Drug Utilization Review of Vancomycin in Febrile Neutropenic Patients Hospitalized at a Bone Marrow Transplantation Center

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Abstract

Introduction: Infections in neutropenic patients are considered as major causes of mortality and emergence of drug resistant 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.

Methods: We conducted a prospective observational study at bone marrow transplantation research center, Shariati teaching hospital in Tehran to evaluate the appropriateness of vancomycin utilization for our adult bone marrow transplantation (BMT) patients for a period of six months.

Results: The charts of a total of 117 patients were prospectively reviewed in 3 adult BMT wards. Seventy four patients (63.2%) received vancomycin treatment during their hospital stay. Most patients received allogienic versus autologous transplantation (62.2%, 18.9%). Majority of patients were under 50 years of age (91.9%). About 58% of cases were febrile neutropenic at the time of vancomycin initiation. Based on the criteria of appropriate indications, vancomycin utilization was justified in 59.5% of cases which 43.2% of those cases received appropriate initial doses.

Conclusion: Based on the results of this study, in the majority of our BMT patients vancomycin was utilized appropriately as a part of their empiric treatment. More attention in the time of initiation and also dose adjustment seems to be necessary to minimize treatment failure and the emergence of drug resistance.

Key words: Vancomycin, Febrile Neutropenic, Empiric Treatment, Gram positive infection

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Introduction

Fever can be the only but not specific symptom of infection in neutropenic patients.(1) More than half of patients with febrile neutropenia have an established infection including bloodstream bacterial infections.(2, 3) Gram positive bacterial species cause up to 70% of infections in patients with low neutrophil counts with Staphylococcus aureus and coagulase negative Staphylococcal species as major causes of catheter related infections(4) Vancomycin, a glycopeptide antibiotic is active against drug resistant Gram positive bacteria including methicillin resistant Staphylococcus aureus (MRSA) and enterococcal species.(5) In order to reduce the rate of bacterial resistance and treatment failures this agent should not be used routinely as a part of initial therapy in febrile neutropenic patients however appropriate initial dosing and treatment duration is critically important to suppress Gram positive bacterial infections.(6)

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

Methods and materials

We conducted this prospective observational study at hematology- oncology and bone marrow transplantation research center, Shariati teaching hospital, one of the major medical centers of Tehran

Table- 1. Demographic and clinical characteristics of patients.

Characteristic	Result
Age- yr	
Mean	30
Range	15-67
Age group – no. (%)	
<20 yr	17 (23.0)
20-40 yr	42 (56.8)
≥40 yr	15 (20.2)
Sex- no. (%)	
Male	48 (64.9)
Female	26 (35.1)
Ward- no. (%)	
BMT1	29 (39.2)
BMT2	23 (31.1)
BMT4	22 (29.7)
Allergy- no. (%)	
Yes	1
No	20 (27.0)
Not found	53 (71.6)
Transplant type- no. (%)	
Allo PBsc	46 (62.2)
Auto PBsc	14 (18.9)
Duration of hospitalization- day	
Mean	26
Range	12-45
Primary diagnosis- no. (%)	
AML	23 (31.1)
Lymphoma	11 (14.9)
ALL	11 (14.9)
Thalassemia	8 (10.8)
MM	8 (10.8)
AA	5 (6.8)
CML	3 (4.1)
MF	2 (2.7)
Ovarian cancer	1 (1.4)
MDS	1 (1.4)

Note: BMT: Bone Marrow Transplantation, AlloPBsct: Allogeneic peripheral blood stem cell transplantation, Auto PBsct: Autologous peripheral blood stem cell transplantation, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, MM: Multiple myeloma, AA: Aplastic anemia, CML: Chronic myeloid leukemia, MF: Myelofibrosos, MDS: Myelodysplastic syndrome.

University of Medical Sciences. A total of 117 patients admitted to the adult BMT wards were included in this study for a period of six months. In order to ease the utilization evaluation process we developed data collection forms including patients' demographic information (age, gender, weight and 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 cells (WBC) counts, serum creatinine and blood urea nitrogen (BUN). Also, based on national comprehensive cancer network (NCCN) and infectious diseases society of America (IDSA) guidelines for empiric treatment of febrile neutropenia, we include the criteria of vancomycin indications as empiric treatment in our evaluation form.(4, 6)

Results

Total of 117 patients in 3 adult BMT wards were evaluated during their hospital stay post transplantation. Seventy four patients (63.2%) were on vancomycin for an average of 9 days (2-31 days). The most common initial diagnosis and reason for BMT were acute myeloid leukemia (AML) (31.1%). Male patients were almost double the number of female patients (64.9% versus 35.1%), also the majority of patients were under 50 years of age (91.9%). Table- 1 shows patients' demographic information.

As mentioned in the study methods section, we used the NCCN criteria to justify the utilization of vancomycin in this group which for the most part the presence or an evidence of drug resistant Gram positive bacterial infection and patient's instability were evaluated. Twelve point two percent of our patients had none of the criteria for justified indication of vancomycin treatment. Table- 2 shows the NCCN criteria of justified vancomycin treatment in febrile neutropenic patients with correspondent number and percentage of patients in this study.

Among patients who received vancomycin, 58.1% were febrile neutropenic at the time of initial dose of this agent, whereas 23% were only febrile and

Table- 2. NCCN criteria for justified vancomycin utilization

Criteria	Frequency	Percent
FP	2	2.7
Hypo	15	20.3
Hypo+FP	3	4.1
Hypo+Soft	1	1.4
Hypo+MRSA	1	1.4
Gram	4	5.4
Gram+Hypo	3	4.1
Gram+MRSA+Hypo	1	1.4
Cath	9	12.2
Cath+Hypo	14	18.9
Cath+Hypo+FP	1	1.4
Cath+MRSA+Hypo	1	1.4
Cath+Gram	5	6.8
Cath+Gram+Hypo	4	5.4
Cath+Gram+Hypo+FP	1	1.4
None	9	12.2

Note: FP: Prophylaxis with fluoroquinilones, Hypo: Hypotension or septic shock without identified pathogen, Soft: 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.

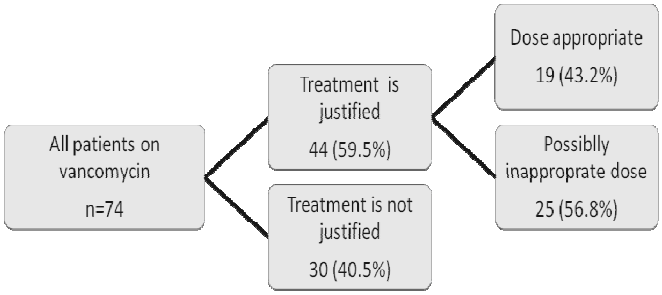

Figure 1 - Treatment justification and dose appropriateness of vancomycin

10.8% had low WBC without fever. The majority of cases received vancomycin for 5 days (mean=9 days, range=2-31 days). Vancomycin was prescribed as one gram per dose for almost all patients either as daily or twice daily dose regardless of their weight and renal function. Since there was no vancomycin serum level monitoring, no dose adjustment was done based on pharmacokinetics parameters. Sixty six point two percent of our patients initiated imipenem prior to initiation of vancomycin, whereas this number was 17.6% for those who received ceftazidime before initiation of vancomycin. According to our evaluation, 59.5% of vancomycin treatments were justified in this study while in 43.2% of these cases, vancomycin was dosed appropriately. Fifty six point eight percent of justified utilization cases seem to be underdosed although there was no serum level available to proof this concept. Figure 1 shows the evaluation of vancomycin utilization and its' dosage in this study.

Discussion

Fever is defined as a single temperature of 38.3 C or higher or a temperature of 38.0 C over an hour. Neutropenia is defined as an absolute neutrophile 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.(1) Over 50 % of neutropenic patients with fever have an occult infection. This is while over 20% of patients with neutrophil counts of less than100 cells/mm3 have bacteremia.(7) During initial days of neutropenia the major pathogens causing infections are bacteria including Gram positive agents: Staphylococcus aureus, coagulase negative Staphylococci, Enterococci and Streptococci, also Gram negative bacteria including Escherichia coli, Klebsiella and Enterobacter species.(8) Chemotherapy related gastrointestinal mucositis increases the risk of exposing blood stream to endogenous bacteria including Enterococcal and Streptococcal species.(9) The same problem occurs when BMT patients have gastrointestinal graft versus host disease (GVHD). Also since most patients at bone marrow transplantation or oncology- hematology wards have long term central or peripheral venous access lines, they are at higher risk for Staphylococcal infections (bacteremia, skin and soft tissue infections).(10)

According to the IDSA and NCCN guidelines for the 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(4, 6):

1) Clinically apparent or suspected serious catheter related infections.
2) Positive results of blood cultures with susceptibility tests, showing resistant Gram positive species (MRSA, penicillin resistant Streptococci, Ampicillin resistant Enteococci).
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 and intense chemotherapy regimen and possible exposure of blood stream to enteral pathogens.

Also in patients who had antimicrobial prophylaxis with ciprofloxacin and sulfamethoxasole-trimetoprim, vancomycin may be initiated in the case of febrile neutropenia.(6)

Vancomycin should not be a routine part of empiric treatment unless specific conditions with strong evidence of Gram positive infections including the above criteria to prevent prevalence of vancomycin resistant Gram positive infections including vancomycin resistant Enterococcus (VRE) and vancomycin resistant Staphylococcus (VRSA). On the other hand when using vancomycin, appropriate dose calculation the right dose and monitoring the drug trough levels is vital in order to keep the serum and tissue concentrations in such a range to suppress the infection.(11)

Since in febrile netropenic patients, catheter related Gram positive infections are the sources of bacteremia and predispose patients to the risk of bacterial endocarditis, serum trough levels of 15-20 mcg/ml is recommended.(4)

For the empiric treatment of febrile neutropenic patients the initial Vancomycin dose would be based on actual body weight and using 15mg/kg/dose every 12 hours with monitoring renal function and serum levels and dose adjustments

would minimize antibiotic resistance and treatment failure while using vancomycin. The duration of the treatment is based on the culture result, clinical finding and site of infection for at least 5 days. Recent studies showed a close correlation between vancomycin levels of less than 10 mcg/ml and treatment failure and the emergence of VRSA and vancomycin intermediate Staphylococcus aureus (VISA). Pharmacokinetics studies showed with the trough ranges of 15-20 mcg/ml the ratio of area under the curve (AUC) over minimum inhibitory concentration (MIC) of 400 or higher which is needed for bactericidal properties of vancomycin will be achieved.(12-14)

Currently, at this BMT center and other medical centers in Iran, there is no vancomycin level monitoring in clinical practice. As mentioned in our results, the majority of our patients regardless of their weight and age received the dose of 1 gram every 12 hours. Over 90% of the patient population in this DUR study was under 50 years old and normal renal function. In this situation, drug level monitoring would theoretically reveal low concentrations if the test was done and dose adjustment would be necessary. Another important endpoint of this study is regarding the time of vancomycin initiation. It seems that more attention is necessary when utilizing this agent including justifying the clinical and microbiological criteria needed to add this agent and closer evaluation of specimen cultures to determine the duration of treatment with vancomycin. The majority of patients in this study who received vancomycin either as monotherapy or in combination with other broad spectrum antibacterial agents did not have positive cultures peri-vancomycin treatment.

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