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A retrospective analysis to estimate target trough concentration of vancomycin for febrile neutropenia in patients with hematological malignancy

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ABSTRACT

Background: The target trough concentration of vancomycin in patients with febrile neutropenia has not been reported. The aim of this study was to estimate the target trough concentration for febrile neutropenia in patients with hematological malignancy.
Methods: In this retrospective, single-center, observational cohort study, 63 hospitalized patients with hematological malignancy who were treated with vancomycin for febrile neutropenia due to bacteriologically documented or presumptive Gram-positive infections were analyzed.
Results: A significant difference in the first trough concentration of vancomycin was observed between the response and non-response groups, and between the nephrotoxicity and non-nephrotoxicity groups. Multiple logistic regression analyses identified the first trough concentration as the only independent variable associated with clinical efficacy and nephrotoxicity of vancomycin. The areas under the ROC curves were 0.72 and 0.83 for clinical efficacy and nephrotoxicity, respectively. The cut-off values of the first trough concentration were 11.1 μg/ml for clinical efficacy (sensitivity 60%, specificity 87%) and 11.9 μg/ml for nephrotoxicity (sensitivity 77%, specificity 82%).
Conclusions: These results suggest a relationship of trough vancomycin concentration with clinical efficacy and incidence of nephrotoxicity. We propose a target trough vancomycin concentration of around 11.5 μg/ml for febrile neutropenia in patients with hematological malignancy.

1. Introduction

Immediate initiation of empirical antibiotic therapy is the standard of care for patients with febrile neutropenia [1], but no single regimen is ideal. Vancomycin is an option for selected patients such as those with hemodynamic instability, pneumonia, clinically evident catheter-related infection, skin and soft tissue infections, severe mucositis while on empirical ceftazidime treatment after fluoroquinolone prophylaxis, and known colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. In general, therapeutic drug monitoring (TDM) of vancomycin is important to improve clinical outcome and to avoid adverse effects such as nephrotoxicity and development of resistance [2,3]. Recent vancomycin therapeutic monitoring guidelines recommend more aggressive vancomycin dosing regimens and maintaining vancomycin trough concentrations between 15 and 20 μg/ml [2,3], in order to maintain an area under the serum concentration–time curve (AUC)/MIC ratio [4–6] at or above 400 [7,8]. On the other hand, a recent prospective multicenter trial suggests that vancomycin trough concentration higher than 15 μg/ml at steady state is a risk factor for nephrotoxicity [9]. Thus, it is necessary to maintain vancomycin trough concentrations between 15 and 20 μg/ml with careful attention to nephrotoxicity. In febrile neutropenia, however, the target trough concentration of vancomycin has not been reported. Thus, the optimal vancomycin dosage in febrile neutropenic patients remains unclear. In this study, we analyzed the correlation of the first trough concentration with clinical efficacy and safety, and estimate the target trough concentration of vancomycin for febrile neutropenia in patients with hematological malignancy.

2. Patients and methods

2.1. Patients

Medical records were reviewed to identify hospitalized patients with hematological malignancy treated with vancomycin for febrile neutropenia due to bacteriologically documented or presumptive

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Gram-positive infections at Oita University Hospital between June 2005 and April 2014. Patients who had received prophylactic antifungal agents such as triazole (fluconazole or itraconazole) and candin (micafungin), and remained febrile after at least 3 days of treatment with anti-Gram-negative antibiotics such as broad spectrum penicillin (tazobactam/piperacillin), fourth generation cephem (cefepime), carbapenem (meropenem or doripenem) and fluoroquinolone (ciprofloxacin or levofloxacin) before initiation of vancomycin therapy were included in the study. Patients who were younger than 12 years of age, patients who were hemodialyzed, patients who co-administered other anti-MRSA agents, and patients with Gram-negative bacteremia were excluded.

Febrile neutropenia was defined as an axillary temperature of ≥37.5 °C sustained for 1 h, with 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 [10]. Axillary body temperatures were measured >4 times a day. Serum trough concentration of vancomycin was obtained from routine TDM data. The following clinical data recorded during vancomycin therapy were collected: gender; age; body weight; and laboratory data including absolute neutrophil count, hemoglobin, platelet count, serum creatinine and blood urea nitrogen. Creatinine clearance was calculated according to the Cockcroft–Gault equation [11]. This study was approved by the Ethics Committee of Oita University Hospital. Since blood samples were collected as part of the routine patient care for TDM and laboratory testing, written informed consent was not necessary.

2.2. Drug concentration monitoring

Vancomycin was infused intravenously over 1 to 2 h. Blood sampling for the measurement of the first trough concentration at steady state was performed between 2 and 6 days after the initiation of vancomycin therapy [2]. Venous blood samples were collected within an hour before the next administration of vancomycin. A vancomycin assay was performed as a routine laboratory test at Oita University Hospital. Serum vancomycin concentrations were determined by a particle enhanced turbidimetric inhibition immunoassay based on Dimension® Xpand (Siemens Inc.). With this method, the limit of detection was 0.8 μg/ml and the coefficient of variation was <5% for routine clinical TDM. Furthermore, the measurement error was less than 10% in serum containing creatinine 30 mg/dl and urea 500 mg/dl.

2.3. Evaluation of clinical efficacy

Treatment outcome was classified as cure (defervescence within 72 h after initiation of vancomycin therapy, sustained for at least 48 h, and improvement of signs and symptoms of infection), improvement (defervescence within 72 h after initiation of vancomycin therapy and improvement of signs and symptoms of infection), minor response (defervescence within 144 h after initiation of vancomycin therapy and improvement tendency of signs and symptoms of infection) or failure (no defervescence within 144 h after initiation of vancomycin therapy and persistence or progression of clinical signs and symptoms of infection, or administration of any additional antibacterial agent for persistent fever, lack of improvement, progressive infection, or new bacterial infection). Defervescence was defined as a maximum axillary temperature of ≤37.0 °C. Response to vancomycin treatment was defined as the achievement of cure or improvement, and non-response was defined as minor response or failure.

2.4. Evaluation of nephrotoxicity

Occurrence of nephrotoxicity was defined as an increase in serum creatinine level of 0.5 mg/dl or an increase of 50%, whichever was greater, between 2 and 10 days after initiation of vancomycin therapy [12].

2.5. Analysis of factors associated with clinical efficacy and nephrotoxicity

For the analysis of factors related to clinical efficacy and nephrotoxicity, univariate and multiple logistic regression analyses were performed using patient background, laboratory data and co-administered drugs as independent variables. Co-administered drugs were analyzed when they were used in more than 10 patients.

2.6. Determination of target range of serum trough vancomycin concentrations

To evaluate the diagnostic accuracy of the first trough concentration of vancomycin, receiver operating characteristic (ROC) curve and area under the ROC curve (AUC_{ROC}) were analyzed. The first trough concentration of vancomycin showing the highest accuracy and specificity for efficacy or safety was defined as the cut-off value.

2.7. Statistics

Data are expressed as mean ± standard deviation (SD). Differences between two groups were analyzed by paired *t* test, 2-sided Student's *t* test or Welch's *t* test. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the R software version 2.15.2 (http://www.r-project.org) and Predictive Analysis Software (PASW) Statistics ver 21 (SPSS Inc.).

3. Results

A review of patient records identified 76 patients who satisfied the selection criteria, and 13 patients who met exclusion criteria were excluded. Table 1 shows the characteristics of 63 patients on the first day of vancomycin administration. Acute leukemia accounted for a substantial fraction of the underlying disease (acute myeloid leukemia, 44.4%; acute lymphoblastic leukemia, 12.7%). Most (84.1%) patients had absolute neutrophil counts of <100 cells/mm^3 at the first day of vancomycin administration. Fever of unknown origin and oral mucositis related infection were the most common etiologies (46.0% and 30.2%, respectively). A wide variety of anti-Gram-negative antibiotics and antifungal agents were administered. The first trough concentration of vancomycin was 10.7 ± 6.8 μg/ml, showing large variability.

Of the 63 patients, 25 were assessed as showing clinical response (response group) and 38 as showing no response (non-response group). As shown in Fig. 1a, a significant difference in the first trough concentration of vancomycin was observed between the response and non-response groups ($p = 0.016$). Univariate and multiple logistic regression analyses by stepwise selection identified the first trough concentration as the only independent variable associated with efficacy. The odds ratio (95% confidence interval) was 1.10 (1.01–1.20) ($p = 0.026$). Fig. 2a shows the optimal ROC curve for predicting response to vancomycin using the first trough vancomycin concentration. The AUC_{ROC} was 0.72 and the cut-off value of the first trough concentration for clinical efficacy was 11.1 μg/ml (sensitivity 60%, specificity 87%).

Nephrotoxicity was observed in 13 patients. The durations of vancomycin treatment were 9.5 ± 4.8 and 8.7 ± 3.5 days in patients with and without nephrotoxicity, respectively, and did not differ significantly between 2 groups (p = NS). Nephrotoxicity occurred 5.8 ± 2.7 days after initiation of vancomycin, and was significantly later than the time of blood sampling for TDM (2.7 ± 0.9 days) ($p = 0.0061$). As shown in Fig. 1b, a significant difference in the first trough concentration of vancomycin was observed between the nephrotoxicity and non-nephrotoxicity groups ($p = 0.0047$). In univariate logistic regression analysis for clinical factors associated with nephrotoxicity, the p values for the first trough concentration ($p < 0.0001$), blood urea nitrogen ($p = 0.0011$) and use of opioids ($p = 0.078$) were less than 0.10. Multiple logistic regression analysis by stepwise selection using the first trough concentration, blood urea nitrogen and use of opioids