Vancomycin Utilization Review in Patients Undergoing Bone Marrow Transplantation

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ABSTRACT

Background: Infections in neutropenic patients are considered as major causes of mortality and the emergence of drug resistance. Gram positive bacterial infections are crucially important to be covered if indicated. Vancomycin is active against most Gram positive bacteria including Methicillin Resistant Staphylococcus Aureus (MRSA). In this study, we evaluated the appropriate utilization of this agent in bone marrow transplantation (BMT) patients.

Methods: In a cross sectional study, all patients who received vancomycin in a seven months period at bone marrow transplantation research center in Shariati teaching hospital in Tehran, Iran, were entered to the study. Clinical and preclinical parameters such as serum creatinine, microbial culture, antibacterial sensitivity, WBC count and fever were collected and recorded for analysis. We also measured vancomycin trough level after administration of three doses.

Result s: Fifty one patients were entered in the study and reviewed in two adult BMT wards. The age range was 18 to 65 years. Most patients received allogenic versus autologous transplantation (56.9%, 43.1%). About 80% of the vancomycin used for the patients with febrile neutropenia was compatible with National Comprehensive Cancer Network (NCCN) guideline. 21.6% of patients received appropriate doses. Vancomycin trough serum concentration range was 15.0±11.9 μg/mL.

Conclusion: Vancomycin is an antibiotic used to treat resistant gram-positive infections and must be prescribed by a specialist. Vancomycin wrong dosing or initiation prescribing with dose 1 gr/q12h increases the resistance and toxicity to drug, and cause an inappropriate response to the drug.

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Introduction

Antibiotic misuse and over prescription has become a major health problem in societies because of the increasing number of multidrug-resistant specimens and crisis of no new and effective antibiotic availability (1).

Vancomycin is a glycopeptide antibiotic which use in treatment of infections caused by Gram-positive pathogens especially Staphylococcus Aureus and Methicillin-Resistant Staphylococcus Aureus (MRSA) (2, 3). It has been manifested that treatment with vancomycin may increase the risk factor of colonization and infection with Vancomycin Resistant Entrococci (VRE), especially among immunocompromised patients (4, 5). Early use of vancomycin was associated with a number of adverse effects, including infusion related toxicities, nephrotoxicity and possible ototoxicity (6).

Fever can be the sole but not specific symptom of infection in neutropenic patient. More than half of patients with febrile neutropenia have an established infection including bloodstream bacterial infections.

Drug Utilization Evaluation (DUE) studies facilitate

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assessing the appropriateness and rational use of medications. DUE studies are still used to identify variability in drug use as well as to support interventions that will improve patient outcomes (7, 8). Over the years, vancomycin has been one of the most studied antibiotics. Proper use of Therapeutic Drug Monitoring (TDM) procedures along with appropriate prescription of vancomycin can help in preventing and controlling excessive use of vancomycin and the emergence of resistant microorganisms (4).

In this study we run a drug utilization review (DUR) for vancomycin in adult patients who undergone bone marrow transplantation (BMT) to evaluate vancomycin usage in neutropenic patients (9).

Patients and Methods

We conducted a prospective cross sectional study at Hematology-Oncology and Bone Marrow Transplantation Research Center, Shariati teaching hospital, one of major medical centers of Tehran University of Medical Sciences between April 2012 and October 2012. A total of 51 patients admitted to the adult BMT wards were included in study for a period of six months. In order to ease the utilization evaluation process we developed a data collection form including patients' demographic information (age, gender, weight, height, reason and type of transplantation, date of admission and duration of hospital stay), antimicrobial regimen and duration including vancomycin, microbiological reports if any, including blood, urine and sputum cultures, vital signs (temperature, blood pressure), white blood cell counts (WBC), serum creatinine and blood urea nitrogen (BUN).

Initial empiric administration of vancomycin in febrile neutropenia was adapted from the Infection Diseases Society of America 2011 (IDSA) guideline (10). The guidelines indicate that febrile neutropenic patients with followings criteria should receive vancomycin beside other antibiotics: hemodynamic instability or other evidences of severe sepsis, pneumonia documented radiographically, positive blood cultures for Gram positive cocci before its final identification and susceptibility testing is available, clinically suspected serious intravascular catheter-related infection, skin or soft tissue infection at any site, colonization with MRSA or penicillin and cephalosporin-resistant pneumococci, severe mucositis, if fluoroquinolone prophylaxis has been given (10).

Patients who have normal renal function, between 18 to 65 years with no vancomycin allergic reactions were included in our study. The serum level concentrations of vancomycin were determined by FPIA (Fluorescence polarization immunoassay) method with the TDXflx apparatus (abbots, USA). Blood samples were taken from the patients who received vancomycin for 3 consecutive days, and just before the administration of the next dose.

The samples were centrifuged for 5 min; the serum were separated and stored at -70°C. It is worth noting that the blood samples were taken as a part of the specified protocol of this study, since serum drug monitoring was not a routine action of this hospital.

Demographic and clinical data were gathered and analyzed using basic descriptive techniques with the statistical program, SPSS-PC (version 21.0). The qualitative variables are presented by their frequency of distribution. The quantitative variables are summarized as mean with standard deviation.

Results

A total of 51 patients entered to the study during their hospital stay post transplantation. Thirty (58.8 %) of patients were male and twenty one (41.2%) were female and the mean age of patients was 33.7 years old. Leukemia including Acute Myelogenous Leukemia (AML) (33.3%) and Acute Lymphoblastic Leukemia (ALL) (13.7%) were the most common reasons of admission (Table 1).

We used the National Comprehensive Cancer Network (NCCN) criteria to justify the utilization of vancomycin (10). Table 2 shows NCCN criteria for justified vancomycin utilization.

The most common indication for vancomycin prescription was fever due to Neutropenia and persistence fever 3 days after imipenem indication (43.1%). 42 (82.3%) patients received vancomycin 1 g every 12 hours and three of them (5.9%) received 1250 mg every 8 hours there was no vancomycin serum level for 35.3% patients. The mean of treatment duration was 9 days (range: 4-17 days). 80.4% of our patients initiated imipenem prior to vancomycin. The most common microorganism in patients' cultures was staphylococcus epidermidis which were 100%vancomycin sensitive. In 31.4% of patients, there was a rise in serum creatinine greater than 0.5 mg/dL.

Vancomycin trough serum concentration range was 15.0±11.9 µg/mL. According to the Alison G. Freifeld (2011) and M Rybak (2009) minimum trough serum concentration should be above 10mg/L (6, 10).

Almost all patients received vancomycin intravenously (98.5 %) in dextrose 5% bag.

According to our evaluation criteria vancomycin indication was justified for 41 (80.4%) patients and not justified for ten (19.6%) patients. Regarding drug dosing, 11 (21.6%) patients received appropriate dose of vancomycin based on serum creatinine level and vancomycin level. Totally 30 patients (59%) received inappropriate dose of vancomycin. Figure 1 shows the evaluation of vancomycin utilization ant it's dosage in this study.

Discussion

Fever is defined as a single temperature of 38.3 °c or

Table1. Demographic and clinical characteristics of patients.

Variables	Results
Age-yr	
Mean ± Std	33.7±13.0
Min-Max	17.0-62.0
Weight-kg	
Mean ± Std	74.2±16.3
Min-Max	32.0-114.0
Gender-n (%)	
Male	30(58.8%)
Allergy-n (%)	
No allergy	51(100%)
Section-n (%)	
BMT1	26(51.0%)
BMT2	25(49.0%)
Transplant type – n(%)	
Autogenic PBCT	22(43.1%)
Allogenic PBCT	29(56.9%)
Hospital stay-day	
Mean ± Std	26.6±9.9
Min-Max	5.0-65.0
Reason of transplantation-n (%)	
AA	4(7.8%)
ALL	8(15.7%)
AML	17(33.3%)

BMT: Bone Marrow Transplantation, PBCT: Peripheral Blood progenitor Cell Transplantation, AA: Aplastic Anemia, ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia

Table 2. NCCN criteria for justified vancomycin utilization.

Criteria	Frequency (%)
Hypo	15 (10.3)
Cath+Hypo	14 (18.9)
Cath	9 (12.2)
None	9 (12.2)
Cath+Gram	5 (6.8)
Gram	4 (5.4)
Cath+Gram+Hypo	4 (5.4)
Hypo+FP	3 (4.1)
Gram+Hypo	3 (4.1)
FP	2 (1.7)
Hypo+Soft	1 (1.4)
Hypo+MRSA	1 (1.4)
Gram+MRSA+Hypo	1 (1.4)
Cath+Hypo+FP	1 (1.4)
Cath+MRSA+Hypo	1 (1.4)
Cath+Gram+Hypo+FP	1 (1.4)

Note: FP: Prophylaxis with fluoroquinilones, Hypo: Hypotension or septic shock Without identified pathogen, Spft: Soft tissue infection, MRSA: Known colonization with MRSA or other penicillin/ cephalosporin resistant Gram positive bacteria, Gram: Gram positive blood gram stains (waiting for bacterial identification). Cath: cath-related infections, cellulitis, Gram positive bacteremia. NCCN: National Comprehensive Cancer Network

higher or a temperature of 38 °c over an hour. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 or an ANC of less than 1000 and prediction of reduction to less than 500 in the next 48 hours. Over 50% of neutropenic patients with fever have an acute infection and over 20% of patients with neutrophil counts of less than 100 cell/mm3 have bacteremia (6, 10).

According to the IDSA and NCCN guidelines for empiric antibacterial treatment options in febrile neutropenic patients, the following conditions are considered as inclusion criteria for utilizing vancomycin either as monotherapy or in combination with other antibacterial agents (10):
1. Clinically apparent or suspected serious catheter related infections.
2. Positive result of blood cultures with susceptibility tests, showing resistant gram positive species (MRSA, penicillin resistant streptococci, ampicillin resistant enterococci).
3. Known colonization with penicillin/cephalosporin –

resistant species including MRSA.
4. Patient's instability including hypotension or septic shock without identified pathogens.
5. Severe mucositis or high dose chemotherapy regimen
6. Fever 3 days after imipenem administration
7. Soft tissue infection
8. Patients who had antimicrobial prophylaxis with ciprofloxacin and sulfamethoxasole-trimetoprim

Initial doses of vancomycin for empiric treatment of febrile neutropenic patients would be based on actual body weight and using 15 mg/kg/dose every 12 hours with monitoring renal function and serum levels (11). The Duration of treatment with vancomycin is at least 5 days and serum level should not be less than 10 mcg/ml because of the risk of treatment failure (12). Pharmacokinetic studies showed with the trough range of 15-20 mcg/ml the ratio of the area under the curve (AUC) over minimum inhibitory concentration (MIC) of 400 or higher which is needed for bactericidal properties of vancomycin to be achieved (6, 13). In complicated
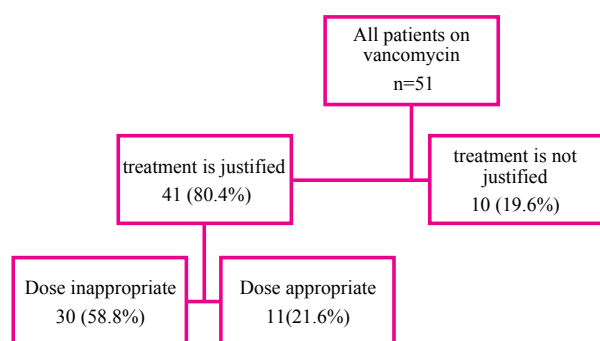
Figure 1. Treatment justification and dose appropriateness of vancomycin.

infections such as meningitis, hospital acquired pneumonia; bacteremia, endocarditis and osteomyelitis, trough serum concentrations range of 15-20 mcg/ml are required to improve penetration to sites of infection and clinical outcome(6).

In our study vancomycin dosing was regardless of patient's weight and age and received 1 gr every 12 hours. Level monitoring of vancomycin was done for 64.7% of patients and doses were justified for 80.4% of them.

The most evident problem in vancomycin utilization in this hematology-oncology ward is that vancomycin was not stopped at the proper time and continued more than it was actually needed. Another considerable problem in vancomycin usage in Iran is the ignorance of the important role of measuring vancomycin levels in optimizing vancomycin use. Providing equipment and trained personnel for TDM, Training health care providers, using antibiotic stop order 72 h after the initiation of vancomycin, supervision of pharmacy and therapeutic committee on continuation of vancomycin and availability of a clinical pharmacist in hospital are recommended.

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