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Original Research

Efficacy of Colistin Therapy in Patients with Hematological Malignancies: What if There is Colistin Resistance?

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ABSTRACT

Objective: The objective of this study was to evaluate the clinical efficacy and appropriateness of colistin therapy in patients with hematological malignancies.

Methods: Age, gender, type of hematologic malignancy, and potential carbapenem-resistant microorganism risk factors were all noted in this retrospective study. In empirical and agent-specific treatment groups, differences in demographic features, risk factors, treatment responses, and side effects were compared.

Results: Sixty-three patients were included, 54% were male, and the median age was 49. In the last three months, the hospitalization rate history was 68%, and four patients had a hospitalization history in the ICU. Carbapenem-resistant K. pneumoniae colonization was present in 22 patients (35%). Gram-negative microorganisms were isolated in 34 patients (54%). The carbapenem, quinolone, and colistin resistance rates were 82%, 76%, and 4% respectively. Clinical and microbiological response rates were 60% and 69%. 7 and 28-day mortality rates were 17% and 35%. There was no significant difference in demographic data and comorbidities in empirical (n=48) and agent-specific (n=15) treatment groups. The rate of carbapenem and glycopeptide treatments before colistin was higher in the empirical treatment group ($p = 0.004$; $p = 0.001$). The rate of starting combined antibiotics was higher in the empirical treatment group ($p = 0.016$). Two of the patients developed renal failure in the first week after treatment.

Conclusion: The use of empirical colistin may be unavoidable given the risk considerations. Shortly, colistin-resistant strains may also be a factor affecting treatment success negatively.

Keywords: Colistin, hematological malignancy, empirical treatment, carbapenem resistance, colistin resistance

INTRODUCTION

Patients with hematological malignancies are more susceptible to infections due to immunosuppression, neutropenia, long-term hospitalization, invasive procedures, bone marrow depression, and mucosal barrier impairment (1). Infections are a leading cause of morbidity and mortality in individuals with hematological malignancies who have received intensive treatment (2,3). Antibiotics may be overused or misused, resulting in the development of antibiotic-resistant bacteria (4,5). Pathogens include multidrug-resistant *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii, and Stenotrophomonas maltophilia* posed a substantial risk in patients with hematological malignancies and who received hematopoietic stem cell transplantation (4,6).

Polymyxin B and Colistin are primarily used as last-resort antibiotics against Gram-negative bacteria that are resistant to other antibiotics. Colistin treatment is as effective and safe as beta-lactam antibiotics or fluoroquinolones in treating infections caused by MDR P. *aeruginosa*, according to recent trials in cancer patients (1). Colistin is typically administered to patients who have a proven or suspected MDR pathogen infection, as evidenced by signs and symptoms of sepsis during broad-spectrum antibiotic therapy and positive culture findings. The possibility of nephrotoxicity is concerning, especially when combined with other nephrotoxic medications. Kidney toxicity is reported to occur in a range of 0 to 50% of people. However, there is a limitation of data on colistin therapy and stem cell transplantation in patients with hematological malignancies (1,3). Although the use of colistin in empirical treatment reduces mortality in eligible patients, the drug's usage is limited because to potential adverse effects, pharmacological interactions, and the rapid development of resistance in gram-negative bacteria. In our hospital's intensive care units, where colistin is often administered, the frequency

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of colistin-resistant *A. baumannii* and *K. pneumonia* isolates has been progressively increasing over the years (7,8). As a consequence, in every department and for each antibiotic, the principles of rational antibiotic usage should be considered (9).

The objective of this study was to determine the clinical efficacy of colistin and whether it should be used as an empirical therapy in patients with hematological malignancies.

METHODS

Patients diagnosed with hematological malignancy and treated with colistin therapy in the Erciyes University Faculty of Medicine Hematology Clinic between January 1, 2019 and January 1, 2020 were included in this retrospective study. The patients' medical records were obtained from hospital information records and medical files.

Age, gender, type of hematologic malignancy, presence of neutropenia even before to colistin therapy, presence of rectal colonization due to Vancomycin-Resistant Enterococci (VRE) and Carbapenem-Resistant K. pneumonia, recent hospitalization in clinics and intensive care units, antibiotic use prior to colistin, and duration of antibacterial therapy were all recorded.

The results of blood cultures taken three days prior to the initiation of colistin therapy were analyzed, and the treatment was classed as either empirical or based on the isolated microorganism. The use of antibiotics in combination with colistin therapy was documented. The antibiotic susceptibility of microorganisms isolated following colistin therapy was documented. It was determined whether empirical colistin therapy was appropriate. The length of the treatment and the use of nephrotoxic medications in combination with the colistin treatment were recorded. C-reactive protein (CRP) levels were measured at the start, third, seventh, and end of treatment.

At the start of treatment, the seventh day of treatment, and the seventh day after treatment, creatinine, glomerular filtration rate (GFR), and potassium values were observed.

Antibiotic initiation criteria: An antipseudomonal antibiotic was started in patients who met the criteria for febrile neutropenia. Antibiotic treatments given to patients who did not receive a clinical response on the third day of treatment or to whom antibiotic changes were made according to the culture results were recorded.

Main Points:

- Infections are important in patients with hematological malignancies
- Antibiotic resistance is gradually increasing in causative microorganisms.
- Colistin can be used in empirical treatment in patients with risk factors
- The nephrotoxic effect of colistin treatment is reversible.
- Colistin resistant strains should also be kept in mind.

The patients who were started on colistin therapy were separated into two groups: those who received empirical treatment and those who received agent-specific treatment. The agent-specific therapy group included patients who had carbapenem-resistant gram-negative bacteria isolated in their blood culture before and on the day of treatment and were started on colistin treatment. In terms of demographic characteristics, risk factors, treatment responses, and side effects, statistical differences between the groups were compared. There were two outcomes in the study:

Clinical response: A clinical response was defined as a 25% decrease in CRP on the third day compared to the initial CRP value, or a decrease of more than 75% on the seventh day, fever response, or hemodynamic stability on the third day.

Nephrotoxicity: The occurrence of nephrotoxicity was classified using RIFFLE criteria based on GFR and creatinine levels.

The patients' fatalities were recorded on the seventh and 28th days.

Confirmation of carbapenem resistance: The BD Phoenix (Beckton Dickinson, USA) automated system was first used to identify isolates and determine antibiotic susceptibility. Kirby Bauer disc diffusion method was used to confirm carbapenem resistance, and liquid microdilution method, The SensiTitreTM system (Thermo Fisher Scientific) (Sensititre GNX3F plates (TREK Diagnostic Systems, Oakwood Village, Ohio)) was used to confirm colistin resistance.

Statistical Analysis

The data of our study was transferred to the SPSS 25.0 package program. Data analysis was done in the same program. Whether the distribution was normal or not would be evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. The parameters were evaluated with mean ± standard deviation or percentages according to their status. Student's t-test or Mann-Whitney U-test was used to analyze continuous parameters, and chi-square or Fisher's exact test was used for the analysis of categorical variables. Analyzes with a p-value of <0.05 were considered significant.

RESULTS

The study included 63 patients who underwent colistin therapy and were hospitalized in a hematology clinic due to hematological malignancy. The median age of the patients was 49 years, and 54 percent of them were men. Acute myeloid leukemia was the most frequent type of hematological malignancy (40%). The hospitalization rate in the last three months was 68 %, including four patients (6 percent) in the intensive care unit having previously been hospitalized. In periodic rectal screenings before treatment, Carbapenem-resistant K. pneumoniae colonization was found in 22 patients (35%), while VRE colonization was found in 13 patients (21%). In 76 percent of the patients, carbapenem was started before colistin, and in 73 %, glycopeptide therapy was started before colistin. A double antibiotic combination was used to treat 82 percent of the patients. Prior to beginning colistin therapy, the average duration of antibiotic treatment was 13 days (Table 1).

Table 1. Comparison of demographic characteristics, hematological malignancy, and risk factors for resistant bacteria, antibiotics combined with Colistin therapy, nephrotoxic agents, clinical response, microbiological response and mortality

Variables	All patients n=63	Empirical treatment n=48	Specific treatment n=15	p
Age (years)	49 (19–76)	48 (19–76)	52 (25–72)	0.955
Male (gender)	34 (54.0)	26 (54.2)	8 (53.3)	0.999
Hematological malignancy				
AML	25 (39.7)	19 (39.6)	6 (40.0)	0.999
Lymphoma	19 (30.2)	15 (31.3)	4 (26.7)	
MM	7 (11.1)	5 (10.4)	2 (13.3)	
ALL	4 (6.3)	3 (6.3)	1 (6.7)	
Other	8 (12.7)	6 (12.5)	2 (13.3)	
Presence of neutropenia	36 (57.1)	28 (58.3)	8 (53.3)	0.772
Colonization of carbapenem resistant Klebsiella pneumonia	22 (34.9)	18 (37.5)	4 (26.7)	0.544
Hospitalization for the last 3 months	43 (68.3)	34 (70.8)	9 (60.0)	0.528
ICU hospitalization for the last 3 months	4 (6.3)	2 (4.2)	2 (13.3)	0.238
Before Colistin				
Carbepenem treatment	48 (76.2)	41 (85.4)	7 (46.7)	**0.004**
Glycopeptide treatment	46 (73.0)	41 (85.4)	5 (33.3)	**0.001**
Combined antibiotic treatment	52 (82.5)	43 (89.6)	9 (60.0)	**0.016**
Duration of antimicrobial treatment (day)	13 (1–56)	14 (1–56)	7 (3–23)	0.071
Antibiotics combined with Colistin				
Carbapenem	49 (77.8)	38 (79.2)	11 (73.3)	0.725
Piperacillin tazobactam	5 (7.9)	2 (4.2)	3 (20.0)	0.083
Glycopeptide	43 (68.3)	37 (77.1)	6 (40.0)	**0.011**
Tigecycline	5 (7.9)	5 (10.4)	0 (0.0)	0.326
Quinolone	5 (7.9)	5 (10.4)	0 (0.0)	0.326
Triple combination therapy	50 (79.4)	42 (87.5)	8 (53.3)	**0.009**
Duration of colistin treatment	9 (2–39)	8 (3–30)	10 (2–39)	0.377
Gram negative bacteria isolation rate	38 (65.0)	23 (47.9)	15 (100)	0.137
Gram positive bacteria isolation rate	8 (12.7)	5 (10.4)	3 (20.0)	0.382
Concurrent cyclosporine therapy	3 (4.8)	2 (4.2)	1 (6.7)	0.564
Concurrent vancomycin therapy	28 (44.4)	25 (52.1)	3 (20.0)	**0.039**
Concurrent nephrotoxic therapy	28 (44.4)	25 (52.1)	3 (20.0)	**0.039**
Clinical response	38/58 (65)	29/43 (67.4)	9/15 (60.0)	0.999
Microbiological response	29/43 (69.0)	19/28 (67.9)	10/15 (75)	0.999
7-day mortality	11 (17.5)	9 (18.8)	2 (13.3)	0.999
28-day mortality	22 (34.9)	19 (39.6)	3 (20.0)	0.222

Values are expressed as n (%), mean ±SD or median (1st-3rd quartiles). AML, Acute myeloid leukemia; MM, multiple myeloma; ALL, Acute lymphoblastic leukemia; ICU, intensive care unit

Because the causative microorganism was isolated before colistin therapy, 15 individuals were treated with colistin based on their antibiotic susceptibility. In the other 48 patients, empirical treatment was started. Carbapenem (78%) and glycopeptide group antibiotics were the most commonly combined antibiotics with colistin (68 %). 79 percent of the patients underwent triple antibiotic combination therapy. In the culture results of 34 patients, Gram-negative bacteria were found (54 %). Carbapenem resistance was found in 82 percent of these isolates, fluoroquinolone resistance was identified in 76 %, piperacillin-tazobactam resistance was found in 68 %, and colistin resistance was found in 4%. (Figure 1). In 13% of the patients, Gram-positive bacteria were found. 44 percent of the patients had previously used nephrotoxic medications while on colistin therapy.

Vancomycin was the most commonly used nephrotoxic agent (44%), and three patients were on cyclosporine therapy. The Gram-positive bacteria isolated in the five patients in the empirical treatment group was used to evaluate clinical response in

the 58 patients. In 65 percent of the patients, a clinical response was obtained, and in 69 percent, a microbiological response was established. The mortality rates at 7 and 28 days were calculated to be 17% and 35%, respectively (Table 1). Figure 2 shows the change in CRP levels of the patients during colistin therapy. It was observed that the decrease in CRP level was slighter in the group in which colistin therapy was started empirically.

Table 2 shows the rate and severity of renal failure after colistin treatment. Nephrotoxicity was observed in 32 patients during the first week of treatment, 23 patients after treatment, and 20 patients in the first week after treatment. Renal failure occurred in two of the individuals.

Between patients who received empirical and agent-specific treatment, there was no significant difference in demographic data or co-morbid diseases. As compared to the other group, the rate of usage of carbapenem and glycopeptide before colistin was higher in the patient group who started empirical treatment ($p = 0.004$; $p = 0.001$). The group receiving empirical treatment had a higher rate of starting combination antibiotics (89% vs. 60%, $p = 0.016$). In the empirical treatment group, the use of glycopeptide antibiotics in combination with colistin was also found to be higher. The empirical treatment group also used more triple-combination antibiotics with colistin. There was no significant difference in clinical response, microbiological response, or mortality in the patients who received empirical and agent-specific treatment.

DISCUSSION

In this study, the rate of starting empirical colistin in the hematology clinics seems to be high. However, patients undergoing empirical treatment appear to have more than one risk factor for carbapenem-resistant Gram-negative microorganisms. In a meta-analysis involving 3627 patients from 16 clinical trials, risk factors for carbapenem-resistant K. pneumoniae were, corticosteroid use OR = 1.43, central catheter use (OR 2.3), previous antibiotic use (OR = 3.31), and exposure to carbapenems (OR = 4.01), aminoglycosides (OR = 2.05), glycopeptides (OR = 2.40), fluoroquinolones (OR = 2.28), and anti-pseudomonal penicillins (OR = 2.67) (10). In an observational retrospective study that analyzed risk factors for carbapenem-resistant K. pneumoniae bacteremia, the use of antibiotics and carbapenem in the previous

Figure 1. Antibiotic resistance rates in isolated Gram negative bacteria

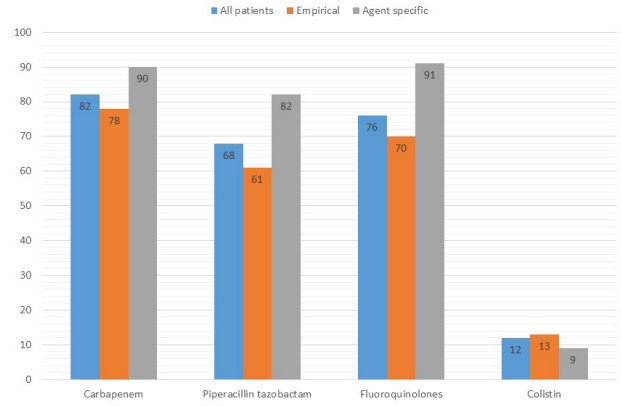

Figure 2. Change in CRP values before treatment, third, seventh and end of treatment

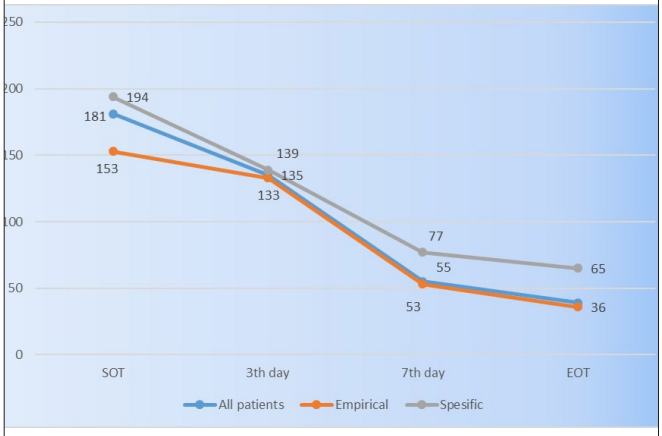

Table 2. Changes in renal function tests according to RIFLE criteria during and after Colistin therapy

	First week of treatment n=32	End of treatment n=23	First week after treatment n=20
Risk (R)	18 (56.3)	4 (17.4)	14 (70)
Injury (I)	5 (15.6)	8 (34.8)	4 (20)
Failure (F)	8 (25.0)	10 (43.5)	2 (10)
Loss (L)	1 (3.1)	1 (4.3)	0 (0.0)
ESKD (E)	0 (0.0)	0 (0.0)	0 (0.0)

ESKD, end stage kidney disease

30 days was reported as a risk factor for carbapenem-resistant K. pneumoniae bacteremia (11). When the risk factors for mortality were evaluated in the same study, inappropriate initiation of empirical antibiotic treatment was found to be a risk factor (11). Hospitalization in the previous three months (68 %), neutropenia (58 %), and carbapenem use (76%) were all risk factors for hospitalization in the patients in this study. In the group that received empirical Colistin, the rate of initiating carbapenem and glycopeptide before Colistin was higher. Because the infectious agent could be MDR or XDR gram-negative bacteria, colistin therapy was selected.

Due to factors such as the patients' malignancies and their severe immunosuppressive treatment, hematology units are departments where empirical antibiotic treatment should be chosen carefully. The colistin-resistant gram-negative bacteria was isolated in four patients in this study. The causative microorganism was isolated at the beginning of treatment in one of these patients. The other three, on the other hand, had ineffective empirical treatment. Patients with colistin-resistant gram-negative isolates had a higher mortality rate (75%) due to a lack of empirical treatment. When the entire patient group in the trial was reviewed, 28-day mortality was found to be 35%, while 28-day mortality was determined to be 40% in patients who were given Colistin as an empirical treatment. The 28-day mortality rate in a study involving carbapenem-resistant A. baumannii as a nosocomial infection agent was calculated to be 52 percent (12), whereas it is 45 percent (13) in P. aeruginosa infections and up to 75 % in K. pneumoniae infections (14). Mortality rates may vary according to the patients' co-morbid diseases and the causative microorganisms (15). In the Extensively-drug resistant A. baumannii bacteremia epidemic reported in our hematology unit in 2012, the mortality rate in 28 patients was reported as 82% (16). Since the carbapenem resistance in Gram-negative bacteria isolated in the patient group included in the study was at a high level of 82%, it seems appropriate to prefer colistin in empirical treatment.

A nephrotoxic agent was co-administered with colistin therapy in % of the patients. Vancomycin was the most common of these medications. In vitro studies have shown that combining colistin and vancomycin had a synergistic impact in colistin-resistant A. baumannii isolates (17,18). Other than colistin and vancomycin, however, nephrotoxic treatment, such as chemotherapy protocols, antibacterial, antiviral, and antifungal prophylaxis, is frequent in this patient population. Nephrotoxicity in this patient group should be closely monitored. In a study comparing nephrotoxicity in 26 patients with hematological malignancies who got colistin therapy to a control group who did not receive colistin therapy, it was found that there was no significant difference in terms of side effects (19). During the treatment, different levels of renal failure were detected in 40% of the participants in this study. However, one week after the treatment was stopped, all of the patients' renal functions improved.

CONCLUSION

Infections in patients with hematological malignancies must be treated with suitable empirical medication immediately away. When beginning empirical treatment, risk factors for probable factors should be considered. In our hospital's hematology unit, empirical initiation of colistin therapy in suitable patients seems to be effective and safe. Colistin-resistant strains, on the other side, may have an immediate negative impact on treatment success.

Ethics Committee Approval: Ethics committee approval was received for this study from the Noninvasive Clinical Research Ethics Committee of Erciyes University (Approval date: 25.12.2019; approval number: 2019/883).

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Competing interest for all authors: No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. The authors declare that they have no relevant conflict of interest.

Author's contributions: ZT, GKU, HNK; performed the analysis and collect the data, ZT, HNK; collect the patient data, ZT; wrote the paper, ZT, AUK,MK critised and edited the paper.

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