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Contribution of pharmacists with expertise in infectious diseases to appropriate individualized vancomycin dosing

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Background/aim: Dose adjustment of vancomycin (VCM) is important in improving clinical outcomes and avoiding adverse effects such as nephrotoxicity. Although pharmacist-managed VCM therapy has been reported to optimize treatment, there are no studies focused on pharmacist expertise to date. In this study, we compared the contribution of pharmacists trained for infectious diseases and general pharmacists to dose adjustment of VCM. *Patients and methods:* We retrospectively investigated VCM trough concentration after dose adjustment by both trained (n = 67) and general (without special training for infectious diseases; n = 85) pharmacists. We also compared the incidence of nephrotoxicity during VCM treatment in both groups. *Results:* The rate of achieving therapeutic VCM trough concentration (10–20 µg/mL) was higher in the trained group than in the control group (80.6 *vs.* 54.1%, p < 0.001). No significant differences in incidence of nephrotoxicity were observed between the two groups (p = 0.744). Trained pharmacists could contribute more successfully to the achievement of therapeutic VCM concentration ranges without increasing the risk of nephrotoxicity.

1. Introduction

Vancomycin (VCM) is a glycopeptide antibiotic used for the treatment of infections caused by gram-positive bacteria, as well as febrile neutropenia (FN) (Freifeld et al. 2011; Matsumoto et al. 2013). In clinical practice, pharmacists should provide medication-related decision support for treatment with drugs having narrow therapeutic ranges, such as VCM (Vincent et al. 2009). Therapeutic drug monitoring (TDM) during VCM treatment is important to improve clinical outcomes and avoid adverse effects such as nephrotoxicity (Matsumoto et al. 2013). To optimize treatment, antimicrobial dosing should be based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug. Pharmacist-managed VCM therapy has been reported to be associated with significant improvement both in clinical and economic outcomes (Bond and Raehl 2005; Sugiura et al. 2009; Teramachi et al. 2006). However, to date, no studies have focused on the impact of pharmacist expertise in VCM dose adjustment.

In Japan, pharmacists trained for infectious diseases are certified as Board Certified Pharmacist in Infection Control (BCPIC) or Board Certified Infection Control Pharmacy Specialists (BCICPS) by the Japanese Society of Hospital Pharmacists and as Infectious Disease Chemotherapy Pharmacists (IDCP) by the Japanese Society of Chemotherapy (JSC). In this study, we compared the contribution of trained pharmacists and general pharmacists without special training for infectious diseases to VCM dose adjustment.

2. Investigation and results

2.1. Patient characteristics

We compared cases where trained pharmacists commenced VCM dose adjustment (trained group; 67 patients from November 2013 to October 2014) and those in which general pharmacists conducted the interventions (control group; 85 patients from November 2012 to October 2013), focusing on the therapeutic ranges of VCM trough concentration and incidence of nephrotoxicity during VCM treatment.

The patient characteristics are summarized in Table 1. No significant differences in gender distribution, age, height, weight, Alb, total protein, Scr, duration of VCM treatment, and rate of FN were found between the control and trained groups. There were no statistically significant differences in VCM trough concentration before dose adjustment by pharmacist between the two groups.

2.2. Comparison of VCM concentration after pharmacist dosing adjustment

The rates of physician acceptance of pharmacist recommendations on VCM dosage were 96.5 and 94.0% in the control and trained groups, respectively (p = 0.476). VCM trough concentrations after dose adjustment are summarized in Table 2. VCM trough concentration after pharmacist intervention was significantly higher in the trained group than in the control group (15.7 *vs.* 12.8 µg/mL, p < 0.001). In addition, the rate of achieving therapeutic VCM trough concentration (10–20 µg/mL) was higher in the trained group than in the control group (80.6 *vs.* 54.1%, p < 0.001). In contrast, no significant differences were observed in the rate of excessive trough concentration (> 20 µg/mL) between the control and trained groups (10.6 and 13.4%, respectively; p = 0.590).

2.3. Comparison of incidence of nephrotoxicity

No significant differences in incidence of nephrotoxicity was observed between the control and trained groups (20.0 and 17.9 %, respectively; p = 0.744).

3. Discussion

In this study, we aimed to compare the contribution of trained pharmacists and general pharmacists to VCM dose adjustment. We found that the rate of achieving therapeutic VCM trough concen-

Table 1: Clinical and demographic characteristics of patients

	Control group (n=85)			Trained group (n=67)			p-value
Male / female		46/39			42/25		p = 0.240[a)]
Age (year)	53.9	±	17.8	54.8	±	17.2	p = 0.745[b)]
Height (cm)	162.1	±	10.5	164.0	±	8.9	p = 0.253[b)]
Weight (kg)	56.4	±	11.7	56.3	±	11.7	p = 0.657[b)]
Serum albumin (g/dL)	2.8	±	0.6	2.8	±	0.7	p = 0.543[b)]
Total protein(g/dL)	5.6	±	0.8	5.6	±	1.0	p = 0.947[b)]
Serum creatinine (mg/dL)	0.66	±	0.25	0.64	±	0.27	p = 0.661[b)]
Treatment duration (days)	13.9	±	8.2	14.1	±	10.2	p = 0.559[b)]
Febrile neutropenia (%)		51.8			41.8		p = 0.221[a)]
VCM trough concentration on day3, before pharmacist intervention (μg/m L)	10.1	±	5.3	10.2	±	4.7	p = 0.358[b)]
< 10 μg/mL		47 (55.3%)			29 (43.3%)		p = 0.142[a)]
10-20 Mg/mL		35 (41.2%)			37 (55.2%)		p = 0.085[a)]
20 μg/mL <		3 (3.5%)			1 (1.5%)		p = 0.436[a)]

[a)] Chi-square test, [b)] Student's *t* test mean±S.D.

Vancomycin trough concentration of 10-20 μg/mL were defined therapeutic range.

Table 2: Vancomycin trough concentration after pharmacist intervention

	Control group (n=85)			Trained group (n=67)			p-value
Trough concentration (μg/mL)	12.8	±	4.8	15.7	±	4.6	p < 0.001[a)]
< 10 μg/mL		30 (35.3%)			4 (6.0%)		p < 0.001[b)]
10-20 μg/mL		46 (54.1%)			54 (80.6%)		p < 0.001[b)]
20 μg/mL <		9 (10.6%)			9 (13.4%)		p = 0.590[b)]

[a)] Student's *t* test, [b)] Chi-square test mean±S.D.

tration (10–20 μg/mL) was higher in the trained group than in the control group. However, no significant difference in incidence of nephrotoxicity was observed between the two groups. According to Japanese guidelines for TDM of VCM, it has been recommended that the trough concentration of VCM should be maintained at ≥10 μg/mL to improve clinical outcome of methicillin-resistant *Staphylococcus aureus* (MRSA) infections (Matsumoto et al. 2013). In previous reports, VCM dose adjustment by pharmacists was demonstrated to achieve the therapeutic concentration for optimized MRSA treatment (Imaura et al. 2011; Marquis et al. 2015). In addition, it has been recommended that the VCM trough concentration should not exceed 20 μg/mL, owing to high risk of nephrotoxicity although nephrotoxicity has been reported in 13–22% of patients with "appropriate" VCM trough concentration (10–20 μg/mL) (Kullar et al. 2011; Lodise et al. 2009; Wunderink et al. 2012). Therefore, active intervention by pharmacists would be beneficial to physicians for the effective treatment of bacterial infections with VCM.

In this study, we observed that dose adjustment by general pharmacists led to lower, insufficient trough concentration of VCM compared to that by trained pharmacists, although the TDM method was the same. This could possibly be because the general pharmacists were more prone to apprehension of nephrotoxicity induced by high VCM concentration than trained pharmacists. However, no significant difference in the incidence of nephrotoxicity during VCM treatment was observed between the control and trained groups.

There are several limitations to our study. First, this is a retrospective study conducted in a single institution. Second, the study patients were unique, with all patients having malignant diseases because our hospital is a cancer center. Finally, since the observation periods of the two groups were different, our data might be affected by factors other than pharmacist intervention, such as deference of attending physicians or concomitant drugs. Therefore, further prospective studies are necessary to confirm our findings.

In conclusion, our results suggest that pharmacists trained for infectious disease could contribute more successfully in achieving therapeutic VCM concentration ranges compared to general pharmacists, without an increased risk of treatment-related nephrotoxicity.

4. Experimental

4.1. Patients

We conducted a retrospective study of patients who received intravenous infusions of VCM at the National Cancer Center Hospital (NCCH), Tokyo, Japan between November 2012 and October 2014. Patients without measurements of baseline VCM concentration on day 3 or after dose adjustment, receiving continuous hemodiafiltration, and treated without pharmacist dose adjustment were excluded (Fig.).

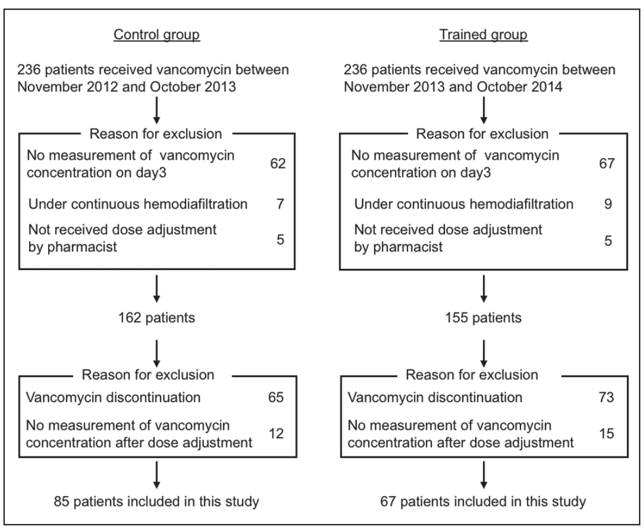

Fig: Study design

4.2. Pharmacist intervention

After initiation of VCM treatment by physicians, pharmacists collected information on diagnosis, treatment, and patient characteristics (age, gender, height, weight, and laboratory test results). Pharmacists derived the optimal VCM dosage and administration interval for each patient using a modified Sawchuk-Zaske method (Sawchuk and Zaske 1976; Takahashi et al. 1983, 1985) and communicated their findings to the physicians. The target range of VCM trough concentration was defined as 10–20 μg/mL in accordance with the guidelines approved by the JCS and the Japanese Society of Therapeutic Drug Monitoring (Matsumoto et al. 2013). From November 2013, three trained pharmacists with BCPIC, IDCP, and both BCICPS and IDCP certification commenced these interventions. Until then, three pharmacists without special training for infectious diseases performed these interventions.

4.3. VCM administration and determination

VCM was infused intravenously over 1–2 h. Serum samples to measure the trough concentration were collected immediately before the administration of the next scheduled dose. As the peak concentration should be assessed after the completion of tissue distribution, the samples were obtained 1–2 h after the end of infusion. The initial trough and peak concentrations at steady state were determined on day 3 of VCM administration, and these concentrations guided the pharmacist intervention. VCM serum concentration was measured by a chemiluminescent immune assay using an ARCHITECT i1000SR (Abbott Japan, Tokyo, Japan).

4.4. Data assessment

We compared the achievement of therapeutic ranges of VCM trough concentration between the control and trained groups. We also investigated the incidence of nephrotoxicity during VCM treatment in both groups. Nephrotoxicity is defined as an increase in serum creatinine levels of 0.5 mg/dL or 50 %, whichever is greater (Lodise et al. 2008).

To obtain background information of the study patients, we reviewed medical records and checked the following characteristics: age, gender, height, weight, serum albumin (Alb), total protein, serum creatinine (Scr) determined at the initiation of VCM therapy, duration of VCM treatment, and FN. FN is defined as an axillary temperature ≥ 37.5 °C that sustains for 1 h and an absolute neutrophil count of <500 cells/mm^3 or <1000 cells/mm^3 with an anticipated decline to 500 cells/mm^3 in the next 48 h (Masaoka 2004).

4.5. Statistical analysis

Data are expressed as means±standard deviation (S.D.). Differences between two groups were analyzed by Student's *t*-test. To compare the two groups, we used Chi-square test for categorical data. A p-value < 0.05 was considered significant. Statistical analyses were performed using JMP11.0 (SAS Institute, Cary, NC).

4.6. Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Cancer Center Hospital and conducted in compliance with the Ethical Guidelines for Epidemiological Research (2014-251). The waiver of informed consent from individual patients was approved by the ethics committee. Anonymized data with serial study ID numbers created by the study hospital were used throughout the study.

Conflicts of interest: None declared

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