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Original Article

Emergence of multidrug resistant isolates and mortality predictors in patients with solid tumors or hematological malignancies

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Abstract

Introduction: Infections are an important preventable cause of death in cancer patients. The aim of this study was to clarify the epidemiologic characteristics and resistance patterns of causative isolates and mortality predictors in infections of cancer patients.

Methodology: Patients with sterile site infections were evaluated in a retrospective cohort study. Etiological agents, antimicrobial resistance patterns of the isolates, and possible risk factors for mortality were recorded. Survivors and non-survivors on day 30 after each infection onset were compared to identify the predictors of mortality.

Results: A total of 205 infection episodes of 132 patients were included in this study. Of them, 75% had hematologic malignancies and 25% had solid tumors. Febrile neutropenia was diagnosed in 61.5%. Bloodstream infections were the most frequent infection (78%). The majority of the pathogens were *Enterobacteriaceae* (44.3%) and nonfermentative isolates (17.6%). Multidrug-resistant (MDR) infections were responsible for 40% of the episodes. The mortality rate was 23.4%. Inadequate initial antibiotic treatment (OR = 4.04, 95% CI = 1.80–9.05, p = 0.001), prolonged neutropenia (> 7 days) before infection (OR = 3.61, 95% CI = 1.48–8.80, p = 0.005), infection due to *Klebsiella* species (OR = 3.75, 95% CI = 1.31–10.7, p = 0.013), and *Acinetobacter baumannii* (OR = 5.00, 95% CI = 1.38–18.2, p = 0.014) were independent predictors of mortality.

Conclusions: Gram-negative isolates were found to be the predominant pathogens with higher mortality rates. Local epidemiological data should be taken into account when administering empirical therapy since the inadequacy of initial antibiotherapy is associated with a poor outcome.

Key words: mortality; infections; hematological malignancies; neutropenia; MDR

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Introduction

Patients with hemato-oncological malignancies have a predisposition towards severe, life-threatening infections that result in prolonged hospitalization and higher mortality rates [1,2]. The majority of cancer patients harbor high risk for infections that are mostly assumed to be caused by immunosuppressive therapies [3]. Because of the high mortality rates due to infections, commencing appropriate empirical antimicrobial therapy is crucial in these patients. The causative pathogens are usually equivocal; therefore, it is important to know the local epidemiological data before starting adequate empirical antimicrobial therapy, especially in patients who are vulnerable to serious infections [4]. The epidemiological characteristics of causative isolates of bloodstream infections (BSIs) in cancer patients have changed recently, with a shift toward Gram-negative infections. In addition, the increasing incidence rate of multidrug-resistant (MDR) microorganisms has become a major problem worldwide [3,5]. To the best of our knowledge, there exist limited data in the literature, especially from Turkey, about the epidemiology and risk factors of mortality in infected patients with hemato-oncological malignancies. Most of the available data are relevant to only bacteremic and neutropenic patients with cancer. In this study, we aimed to identify the recent epidemiology of infections and mortality risk factors in infected neutropenic and non-neutropenic patients with hemato-oncological malignancies.

Methodology

Study design, setting, and patients

This retrospective cohort study was conducted at Ankara Numune Training and Research Hospital

(ANTRH) in Turkey. The medical records of the patients admitted to hemato-oncology wards of the 1,140-bed tertiary care hospital between 2008 and 2013 were investigated. The results of sterile site cultures of patients with hemato-oncological malignancies were analyzed. Clinical significance (infection or colonization) of each positive culture was assessed by an infectious disease specialist, and the infections of the patients were defined according to the Centers for Disease Control (CDC) definitions [6]. The patients with laboratory-confirmed BSIs and urinary tract infections were included into the study.

Statistical analyses were based on the infection episodes. A new infection episode was defined as positive blood or urine culture meeting the CDC case definition and at least seven afebrile intervening days since the previous infection [7]. The patients were divided in two groups, survivors and non-survivors, according to the outcome on day 30 after each infection onset. The demographic, clinical, and laboratory characteristics of the two groups were compared statistically and the impact of the risk factors on mortality was defined. The effect of fluoroquinolone prophylaxis on the acquisition of infections with MDR isolates in 126 febrile neutropenic episodes was also evaluated, since quinolone prophylaxis was used in only high-risk neutropenic patients.

Data collection

The data were recorded for each patient during every episode of infection and included demographics, malignancy type, presence or absence of stem cell transplantation, site of infection, time to the onset of infection, presence of fever (≥ 38°C), absolute neutrophil count, duration and severity of neutropenia, causative isolates and their antimicrobial resistance patterns, presence of quinolone prophylaxis for neutropenic patients, empirical antimicrobial therapy during the onset of infection before positive culture results, antimicrobial therapy, length of time to infection, and outcome on day 30 after infection onset.

Definitions

Definitions are provided in Table 1 according to previous studies and guidelines [6,8-11].

Microbiological studies

Identification and antimicrobial susceptibility tests of the microorganisms were performed using a VITEK automated system (BioMerieux, Marcy I'Etoile, France). The Clinical and Laboratory Standards Institute (CLSI) criteria were used to determine the resistance or susceptibility to the antimicrobial agents [12]. Extended-spectrum beta lactamase (ESBL) production was investigated and confirmed using a double-disk synergy test in accordance with CLSI guidelines [13].

Table 1. Definitions

Laboratory-confirmed bloodstream infection (LCBI) [6]	Patients with at least has one of the following criteria: 1) Isolation of microorganisms from blood (such as *S. aureus, Enterococcus* spp., *E. coli, Klebsiella* spp., *Pseudomonas* spp., *Candida* spp., and others) for ≥ 1 positive culture that was not related to an infection of other body sites; 2) Patients with one of the following signs that was not related to an infection of other body sites: fever (38°C), chills, or hypotension and ≥ 2 positive separate culture results for possible skin contaminant pathogens, such as coagulase-negative *Staphylococcus*
Symptomatic urinary tract infection [6]	Patients with one of the following signs with no other cause: fever (38°C), urgency, dysuria or suprapubic tenderness, and has a positive urine culture with ≥ 10^5 colony forming units (CFUs)/mL bacteria with no more than two species
Neutropenia [8]	Absolute neutrophil count (ANC) of < 500 cells/mm^3 or ANC which was expected to decrease to < 500 cells/mm^3 during the next 48 hours
Prolonged neutropenia [8]	ANC < 500 cells/mm^3 for > 7 days
Profound neutropenia [8]	ANC < 100 cells/mm^3
Febrile neutropenia [8]	A single value of oral temperature 38.3°C or 38°C sustained for at least 1 hour according to Infectious Diseases Society of America (IDSA) guidelines
Quinolone prophylaxis [8]	According to IDSA guidelines, prophylactic therapy with ciprofloxacin or levofloxacin in the high-risk patients with profound neutropenia predicted for > 7 days was noted as quinolone prophylaxis.
Multidrug resistant bacteria infection [9,10]	An infection due to a Gram-negative bacteria which has a resistance to ≥ 3 classes of antimicrobial agents, and for Gram-positive bacteria, methicillin resistance for *Staphylococcus* and vancomycin resistance for *Enterococcus*
Inadequate initial antibiotic therapy [11]	Administrated drug has no *in vitro* activity against the strain responsible for the infection according to antimicrobial susceptibility test results or administration of the drug after 48 hours of positive culture results
Prior antimicrobial therapy [11]	The use of antimicrobial within the last three months before the infection episode
30-day mortality	Death within 30 days of infection onset
Length of time to adequate antibiotic therapy	Length of time from positive culture results to the initiation of adequate antibiotic therapy

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0 Descriptive statistics are presented as mean, standard deviation, median, minimum, and maximum for quantitative variables, and as number and percentage for categorical variables. In numerical comparisons, when a normal distribution was provided, the Mann-Whitney U test was used for paired independent groups. In categorical comparisons, the Chi-square test was used for paired and multi-groups. For multi-group and paired group comparisons that did not meet the Chi-square requirement, Monte-Carlo simulation and Fisher's exact test were used, respectively. Logistic regression analysis was used in the determination of risk factors for categorical variables. Statistical level of significance was set at $p < 0.05$.

Results

Demographic and clinical characteristics of the patients

During the six-year study period (2008–2013), a total of 205 infection episodes of 132 patients (43.2% males) were identified. Characteristics of the patients, infection episodes, and causative pathogens are listed in Tables 2, 3, and 4.

The mean age of the patients was 48.3 ± 15.5 years (16.7% were > 65 years of age). Of them, 75% had

Table 2. Basal characteristics of the patients (n = 132)

Characteristics	Number of patients n (%)	Survivors (n = 96)	Non-survivors (n = 36)	P value
Age (years, mean ± standard deviation [SD])	48.3 ± 15.5	47.59 ± 15.0	50.44 ± 16.9	> 0.05
Age > 65 years	22 (16.7)	12 (12.5)	10 (27.8)	**0.03**
Gender (male)	57 (43.2)	54 (56.3)	21 (58.3)	> 0.05
Solid organ tumor	25 (18.9)	19 (19.8)	6 (16.7)	> 0.05
Hematologic malignancy	107 (81.1)	77 (80.2)	30 (83.3)	> 0.05
Acute leukemia	62 (47.0)	42 (43.8)	20 (55.6)	> 0.05
Lymphoma	21 (15.9)	17 (17.7)	4 (11.1)	> 0.05
Multiple myeloma	16 (12.1)	15 (15.6)	1 (2.8)	> 0.05
Other hematologic malignancies	8 (6.1)	3 (3.1)	5 (13.9)	> 0.05
Prior HSCT	34 (25.8)	30 (31.3)	4 (11.1)	**0.01**
Comorbidities	17 (12.9)	10 (10.4)	7 (19.4)	> 0.05
Diabetes mellitus	12 (9.1)	7 (7.3)	5 (13.9)	> 0.05
COPD	2 (1.5)	0 (0.0)	2 (100.0)	-
Renal failure	8 (6.1)	4 (4.2)	4 (11.1)	> 0.05

HSCT: hematopoietic stem cell transplantation; COPD: chronic obstructive pulmonary disease

Table 3. Characteristics of the infection episodes (n = 205)

Characteristics	Number of episodes n (%)	Survivors n = 157	Non-survivors n = 48	P value
Presence of CVC	106 (51.7)	80 (51.0)	26 (54.2)	> 0.05
Presence of mucositis	30 (14.6)	25 (15.9)	5 (10.4)	> 0.05
Ongoing chemotherapy	150 (73.2)	115 (73.2)	35 (72.9)	> 0.05
Previous chemotherapy (within 3 months)	41 (20)	33 (21.0)	8 (16.7)	> 0.05
Fluoroquinolone prophylaxis	66 (32.2)	54 (34.4)	12 (25.0)	> 0.05
Prior antibiotic therapy	118 (57.6)	86 (92.4)	32 (96.9)	> 0.05
Neutropenia (< 500 cells/mm^3)	126 (61.5)	91 (58.0)	34 (70.8)	> 0.05
Profound neutropenia (< 100 cells/mm^3)	107 (52.2)	81 (51.6)	26 (54.2)	> 0.05
Prolonged neutropenia prior to infection (> 7 days)	59 (28.8)	37 (23.6)	22 (45.8)	**0.003**
Duration of neutropenia (mean ± SD, days)	12.2 ± 17.0	11.7 ± 17.2	13.96 ± 16.3	> 0.05
Febrile neutropenia	126 (61.5)	92 (58.6)	34 (70.8)	> 0.05
Site of infection				
Bloodstream infection	160 (78.0)	119 (75.8)	41 (85.4)	> 0.05
UTI	45 (22.0)	38 (24.2)	7 (14.6)	
Inadequate initial antimicrobial therapy	86 (42.0)	55 (35.0)	31 (64.6)	**< 0.001**
Length of time to adequate antimicrobial therapy (mean ± SD, days)	1.6 ± 2.8	1.6 ± 2.9	1.3 ± 1.9	> 0.05
Length of time to infection (mean ± SD, days)	21.3 ± 17.2	20.3 ± 15.7	24.5 ± 21.1	> 0.05

CVC: central venous catheter; UTI: urinary tract infection

hematologic malignancies (acute leukemia, 47%) and 25% had solid tumors. Thirty-four patients (25.8%) were hematopoietic stem cell transplantation (HSCT) recipients. Febrile neutropenia was detected in 61.5% (126/205) of all episodes. The mean length between hospital admission and emergence of infections was 21.35 ± 17.22 days. Polymicrobial infection was not detected. BSI was the most frequent infection (78%), followed by urinary tract infection (UTI).

Characteristics of causative pathogens

Regarding the isolated microorganisms, the majority of the pathogens were *Enterobacteriaceae* (44.3%, n = 91), followed by nonfermentative pathogens (17.6%, n = 36), Gram-positive coccus (30.2%, n = 62), and *Candida* species (7.8%, n = 16). The most frequently isolated pathogen was *Escherichia coli*, which was responsible for 29.2% of all infection episodes. The ESBL rate of the isolates was 36.6% (n = 75). MDR pathogens were isolated in 56.1% of the episodes (115/205 episodes). Of the total MDR infections, 16.1% (n = 33) were caused by Gram-positive isolates (vancomycin-resistant enterococcus, 1.5% [n = 3], methicillin-resistant staphylococcus, 14.6% [n=30]), whereas 40% (n = 82) were caused by Gram-negative isolates. MDR rates were higher in *Klebsiella* spp. (13/23, 56.5%) and *Acinetobacter baumannii* (14/16, 87.5%). The antimicrobial resistance patterns of the isolates is summarized in Table 5.

Treatment and outcomes

Empirical antibiotic therapy was started in 92.2% (189/205) of all episodes. After comprehensive evaluations of the patients, inadequate initial antibiotic treatment was detected in 42% (86/205) of the episodes, and it was significantly higher in fatal cases (64.6%). Moreover, it was demonstrated to be an independent predictor of mortality ($p < 0.013$, odds ratio [OR] = 2.78, 95% confidence interval [CI] = 1.24–6.26). The mean length of time to adequate antibiotic therapy was 1.63 ± 2.83 days, and there was no statistical difference between the fatal and non-fatal groups.

The mortality rate on day 30 after each infection onset was 23.4% (48/205 episodes). There was no significant mortality difference between groups in terms of the type of infection (BSI or UTI). When the effect of HSCT was evaluated, HSCT recipients with infections had significantly lower mortality rate (8% *versus* 28.4%, p = 0.003, OR = 0.21, 95% CI = 0.07–0.64) compared to other infected patients. Moreover, HSCT recipients had significantly lower rates of MDR Gram-negative infections (30% *versus* 43.2%, p = 0.049). Mortality predictors for infected patients are summarized in Table 6.

Mortality according to isolated pathogens

Etiological agents were found to be statistically different in fatal and non-fatal groups ($p < 0.001$). Gram-negative infections were found to be a

Table 4. Causative pathogens of 205 infection episodes

Causative pathogens	Total n (%)	Survivors n = 157 (%)	Non-survivors n = 48 (%)	P value
Gram-negative bacteria	127 (62.0)	89 (56.7)	38 (79.2)	**0.005**
Escherichia coli	60 (29.3)	48 (30.6)	12 (25.0)	> 0.05
Klebsiella spp.	23 (11.2)	12 (7.6)	11 (22.9)	**0.003**
Acinetobacter baumannii	16 (7.8)	6 (3.8)	10 (20.8)	**< 0.001**
Pseudomonas aeruginosa	12 (5.9)	9 (5.7)	3 (6.3)	> 0.05
Other Gram-negative bacteria	16 (7.8)	14 (8.9)	2 (4.1)	> 0.05
Gram-positive bacteria	62 (30.2)	55 (35.0)	7 (14.6)	**0.02**
Coagulase negative staphylococci	36 (17.6)	33 (21.0)	3 (6.3)	**0.019**
Enterococcus spp.	17 (8.3)	15 (9.6)	2 (4.2)	> 0.05
Stapylococcus aureus	8 (3.9)	6 (3.8)	2 (4.2)	> 0.05
Streptococcus spp.	1 (0.48)	1 (0.6)	0 (0.0)	-
Candida spp.	16 (7.8)	13 (8.3)	3 (6.3)	> 0.05

Table 5. Antimicrobial resistance patterns of the isolates of 205 infection episodes

Resistance pattern of isolates	Total isolates n (%)	Survivors n (%)	Non-survivors n (%)	P value
ESBL (+) isolates	75 (36.6)	49 (31.2)	26 (54.2)	**0.004**
Gram-negative MDR isolates	82 (40)	54 (34.4)	28 (58.3)	**0.003**
Gram-positive MDR isolates	33 (16.1)	28 (17.8)	5 (10.4)	>0.05

ESBL: extended-spectrum beta lactamase; MDR: multidrug-resistant

Table 6. Univariate and multivariate predictors of mortality

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age > 65 years	2.69 (1.04–6.94)	0.036	-	> 0.05
Prior HSCT	0.21 (0.07–0.64)	0.003	0.30 (0.09–0.95)	**0.041**
Prolonged neutropenia prior to infection (≥ 7 days)	2.74 (1.39–5.40)	0.003	3.82 (1.53–9.47)	**0.004**
Inadequate initial antibiotic treatment	0.29 (0.15–0.58)	<0.001	2.78 (1.24–6.26)	**0.013**
Gram-negative bacterial infection	2.65 (1.25–5.59)	0.005	-	> 0.05
Infection with coagulase negative *Staphylococci*	0.25 (0.07–0.85)	0.019	-	> 0.05
Infection with *Acinetobacter baumannii.*	6.62 (2.26–19.36)	< 0.001	5.00 (1.38–18.2)	**0.014**
Infection with *Klebsiella* spp.	3.59 (1.47–8.78)	0.003	3.75 (1.31–10.7)	**0.013**
Infection with ESBL-producing bacteria	0.49 (0.30–0.79)	0.004	-	> 0.05
Infection with Gram-negative MDR bacteria	2.67 (1.37–5.17)	0.003	-	> 0.05

OR: odds ratio; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; MDR: multidrug-resistant

statistically significant risk factor for mortality (p = 0.005, OR = 2.65, 95% CI = 1.25–5.59). When the causative pathogens of the infections were evaluated for mortality, infections with *Klebsiella* spp. (OR = 3.75, 95% CI = 1.31–10.7, p = 0.013) and *A. baumannii* (OR = 5.00, 95% CI = 1.38–18.2, p = 0.014) were determined to be independent predictors of mortality. The rate of infections due to coagulase-negative *Staphylococcus* (CoNS) was found to be significantly higher in non-fatal cases (p = 0.019, OR = 0.25, 95% CI = 0.07–0.85). Mortality rates according to causative pathogens are summarized in Table 4.

Mortality for ESBL and MDR pathogens

ESBL-positive and MDR Gram-negative isolates were found significantly more frequently in the non-survivor group (26/48, 54.2%, p = 0.004 and 28/48, 58.3%, p = 0.003, respectively). There was no significant mortality difference between groups in terms of the rate of Gram-positive MDR isolate infections (Table 5).

The effect of quinolone prophylaxis on the acquisition of infections with MDR isolates

The analysis of 126 febrile neutropenic episodes showed no significant association between the use of quinolone prophylaxis and Gram-negative MDR infections. However, quinolone prophylaxis was significantly higher in infectious episodes with MDR Gram-positive isolates (78.3% *versus* 21.7%, p < 0.001, OR = 7.64, 95% CI = 2.61–22.35).

Univariate and multivariate predictors of mortality

When the risk factors for mortality were evaluated in univariate analysis, older age (> 65 years), inadequate initial antibiotic treatment, prolonged neutropenia (> 7 days) before infection, infections due to Gram-negative isolates (especially *Klebsiella* spp. and *A. baumannii*), and ESBL (+) and Gram-negative MDR (+) isolate infections were found to be significant risk factors for mortality. When the severity of neutropenia was evaluated in the infection episodes with prolonged neutropenia before infection onset, 86.4% of the cases had profound neutropenia, and mortality was significantly higher in this group (p = 0.047, OR = 2.94, 95% CI = 2.04–4.24). HSCT recipients and patients with Gram-positive isolate infections (especially with CoNS) had significantly lower mortality rates in univariate analysis (Tables 4–6).

Multivariate analysis showed that inadequate initial antibiotic treatment (OR = 4.04, 95% CI = 1.80–9.05, p = 0.001), prolonged neutropenia (> 7 days) before infection onset (OR = 3.61, 95% CI = 1.48–8.80, p = 0.005), and infection due to *Klebsiella* spp. (OR = 3.75, 95% CI = 1.31–10.7, p = 0.013) and *A. baumannii* (OR = 5.00, 95% CI = 1.38–18.2, p = 0.014) were independent predictors of mortality. HSCT recipients had a significantly lower mortality rate (OR = 0.30, 95% CI = 0.09–0.95, p = 0.041) (Table 6).

Discussion

Gram-negative bacteria infections have an increasing incidence in cancer patients. Recently, there have been alterations reported about the emergence of antimicrobial resistance to some Gram-negative isolates in patients with hemato-oncological malignancies [14]. Until now, most of the studies in the literature have reported mortality risk factors or resistance patterns of isolates in BSIs of neutropenic cancer patients. Appropriate antimicrobial therapy is very important in patients with hemato-oncological malignancies, who are highly vulnerable to serious infections. Therefore, having information about the local distribution of pathogens and their antimicrobial resistance patterns is crucial in order to start proper

empirical antibiotic therapy. The present study focused on the identification of the epidemiologic characteristics and antimicrobial resistance patterns (ESBL, MDR condition) of causative isolates from infections of cancer patients with or without neutropenia. Mortality risk factors in this group were also evaluated in the study. We determined the 30-day mortality rate as the main outcome measure; the mortality rate was 23.4% in 205 infection episodes of 132 patients. BSI was the most frequently detected infection (78%), followed by urinary tract infection. The type of infection was determined as statistically insignificant with regard to mortality. The microorganisms most frequently isolated in our study were Gram-negative bacteria; this result was consistent with the literature [15]. The predominant pathogen was *E. coli* (29.2%), followed by *Klebsiella* spp., *A. baumannii*, and *Pseudomonas aeruginosa*. Consistent with the findings of Chong *et al*., CoNS was the most common isolate among the Gram-positive bacteria [16]. Previous studies have indicated that Gram-negative BSIs had higher mortality rates than Gram-positive infections [17,18]. The early appropriate treatment of Gram-positive isolates (such as CoNS) is possible by quick and easy isolation of these pathogens, which explains the lower mortality for infection with these microorganisms [17]. In accordance with the literature, infections with Gram-negative isolates had significantly higher and Gram-positive isolates had lower mortality rates in our study as well. We thought that the low virulence of CoNS isolates may also cause the lower mortality in bacteremic patients. When the impact of isolated pathogens on mortality was evaluated, etiological agents were found to be statistically different between fatal and non-fatal cases. Infections with *A. baumannii* and *Klebsiella* spp. were found independent predictors of mortality. *Klebsiella* spp. and *A. baumannii* isolates were usually resistant to most of the antimicrobial agents used empirically. Thus, the initial antimicrobial therapy was inappropriate for most *A. baumannii* and *Klebsiella* spp. infections. We thought that this resistance pattern and the invasive characteristics of the *A. baumannii* isolates had an impact on increased mortality.

Increasing incidences of BSIs with MDR Gram-negative strains as well as MDR Gram-positive strains among patients with malignancies have been recently reported. Since BSIs is associated with higher morbidity and mortality, it is important to know local epidemiology and resistance patterns of causative isolates [14,15]. Various studies have reported adverse effects of antimicrobial resistant Gram-negative infections on mortality in cancer patients with BSIs [5,14,18]. In our study, Gram-negative MDR isolates were responsible for 40%, whereas Gram-positive MDR isolates were responsible for 16.1% of all infection episodes. Similar to the findings of Rosa *et al*., methicillin resistance and the production of ESBL were the most commonly encountered resistance patterns of infectious agents in our study [10]. Although it was assessed widely in many studies, a clear relationship between fluoroquinolone prophylaxis and antibiotic resistance has not been demonstrated to date [14,19,20]. Since it was used in high-risk neutropenic cancer patients, we evaluated the effect of fluoroquinolone prophylaxis on the acquisition of MDR isolate infections in 126 febrile neutropenic episodes. Subgroup analysis showed no significant association between the use of quinolone prophylaxis and acquisition of Gram-negative MDR infections. However, the use of quinolone prophylaxis was significantly higher in infections with MDR Gram-positive isolates of the febrile neutropenic patients.

Unlike Gram-positive MDR isolate infections, the mortality rate was found to be significantly higher in Gram-negative MDR strain infections in the present study. Moreover, inadequate initial antibiotic treatment was determined to be an independent risk factor for mortality, similar to previous studies [15,21]. Since the multidrug resistance pattern reduces the number of effective antibiotic options, it is frequently associated with inadequate initial antibiotic therapy and poor outcome [14]. In addition to adequate empirical antimicrobial therapy, the status of host defenses also plays an important role in patient outcome. Poor outcomes of neutropenic patients with acute leukemia showed the importance of neutrophils in survival from Gram-negative sepsis [22]. It has also been reported that the severity of neutropenia has an impact on survival [23]. In the present study, prolonged neutropenia prior to the onset of infection was found to be an independent predictor of mortality. It is likely to be associated with profound neutropenia. It was observed in the present study that prolonged and profound neutropenia before infection onset has a statistically significant impact on mortality. In our study, HSCT recipients with infections had a significantly lower mortality rate than did other infected patients. We thought that this was due to improved physical conditions of HSCT units, including HEPA-filtered single rooms, higher compliance rates of the healthcare professionals to the

strict contact precautions, and lower rates of infections due to MDR isolates compared to hemato-oncology units.

Conclusions

Infections due to the Gram-negative isolates were found to be predominant in patients with hemato-oncological malignancies. The emergence of MDR isolates should be taken into account before starting empirical antibiotherapy, which is crucial in these high-risk patients. Because of the importance of appropriate empirical therapy to survival, it is becoming a clinical challenge to overcome infections in patients with hemato-oncological malignancies. Therefore, an empiric antimicrobial therapy protocol for hemato-oncology units according to local surveillance data of the hospital is crucial.

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