13)	4 (13)	
	3	3 (8)	0	
Cycle (%)	1	9 (23)	2 (6)	0.129 [b]
	2	7 (18)	7 (22)	
	3	3 (8)	7 (22)	
	4	2 (5)	4 (13)	
	5	3 (8)	4 (13)	
	6	3 (8)	0	

[a] Fisher's exact probability test. [b] The Chi-square test.

2.3. The date of start of peripheral neuropathy

In the rapid group, the median date of the start of peripheral neuropathy was the second course (range, 1–6 courses). In the drip group, the median date of the start of peripheral neuropathy was the third course (range, 2–5 courses). There was no significant difference in the date of the start of peripheral neuropathy in the rapid group and drip groups (Table 2).

2.4. Number of patients requiring dose reduction and discontinuation of VCR

Seven patients required dose reduction, and two patients required discontinuation in the rapid group. Grade 1 peripheral neuropathy was observed, whereas no patients in the drip group needed dose reduction and discontinuation due to peripheral neuropathy (Table 3). Patients with reduced VCR dose due to peripheral neuropathy were higher in the rapid group than in the drip group, while the ratio of patients who discontinued VCR due to peripheral neuropathy was not significantly different between the two groups.

Table 3: Number of patients required dose reduction and discontinuation of VCR

	Rapid group (n = 39)	Drip group (n = 32)	P-value
Dose reduction (%)	7 (18)	0	0.014 [a]
Discontinuation (%)	2 (5)	0	0.498 [a]

VCR, vincristine; Dose reduction, patients required dose reduction of VCR; Discontinuation, patients required discontinuation of VCR.
[a] Fisher's exact probability test.

2.5. Number of patients developing peripheral neuropathy in the combination VCR and CYP3A4 inhibitor

We investigated azole antifungal agents and aprepitant as CYP3A4 agents. In the rapid group, peripheral neuropathy developed in five patients with a CYP3A4 inhibitor and in 22 patients without a CYP3A4 inhibitor. In the drip group, peripheral neuropathy developed in four patients with a CYP3A4 inhibitor and in 20 patients without a CYP3A4 inhibitor (Table 4). In this study, the ratio of peripheral neuropathy was not different according to the presence or absence of a CYP3A4 inhibitor.

Table 4: Number of patients express peripheral neuropathy in the combination vincristine and CYP3A4 inhibitor

	CYP3A4 inhibitor (+)		CYP3A4 inhibitor (-)		P-value
Rapid group Peripheral neuropathy (+), %	100	(5/5)	65	(22/34)	0.299 [a]
Drip group Peripheral neuropathy (+), %	80	(4/5)	74	(20/27)	1.000 [a]

[a] Fisher's exact probability test.

3. Discussion

In the present study, we compared the expression of peripheral neuropathy between rapid intravenous infusion and intravenous drip infusion of VCR. The results showed that there was no difference in the degree and frequency of peripheral neuropathy due to differences in the administration method. However, the doses of VCR and ARDI were high in the drip group. Intravenous drip infusion of VCR may be useful in the treatment of lymphoma, where ARDI is an important prognostic factor. This study is useful because there are few reports that focus on the administration method of VCR.

It has been reported that the total dose of VCR and the number of treatment courses correlate with the expression of peripheral neuropathy, and peripheral neuropathy is more likely to develop when the dose is larger (Ocean et al. 2004; Kanbayashi et al. 2010). Although the average dose of VCR in the drip group was larger than that in the rapid group, the incidence of peripheral neuropathy did not increase in the drip group. The results of this study differ from those of previous studies in that peripheral neuropathy is related to the total dose of VCR. Despite the ARDI, the dose and RDI of VCR were higher in the drip group than in the rapid group. There was no difference in the ratio and the date of start of expression of peripheral neuropathy. Utsu et al. (2016) reported that the RDI of VCR affected the treatment of non-Hodgkin's lymphoma. We considered that the intravenous drip infusion of VCR was useful in the treatment of lymphoma, where the RDI of VCR is an important prognostic factor. Previous studies have reported that peripheral neuropathy caused by VCR is expressed in 30%–40% of patients receiving VCR (Windebank et al. 2010; Rummel, et al. 2013). However, peripheral neuropathy of VCR was observed in nearly 70% of patients in this study, more than in previous studies. Even if peripheral neuropathy develops it may not be severe in the drip group. There was no significant difference between the two groups, but there were no discontinuing patients in the drip group. Therefore, it was suggested that intravenous drip infusion of VCR reduced serious peripheral neuropathy because the ratio requiring dose reduction and discontinuation was less than that in the rapid group.

VCR is metabolized by CYP3A4. Previous studies have reported that VCR causes serious peripheral neuropathy when concurrently using drugs with the capacity to inhibit CYP3A4 (Moriyama et al. 2012; Lin et al. 2018; Okada et al. 2014). Therefore, peripheral neuropathy in the VCR is expected to be affected by blood concentration. In this study, the ratio of developing peripheral neuropathy did not differ regardless of the presence or absence of a CYP3A4 inhibitor. In the case of using a combination of CYP3A4 inhibitors, it is difficult to evaluate the correlation between the blood concentration and the degree of peripheral neuropathy.

Intravenous drip infusion of VCR also contributes to medical safety. Patients are often intrathecally administered with other drugs at the same time. Accordingly, intrathecal infusion of VCR is contraindicated in the package insert, medical accidents that misdirected VCR into the intrathecal space have been reported worldwide (D'Addario et al. 2010; Hennipman et al. 2009). When administration of VCR is changed from rapid intravenous infusion to intravenous drip infusion, it is difficult to think that it is erroneously administered into the intrathecal space. Because it is not dispensed by a syringe after mixing, it will be dispensed using a bottle. Thus, intravenous drip infusion of VCR is safer than rapid intravenous infusion. It is considered to be useful not only for the possibility of reducing serious peripheral neuropathy but also for avoiding erroneous administration into the intrathecal space.

There were some limitations to this study. First, we did not measure blood concentrations of VCR. The incidence of peripheral neuropathy was considered to differ greatly due to the difference in the maximum blood concentration. Although blood concentrations were not measured in this study, it was expected that the maximum blood concentration would be lower than the rapid intravenous infusion by intravenous drip over 30 min. Compared to the rapid group, the maximum blood concentration decreased in the drip group, and peripheral neuropathy of the VCR group may not have been severe in this study. We did not consider whether changes to intravenous drip infusion affected overall survival and progression-free survival. In addition, since blood concentration was not measured, the pharmacokinetics were not considered. However, since it was considered that the area under the blood concentration time curve (AUC) of VCR did not change significantly between both administrations if the dose of VCR was the same, it was expected that overall survival and progression-free survival were not significantly different between the two groups. Second, since it is retrospective, there is a possibility that bias may exist due to the evaluation of peripheral neuropathy, and dose reduction and discontinuation criteria differ among medical staff. Additionally, criteria for reducing vincristine by physicians may differ between institutions. Therefore, although it is necessary to conduct a multicenter examination, it is thought that intravenous drip infusion of VCR is more useful in terms of the possibility of reducing serious peripheral neuropathy, convenience of medical staff, and the avoidance of erroneous administration into the intrathecal space.

4. Experimental

4.1. Patients characteristics

Between January, 2015 and December, 2016, a total of 71 patients had received six or more courses of R-CHOP at Komaki City Hospital (Komaki, Japan) and Ogaki Municipal Hospital (Ogaki, Japan). We retrospectively surveyed sex, age, the dose of VCR, ARDI, the RDI of VCR, the ratio and degree of express peripheral neuropathy, the period of express peripheral neuropathy, the number of patients requiring dose reduction and discontinuation of VCR, and the presence or absence of a CYP3A4 inhibitor for each patient in electronic records.

4.2. Administration of VCR and evaluation of the degree of peripheral neuropathy

VCR was administered slowly over 1 min (rapid intravenous infusion) at Komaki City Hospital and for 30 min (intravenous drip infusion) at Ogaki Municipal Hospital. Rapid intravenous infusion: VCR was dissolved in 20 mL of saline in a syringe, and administered slowly over 1 min. Intravenous drip infusion: VCR was dissolved in 100 mL of saline in a bottle, and administered for 30 min. Peripheral neuropathy was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) ver.4.0, based on the medical records.

4.3. Treatment

The R-CHOP regimen, it is consisted of rituximab (375 mg/m^2 intravenously on day 1), cyclophosphamide (750 mg/m^2 intravenously on day 2), doxorubicin (50 mg/m^2 intravenously on day 2), vincristine (1.4 mg/m^2 intravenously on day 2, max. 2.0 mg/body), and prednisolone (100 mg/body or 60 mg/m^2 [for patients >65 years] intravenously or orally on day 2-6). R-CHOP was administered every 3 weeks.

4.4. Calculation of DI (dose intensity)

The DIs of cyclophosphamide, doxorubicin, and VCR were calculated by dividing the dose of each drug by the number of weeks required for treatment. The RDI of each drug was calculated as the ratio of the DI calculated from the actual dose to the DI calculated from the scheduled dose. The ARDI was defined as the average of RDI of the three drugs. In addition, the scheduled dose of VCR was 2 mg as the maximum dose when the body surface area exceeded 1.43 m^2, and when less than 1.43 m^2, the dose calculated from the actual body surface area was used.

4.5. Statistical analysis

The Fisher's exact probability test, or the Mann-Whitney U test was performed to compare the patient characteristics. Fisher's exact probability test or the Chi-square test was performed to compare the two groups. All statistical analyses were performed with EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R version 3.12 (R Foundation for Statistical Computing). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics (Kanda 2013).

4.6. Ethical considerations

This study was approved by the Institutional Review Board of the Komaki City Hospital and the Ogaki Municipal Hospital. (181014, 20181122-6).

Conflict of interest: The authors have conflicts of interest to declare.

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