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Vancomycin Pharmacokinetic Parameters in Patients Undergoing Hematopoietic Stem Cell Transplantation (HSCT)

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ABSTRACT

Background: Vancomycin is used abundantly in patients undergoing HSCT, especially during neutropenic fever. Despite its widespread use little is known about vancomycin pharmacokinetics in HSCT patients. We conducted this study to investigate vancomycin pharmacokinetic parameters in our HSCT patients and to evaluate current dosing regimen based on trough vancomycin concentrations measurement.

Methods: Vancomycin serum concentration at steady-state was determined prospectively in 46 adult HSCT patients who received vancomycin as empirical treatment of neutropenic fever. Individual steady-steady pharmacokinetic parameters were also determined in 20 patients who had two vancomycin levels from an administered dose, assuming one-compartment model. Acute kidney injury was also evaluated in our patients during vancomycin therapy.

Results: Mean (±SD) apparent volume of distribution (L/kg) and clearance (mL/min) were 0.6 (± 0.33) and 109.7 (± 57.5) respectively. With mean (±SD) total daily dose of vancomycin 31.9 (±10.5) mg/kg/day that was administered, more than 90 % of measured vancomycin trough concentrations were outside the range of 15-20 mg/L and 54.3% of patients had trough concentrations below 10 mg/L. Of 46 patients, 21 patients (45.7%) developed acute kidney injury (AKI) during vancomycin therapy; among them 19 patients were receiving nephrotoxic drug(s) concomitantly.

Conclusion: Current vancomycin dosage regimen could not lead to recommended therapeutic serum concentrations in our patients. Large variation in vancomycin pharmacokinetic parameters observed among patients of this study along with difference of vancomycin pharmacokinetics in our study and other similar studies further explain the need for therapeutic drug monitoring and individualization of vancomycin dosing.

KEY WORDS: Neutropenic fever, Vancomycin, Hematopoietic stem cell transplantation, Pharmacokinetic parameters

INTRODUCTION

Infections are currently one of the major causes of morbidity and mortality in patients undergoing hematopoietic stem cell transplantation (HSCT). One of the most prevalent bacterial infections in these patients is due to gram-positive organisms

which have been rising during last decade.[1-3] Hence many of these patients require empirical antibiotic with aerobic gram positive coverage when developing neutropenic fever.[4]

Recent update of clinical practice guideline by the Infectious Diseases Society of America (IDSA) for the use of antimicrobial agents in neutropenic patients with cancer, does not recommend vancomycin (or other agents active against aerobic gram positive cocci) as a standard part of the initial antibiotic regimen for fever and neutropenia. These agents have been suggested as an integral part of the empirical management of febrile neutropenia for specific clinical indications, including suspected catheter-related infection, skin or soft-tissue infection, pneumonia, or hemodynamic instability.[5] Adequate empirical antibacterial therapy in febrile neutropenia after HSCT may reduce infection-related morbidity and mortality.[6]

When deciding to use an antibiotic active against aerobic gram positive cocci as an empirical treatment in febrile neutropenic patients who have underwent HSCT, vancomycin is often used concerning its availability and cost. Serum vancomycin concentrations should be monitored to minimize the risk of development of microorganism resistance and to avoid potential concentration-dependent adverse events. Therapeutic drug monitoring (TDM) of vancomycin is crucial in optimizing therapy.[7] It is especially important in HSCT patients who often receive vancomycin for longer duration and are under therapy with other nephrotoxic drugs. Optimal vancomycin dosing regimen for empirical treatment of febrile neutropenia in these patients has not been defined and therefore managing the clinical use of vancomycin in this population with complicated medical problems, is very challenging.

Pharmacokinetic studies in patients with cancer have shown an increase in volume of distribution (Vd) and clearance (CL) of vancomycin.[8-12] Moreover such pharmacokinetic changes during neutropenia and fever necessitate higher vancomycin doses and routine dosing regimen would be sub optimal in many of these patients.[13]

On the other hand, recent recommendations by a consensus statement from three groups, the American Society of Health-System Pharmacists, IDSA, and the Society of Infectious Diseases Pharmacists consisted increasing vancomycin doses to form elevated target trough levels (15 – 20 mg/l) especially in severe infections like pneumonia and bacteremia which are common during febrile neutropenia in high risk HSCT patients.[7] Determining initial vancomycin dosing regimen in this population of patients is one of the mentioned challenges. Furthermore a single vancomycin dosing regimens cannot be applied to all patient populations and it becomes more important to initiate regimens with a good understanding of population-specific pharmacokinetic parameters.

To the best of our knowledge, despite widespread use of vancomycin in HSCT, there is just one study regarding adult patients who underwent autologous HSCT.[11] Even though, there are some studies evaluating the pharmacokinetic of vancomycin in cancer and hematological malignancies.[8, 10, 11, 14, 15]

The purpose of this study was to investigate vancomycin pharmacokinetic parameters in HSCT patients and to evaluate current dosing regimen based on trough vancomycin concentration measurement.

MATERIALS AND METHODS

This prospective study included patients who were treated with vancomycin for neutropenic fever after HSCT, in the adult (>15 yrs) HSCT unit at Hematology-Oncology and Stem Cell Transplant Research Center/ Tehran University of Medical Sciences (Shariati hospital), between December 2012 and April 2013. The protocol was reviewed and approved by the Institutional Review Board and Ethics Committee. An informed written consent was obtained from each patient prior to the study.

The inclusion criterion was receiving at least 3 successive doses of vancomycin (fixed dose and dosing interval) as empiric treatment of febrile neutropenia. Patients, for whom vancomycin was discontinued prior to achieving a steady state, were excluded.

Vancomycin was administered by intermittent intravenous infusion. Blood samples (5 mL) were collected from central vein and sent to the laboratory within two hours of collection. First steady-state trough vancomycin serum concentrations were measured in blood samples

which were drawn within 30 minutes prior to the administration of the fourth dose (Css trough or pre-dose sample). Samples collected 60-180 minutes after end of vancomycin infusion were used for determination of Css peak (post dose sample). Random steady state vancomycin serum concentrations were measured in some patients, instead of determining peak levels.

Serum concentrations of vancomycin were analyzed by Fluorescence Polarization Immunoassay (FPIA) (Cobas Integra 400 system from Roche Diagnostics, Switzerland). The lower detection limit of this assay was 0.74 µg/mL, and the coefficients of variation (CV%) were 3.0% at 8.70 µg/mL, 2.2 at 26.3 µg/mL, and 3.3% at 54.6 µg/mL.

For each patient, the data including concomitant medications, patient weight, height, sex, age, daily laboratory data (such as serum creatinine, BUN and albumin), vancomycin dosage and serum sampling histories, including the date, time, dosage, and duration of infusion were registered. Creatinine clearance was calculated using the Cockcroft and Gault equation using the ideal body weight.[16] Only the first course of therapy was analyzed in patients who received more than one course of therapy with vancomycin.

The AKIN definition was used to identify acute kidney injury (AKI) during vancomycin therapy.[17] Severity of kidney injury in patients who developed AKI was staged according to the AKIN criteria.[17]

Individual vancomycin pharmacokinetic parameters including elimination rate constant (k, in hour-1), elimination half-life (t1/2, in hour), apparent volume of distribution at steady state (Vd, L/kg) and clearance (CL, L/h/kg) were determined assuming a one-compartment model using the following equations:[18, 19]

$$k_e = (\ln Css_{max} - \ln Css_{min}) / \tau - t'$$

$$Cl = k_e V$$

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e [Css_{max} - (Css_{min} e^{-k_e t'})]}$$

Ke is the elimination rate constant (in hour-1), Css max and Css min are peak and trough concentrations (in mg/L) at steady-state as described above, Vd is apparent volume of distribution at steady state in L, D is the administered vancomycin dose (mg), t′ and τ are the infusion time and dosage interval (hr).

In cases that trough and a random concentration were measured following equation was used to calculate Css max and then above equation were used to calculate parameters.[18, 19]

$$Css_{max} = C_1 / (e^{-k_e t})$$

C1 is the random steady-state concentration, ke is the elimination rate constant, and t is the time between C1 and Css max.

Correlations between patients' demographic and clinical characteristics and vancomycin pharmacokinetic parameters were investigated using bivariate correlations procedure including Pearson's correlation coefficient or Spearman's rho based on data distribution. Calculated parameters between males and females were compared by Mann-Whitney U test or independent-sample T test. Median and inter-quartile of pharmacokinetic parameters range are also reported. To compare the values of this study with other reports, mean and 95% confidence interval of the mean pharmacokinetic parameters were determined. All the analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$ to reject the null hypothesis.

RESULTS

Total of 46 patients (mean age of 32.9 ± 12.45), 30 men and 16 women, were included in the study. Patients' demographic data and clinical characteristics are shown in Table1 and 2.

Of the 46 patients, 13 (28.2%) were more than 30% above their ideal body weight. Among 20 patients in whom pharamacokinetic parameters calculated, 7 (35%) patients were more than 30% above their ideal body weight (IBW). The most popular dosing regimens were 1000 mg q12hr in 32 patients (69.6%) and 1000 mg q8hr in 8 patients (17.4%). Mean (±SD) vancomycin total daily dose was 31.9 (±10.5) mg/kg.

A total of 76 vancomycin serum concentration (46 trough, 18 peak and 2 random levels) were measured of which, 18, 2 and 26 patients had both peak and trough samples, both random and trough samples and only trough samples respectively.

Table1. Patients' Demographic Data

Characteristics	N
Gender (M/F)	30/16
Underlying disease	
AML	20
ALL	9
Aplastic anemia	2
Fanconi's anemia	1
GCT	1
HD	4
MDS	2
MM	4
NHL	1
PNH	1
Thalassemia major, class3	1
Transplantation Type	
Allo PBSCT	31
AutoPBSCT	15

Median (Inter-quartile Range) steady-state peak and trough concentrations in mg/L were 29.8 (23.9) and 9.3 (6.4) respectively. 21 patients (45.7%) had trough concentrations above 10 mg/L. Of these, 9 patients (19.6% of all patients) had trough concentrations above 15 mg/L, 5 of whom (10.9% of all patients) had trough concentrations above 20 mg/L. 25 (54.3%) patients had trough concentrations of <10 mg/L and 6 patients (13%) had trough levels of <5mg/L. More than 90 % of measured vancomycin trough concentrations were outside the range of 15-20 mg/L. About 38.9% of measured peak levels were either greater than 40 mg/L or lower than 20 mg/L.

For 20 patients who had peak (or random) and trough measurements, pharmacokinetic parameters were calculated and are presented in Table 3.

Table2. Patients' Clinical Characteristics

Characteristics	Mean ± S.D.	Median (Minimum - Maximum)
Actual body weight (ABW) (kg)	74.8 ± 16.6	76 (32 – 109)
Ideal body weight (IBW) (kg)	63.5 ± 12.19	67.25 (45.5 – 88.6)
%IBW[a]	19.27 ± 24.4	18.68 (-31.7 – 108)
Serum creatinine (mg/dL)[b]	0.9 ± 0.18	0.9 (0.6 – 1.4)
Serum creatinine (mg/dL)[c]	0.87 ± 0.18	0.8 (0.5 – 1.6)
Serum creatinine (mg/dL)[d]	0.93 ± 0.3	0.8 (0.6 – 1.9)
Estimated CLcr (IBW)(mL/min)[c]	95.66 ± 28.16	91.7 (44.8 – 159)
Estimated CLcr (IBW)(mL/min)[d]	102. 5 ± 35.33	99.00 (38.43 - 196)
Vancomycin dose (mg)	1009.7 ± 131	1000 (500 – 1500)
Administration interval (hr)	10.96± 1.77	12 (8 – 12)
Vancomycin total daily dose (mg/kg)	31.9 ± 10.5	28.7 (18.3 – 60.4)

Table3. Summary of Pharmacokinetic Parameters Calculated for 20 Patients of the Study

	Vd (L/kg)	CL (L/kg/hr)	Ke (hr^{-1})	t1/2 (hr)
Mean	0.60	0.090	0.16	4.9
Standard error of mean	0.07	0.009	0.01	0.5
95% confidence interval for mean	0.44 – 0.76	0.071 – 0.109	0.13 – 0.19	3.8 – 6.0
Median	0.46	0.089	0.17	3.9
Interquartile range	0.40	0.062	0.08	2.9
Percentile 90	1.23	0.159	0.23	9.5
Percentile 5	0.23	0.026	0.06	2.2

Vancomycin pharmacokinetic parameters did not differ significantly between males and females. Values of pharmacokinetic parameters with assumption of one-compartment pharmacokinetic model for vancomycin in this study and different studies on similar populations[11, 14, 20] are shown in Table 4. 95% confidence interval for mean of vancomycin CL and Vd were calculated and compared between our results and other studies on similar population to evaluate differences. Mean vancomycin Vd in our patients is smaller than those observed in two studies on patients with cancer and hematological malignancies[3, 24] but mean vancomycin CL does not differ significantly (Table 4).

Correlation of different demographic and clinical factors with vancomycin pharamacokinetic parameters in enrolled patients was investigated. Creatinine clearance of patients on day of vancomycin sampling was correlated with

vancomycin clearance (P<0.01). None of other correlations were statistically significant.

38 of 46 patients (82.6%) were on nephrotoxic drugs concurrent with vancomycin. Among them, 16 patients (42.1%, 34.8% of all included patients) and 22 patients (57.9%, 47.8% of all included patients) received one and two nephrotoxic drug(s) concomitant with vancomycin respectively.

Of 46 patients, 21 patients (45.7%) developed acute kidney injury (AKI) during vancomycin therapy. Among patients who developed AKI, 4 and 15 patients were receiving one and two nephrotoxic drug(s) concomitant with vancomycin respectively.

17 patients did not develop AKI, even though they were also on nephrotoxic drugs.

Of 21 patients who developed AKI, 19 patients were AKIN stage one and 2 patients were AKIN stage two respectively. Two patients who developed AKIN stage two AKI were on cyclosporine and amphotericin B concurrent with vancomycin therapy. Of 19 patients who developed AKIN stage one AKI, 2 of them did not receive concurrent nephrotoxic drug but remainder were on concurrent nephrotoxic drugs. 13 of these 17 patients were on 2 nephrotoxic drugs, cyclosporine and amphotericin B, concurrent with vancomycin. None of the patients who developed AKI needed hemodialysis.

Table 4 - One-Compartment Pharmacokinetic Parameters (mean ± standard deviation (95%CI of mean)) of Vancomycin from some Studies on Cancer patients versus this Study (boldface)

n	Type of patient	Age (yrs)	TBW (kg)	CLCR (ml/min)	CL (ml/min)	V (L/kg)	Reference
330	Leukemic and others [a]	47 (12 – 87)	71 (37 – 130)[b]	103 (21 – 273)[b]	95.8	0.75 ± 0.27 (0.72 – 0.77)	20
18	Cancer [c]	43.5 ± 22.02	66.8 ± 17.1 (58.9 – 74.6)	105.4 ± 62.3	110.1 ± 42 (90.7 – 129.5)	1.04 ± 0.42 (0.86 – 1.22)	14
215	Hematological malignancies	51.5 ± 15.9	64.7 ± 11.3 (63.1 – 66.2)	89.4 ± 39.2	96.5 ± 27.19 (92.7 – 100.13)	0.98 ± 0.36 (0.93 – 1.02)	11
20		29.9 ± 9.5	72.5 ± 15.2 (65.3 – 79.6)	104.7 ± 37.0	109.7 ± 57.5 (82.7 – 136)	0.60 ± 0.33 (0.44 – 0.76)	

[a] Sixty-five percent of patients were leukemic, and the other patients were from other clinical units.
[b] Ranges of values are shown in parentheses.
[c] Eighty-eight percent of patients had Hematological malignancies.

DISCUSSION

We conducted our study in order to evaluate vancomycin pharmacokinetics in patients undergoing HSCT and to determine if the changes in pharmacokinetic parameters seen in previous studies in cancer and febrile neutropenic patients in different countries are evident in our patients.

Several studies showed that vancomycin CL and Vd tends to be higher in patients with malignancies and during febrile neutropenia.[8, 10, 11, 14] Fernández de Gatta et al., have shown that patients with neutropenia have an increased total clearance of vancomycin compared with both intensive care unit and control patients, and an increased Vd compared with controls.[10] These results were confirmed by Le Normand et al., who further found that the elimination half-life of vancomycin in patients with neutropenia was twice as short as in healthy individuals.[8] Buelga et al., also reported greater Vd (26 to 42%) and CL of vancomycin in patients with hematological malignancies relative to other adult patients population.[11] In a study by Al-Kofide et al., on comparison of vancomycin pharmacokinetics in cancer (88% leukemic) and non-cancer patients, both Vd and CL were significantly higher in the cancer group.[14] Based on these results, malignancy was suggested to be a covariate of the pharmacokinetic variability. Teramachi et al., also reported that CL and Vd were significantly greater in the malignancy group than non-malignancy group in Japanese patients. However, in their report some patients in the malignancy group showed similar values of CL and Vd to those in the non-malignancy group.[15]

Mean vancomycin CL in our patients is similar to results of above studies and nearly 70-80% higher than mean CL observed in adult medical & surgical patients. But vancomycin Vd in our patients is lower

than what were shown in studies on patients with cancer, hematological malignancies or neutropenic fever and is near to what observed in other medical patients. Mean total body weight of our patients was not significantly different with patients included in above studies.

In our study, patients were heterogeneous as they had different types of hematological diseases and malignancies. Since our patients with hematological malignancies were in remission when they were admitted for HSCT, they may affect vancomycin distribution and clearance during febrile neutropenia in a different way from patients who receive induction chemotherapy for their malignancy and develop neutropenic fever. Moreover little is known how underlying non-malignant hematological diseases like thalassemia would affect vancomycin pharmacokinetics.

Some of the studies on patients with hematological malignancies that developed neutropenic fever included few patients who underwent autologous HSCT but they were not evaluated separately.[11] To the best of our knowledge, there is no data about vancomycin pharamcokinetics in patients who underwent autologous and allogeneic HSCT.

In order to investigate factors affecting vancomycin pharmacokinetics in our patients, some demographic and clinical characteristics of patients such as age, total body weight, gender, creatinine clearance, diagnosis and transplantation type were analyzed, and no significant correlation or effect on vancomycin pharmacokinetic parameters was found except for creatinine clearance, which were correlated with vancomycin clearance. This correlation would be expected in vancomycin that its main way of elimination is renal and was shown in other studies on cancer and hematological malignancy patients.[11, 12, 14] Non significance of other expected or presumed correlation may be due to heterogeneity in our patients' underlying disease and small number of patients.

The mechanism behind the different pharmacokinetic parameters seen in cancer patients is little known. Al-Kofide et al., recommended several theories regarding why vancomycin CL is significantly increased in this subgroup of patients: (1) Glomerular filtration is the main mechanism of vancomycin elimination but there may be some tubular secretion which have been proved in previous trials on vancomycin pharmacokinetics, as this pathway may be enhanced in cancer patients leading to higher CL than expected; (2) Vancomycin has some hepatic metabolism mainly through conjugation and this pathway of vancomycin deactivation may be increased in cancer patients leading to lowered vancomycin levels; (3) As a result of high amount of intravenous fluid given to those patients, urine flow may have increased leading to decrease in the re-absorption of vancomycin and enhancing its clearance. High vancomycin clearance that is observed in our patients could be resulted from these proposed mechanisms.[14]

Median (Inter-quartile Range) and mean (±SD) steady-state trough concentration in our patients were 9.59 (6.67) and 11.2 (±7.4) respectively and 25 (54.3%) patients had trough concentrations of <10 mg/L. Based on evidence suggesting that S. aureus exposure to trough serum vancomycin concentrations of <10 mg/L can produce intermediate resistant strains, recent IDSA, ASHP and SIDP consensus guideline on vancomycin TDM, recommends that trough serum vancomycin concentrations always be maintained above 10 mg/L to avoid development of resistance and therapeutic failure. On the other hand, this guideline recommends vancomycin trough concentrations of 15-20 mg/L in patients with serious infection like pneumonia, bacteremia, meningitis and osteomyelitis.[5] It is not clear whether this level would be recommended when vancomycin is used as empiric treatment of neutropenic fever and target vancomycin trough level for this indication is not defined in guidelines on neutropenic fever management in cancer patients.[5, 21] But in many febrile neutropenic patients who fulfill the criteria of starting vancomycin empirically, suspected infection is serious enough to dose vancomycin aiming at steady-state trough concentrations of at least 15 mg/L.

In a vancomycin drug utilization review done by Hayatshahi et al., in our center, it was shown that among patients in whom vancomycin administration was justified, 42.3% received

appropriate dose. But in this study, vancomycin concentrations were not measured and clinical outcomes were not evaluated.[22] In another study of vancomycin utilization evaluation at hematology-oncology ward of a teaching hospital that was conducted by Vazin et al., mean vancomycin trough serum concentration was 15.59 ± 13.02 mg/L.[23] This trough levels seem to be higher than our patients' but comparison of 95% CI of means shows that this difference is not statistically significant. Although patients included in above study received fix doses of 1000 mg q 12 hr, mostly as empirical treatment of neutropenic fever, only 3.6% of patients, far from our results, had trough vancomycin concentration less than10 mg/L. Mean (±SD) total daily dose of vancomycin was 31.9 (±10.5) mg/kg/day in our study and it seems to be higher than 14.7 mg/kg/day that was administered in mentioned study. Furthermore, mean ± SD (95% CI of mean) TBW of patients in above study is 68.05 ± 12.26 kg (68.89-71.20) that seems to be lower than our patients' with 74.83 ± 16.6 kg (69.89-79.77) but this difference is not significant. On the other hand more than half of their patients had supra-therapeutic trough level which is shown in 10.9% of our patients. By the way, broad spectrum of trough levels among included patients despite fixed equal doses in the study done by Vazin et al., which is shown to some extent in our study, confirms inter and intra individual variability of vancomycin pharmacokinetics which necessitates using individual or same population based pharmacokinetic approach in dosing vancomycin.[23]

Based on these findings, we consider that pharmacokinetics of vancomycin may change in HSCT patients from other patients' and our patients need its unique population based pharamcokinetic approach in vancomycin dosing. Furthermore, considering the observed inter individual variability of vancomycin pharmacokinetics, dosage should be adjusted and individualized based on drug concentrations.

The most frequent dosing regimen in our patients was 1000 mg q12hr (69.6%) which is usually determined based on 15-20 mg/kg q 8-12 hr and often lower doses were chosen due to concerns about nephrotoxicity. Patients who undergo HSCT usually receive concurrent nephrotoxic drugs especially after transplantation and during neutropenia. This becomes more important in allogeneic HSCT in which, patients receive a calcineurin inhibitor, most of the time cyclosporine in our center, as prophylaxis and treatment of graft versus host disease (GVHD). Calcineurin inhibitors are nephrotoxic drugs and cyclosporine is more nephrotoxic than tacrolimus.[24] In HSCT patients if serum creatinine rises with any reason and becomes stable, might lead to changes in cyclosporine dosing regimen which can put the patients under the risk of acute GVHD. Another nephrotoxic drug which might be administered in these patients is amphotericin B which induced AKI in a dose dependent manner.[25]

Although vancomycin is not considered a nephrotoxic drug, it can aggravate nephrotoxicity of other drugs. Concomitant nephrotoxic agents can increase the incidence of vancomycin-associated nephrotoxicity by up to 35%.[26] AKI due to vancomycin was infrequent after modifying and purification in its manufacturing.[27] But it is shown in a recent systematic review that higher doses administered in order to achieve new target trough levels (15-20 mg/L) recommended by guideline in recent years, increases the risk of AKI.[28] But it is reported to be dependent on vancomycin therapy duration (mostly occurs after 7 days of therapy) and reversible.[28] AKI occures in 45.7% of our patients which seems to be higher than vancomycin induced AKI rate reported in literature. On the other hand 36% of our patients did not develop AKI while they were receiving nephrotoxic drugs concomitantly. Vazin et al., also reported AKI rate of 35%. Most of patients who develop AKI in our study were receiving concurrent cyclosporine and amphotericin B and this high rate of AKI cannot be related absolutely to vancomycin.[23] Moreover AKI is a common early complication after HSCT. In a study by Saddadi et al., on AKI in HSCT patients in our center it is reported that 37.6% developed AKI and higher frequency of AKI was observed in patients who received cyclosporine A (40%), patients with allogeneic HSCT(42.1%), and those who developed gastrointestinal GVHD (47.3%).[29] Schrier et al., showed the frequency of AKI increased significantly from autologous HSCT (21%) to non-myloablative allogeneic HSCT (40%) to myeloablative allogeneic

HSCT (69%).[30] Correlation between vancomycin dose or concentration and AKI rate and influence of concurrent nephrotoxic drug could not be shown in our study may be due to small number of patients. With regard to indeterminacy about optimal trough vancomycin concentration in HSCT patients with neutropenic fever and existence of many predisposing factor to AKI in these patients, we suggest that clinical and microbiological outcome and safety of dosing regimen versus different target trough vancomycin concentration (10-15mg/L or 15-20 mg/L), be assessed in a randomized clinical trial on these patients. On the other hand, not only therapeutic drug monitoring and dose adjustment is necessary in our patients' population and is recommended by mentioned guidelines, but also initial dosing regimen determination method needs to be changed.

This study had several limitations, as small sample size and including patients with heterogeneous underlying diseases and different HSCT type. Since blood sampling is limited in the clinical setting, therefore only one-compartment model could be used for pharmacokinetic analysis and this could be another limitation of the study.

CONCLUSION

In summary, conventional vancomycin dosage regimens could not lead to recommended therapeutic serum concentrations in our patients although, optimal trough vancomycin concentration in febrile neutropenia in HSCT patients needs to be defined. Large variation in vancomycin pharmacokinetic parameters observed among patients of this study along with the difference of vancomycin pharmacokinetics between our patients and other similar studies further explain the need for level monitoring and individualization of vancomycin dosing. A population pharmacokinetic approach in determining vancomycin dosing for these patients needs to be described.

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