ORIGINAL PAPER

Inappropriate initial antimicrobial therapy for hematological malignancies patients with Gram-negative bloodstream infections

Yishu Tang[2] · Xinyu Wu[1] · Qian Cheng[1] · Xin Li[1]

Abstract

Background Inappropriate initial antimicrobial therapy (IIAT) may increase the mortality rate of hematological malignancies (HMs) patients with Gram-negative bacteria bloodstream infections (GN-BSI). The aim of this study is to determine whether IIAT affects the prognosis in this patient population and recommend the appropriate antibiotic regimen to minimize IIAT.
Methods We reviewed a retrospective cohort study of 361 HM patients with neutropenic fever from GN-BSI. The patients' clinical characteristics and the results of the drug sensitivity test in vitro were analyzed.
Results IIAT rate was 21.3% in HM patients with neutropenic fever caused by GN-BSI. There was a significant difference in 7-day mortality rate between patients treated with appropriate antibiotics and those with IIAT (7.7% vs 29.9%, $p < 0.01$). Multivariate analysis confirmed that IIAT was an independent risk factors for early mortality [4.860 (1.541–15.323)]. Drug sensitivity data of GN-bacteria suggested that carbapenems monotherapy or beta-lactamase inhibitors (BLBLI) combined with amikacin as the initial therapy can effectively reduce the IIAT rate. In the stratified antibiogram based on prior antimicrobial exposure, our results showed that BLBLI monotherapy could be initially used as an empirical treatment in patients without prior antimicrobial exposure. In those who had received prior antimicrobial exposure, BLBLI (especially piperacillin–tazobactam) combined with amikacin is recommended.
Conclusions IIAT was a critical factor contributing to the mortality of HM patients with neutropenic fever from GN-BSI.

Keywords Inappropriate initial antimicrobial therapy · Hematological malignancies · Gram-negative bloodstream infections · Febrile neutropenia

Introduction

Due to the baseline immunodeficiency, mucosal barrier destruction and neutropenia by cytotoxic treatments, patients with hematological malignancies (HMs) are at higher risk for bloodstream infections (BSI). According to estimated data, 11–38% of HM patients develop BSI while undergoing chemotherapy [1–3], resulting in 12–42% mortality [1, 2, 4–6]. Our previous study showed that Gram-negative bacteria (GN-bacteria) were the main pathogen for BSI in HM patients [7]. This subgroup in particular carries high mortality [1]. Early use of appropriate antibiotics has been shown to be one of the most important factors in improving the outcome of these patients.

Inappropriate initial antimicrobial therapy (IIAT) refers to the antibiotic regimen prescribed and administered during the first 72 h after suspecting BSI that was not active against the pathogen identified by culture and in vitro susceptibility testing [8–10]. IIAT plays an important role in the prognosis of patients with severe infections [9]. Previous studies reported that IIAT increased the hospital mortality rate and length of stay in solid cancer patients and critically ill patients complicated by GN-BSI [8, 9]. Among patients with sepsis or septic shock, the mortality rate of those treated with inappropriate initial antibiotics was significantly higher than those treated with appropriate antibiotics from the

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beginning [8, 9]. However, little data exist about IIAT in hematologic cancer patients.

In order to increase appropriate antibiotic usage and reduce the incidence and mortality of IIAT, guidelines recommend the application of cephalosporins (e.g., cefepime), beta-lactamase inhibitors (BLBLI) (e.g., piperacillin and tazobactam), and carbapenems as first-line empirical drugs or other antibiotics according to the local epidemiological data in HM patients presenting with neutropenic fever [11, 12]. However, in China, as reported by the CHINET monitoring network, the rate of drug resistance to fourth-generation cephalosporins is relatively high at 21.6–28.1% [13]. Moreover, in our study on HM patients, resistance to fourth-generation cephalosporins was as high as 37.3% (Table 4). This means that in Chinese HM patients with suspected severe infections, cephalosporins are not suitable as initial empirical treatment. On the other hand, with increased use of carbapenems in recent years, resistance to carbapenems has also risen,especially in *Klebsiella pneumoniae* (2.9% in 2005 to 24% in 2017) [13].

Therefore, we are faced with the challenge to choose the effective antibiotic for HM patients while avoiding breeding more drug resistance. In this retrospective study, we analyzed clinical data in patients with HMs and GN-BSI in South Central China to determine whether IIAT affects the prognosis of this population and to identify the risk factors leading to IIAT. Combined with the results of in vitro drug sensitivity tests, we aimed to formulate an algorithm for selecting the appropriate antibiotic regimen for patients with HMs complicated by GN-BSI, in order to reduce the occurrence of antibiotic resistance and achieve effective infection control.

Patients and methods

Setting and study design

This retrospective cohort study was evaluated by the Ethics Committee of the Central South University and deemed exempt from a formal review as no personally identifiable information would be collected. The requirement for informed consent from patients was waived. Data were extracted from the medical records of patients admitted to three university-affiliated tertiary care hospitals in Hunan Province, China, from January 2010 to April 2015.

Figure 1 shows the process of case selection. A total of 520 blood culture samples were collected from febrile patients during the study period, 361 (69.4%) of which were GN-bacterial. The utilization of anti-infection therapies was performed according to the guidelines [11, 14]. For patients who had more than one positive culture with the same speciation and sensitivity, only the first one was included for
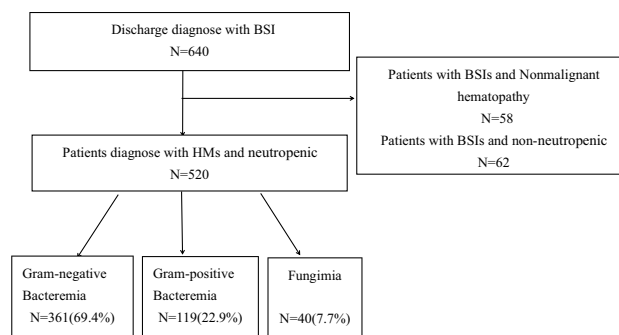

Fig. 1 Flowchart of patient selection

analysis. Blood culture samples which showed different bacterial strains within 48 h of each other were defined as polymicrobial bacteremia and were excluded from this study due to the limited sample size. Information about patients with positive blood cultures was then obtained and the utilization of antimicrobial therapy examined. Exclusion criteria for patients were: (1) no diagnosis of hematologic malignancy or diagnosed with other malignancies; (2) blood culture contamination; (3) loss to follow-up; (4) < 16 years old; (5) history of hematopoietic stem cell transplant (HSCT). The primary outcome was all-cause mortality within 7 days after BSI onset.

Definitions

The following data were collected for each patient: demographic information, malignancy diagnosis, disease status, comorbidities, causal species, presence of multi-drug resistance (MDR) infection, vital sign trends, laboratory data, and history of antibiotic therapy. BSI was defined by the isolation of infectious organisms from blood culture specimens in patients with compatible clinical signs and symptoms [15, 16]. Patient must have had either at least two blood cultures positive for bacteria other than skin contaminants (e.g., diphtheroids, *Bacillus* species., *Propionibacterium acnes*, coagulase-negative Staphylococcus, micrococci) or the presence of any bacterial species in at least one blood culture in patients with an central intravascular catheter (e.g., port-a-cath, central venous catheter, or peripherally inserted central catheter) [17]. In addition initiation of antimicrobial therapy was required as well as at least one of the following findings: temperature of > 38.0 °C or < 36.0 °C, chills, and systolic blood pressure < 90 mmHg. When single blood culture yielded skin contaminants and without compatible clinical signs and symptoms, the blood cultures were considered as contaminants and theses cases were not included [17]. Neutropenia and profound neutropenia were defined as an absolute neutrophil count (ANC) of < 500 cells/mm^3 and < 100 cells/mm^3, respectively [15]. Pitt bacteremia score

was calculated at the time of fever. Pitt bacteremia score is a simple score evaluation by calculating values of temperature, blood pressure, mental status, the presence or absence of mechanical ventilation and cardiac arrest [18]. The date of collection of the first positive blood culture (index culture) was regarded as the date of BSI onset. BSI were classified as nosocomial if the index blood culture was drawn more than 48 h after hospital admission [11]. MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories [19]. Disease status was assessed by the most recently available bone marrow biopsy and categorized as remission, relapsed, or uncontrolled malignancy, as previously defined [20]. According to our population characteristics and cutoff value, sustained neutropenia exceeding 21 days was defined as prolonged neutropenia. Acute respiratory failure and acute renal failure was defined as previously described [20]. Antibiotic exposure was defined as any antimicrobial therapy for more than 48 h in the previous month [21]. Our hospitals performed susceptibility testing using standard bacteriological methods and an automated system (Vitek II System; bioMerieux, Durham, NC, USA) according to Clinical & Laboratory Standards Institute (CLSI) guidelines [22].

Statistical analysis

Statistical analysis was done in SPSS version 19.0 for Windows. Chi-square tests were used for bivariate, and logistic regression was used for multivariate analyses. The cutoff value for continuous variables were set according to clinical practice or laboratory references by use of receiver operating characteristic curve (ROC). When fewer than 5% of data were missing, missing values for continuous variables were imputed to the mean and for categorical variables to the mode. All p values were two sided, and $p \leq 0.05$ was considered significant.

Results

Patient characteristics

We reviewed the clinical data of 361 HM patients complicated by GN-BSI, all of whom were admitted for neutropenic fever (Table 1). Over half of the patients were diagnosed with AML (55.4%), followed by ALL (34.3%). A majority (69.8%) was in relapse or uncontrolled disease states. Almost all (93.9%) had profound neutropenia, and 30.5% had prolonged low counts for more than 21 days. The most common pathogenic GN-bacteria was *Enterobacter* spp. (51.8%), followed by *K. pneumoniae* (19.9%), *P. aeruginosa* (14.1%), and *Enterobacter cloacae* (4.7%). Seventy-seven patients (21.3%) had received appropriate

Table 1 Demographic and clinical characteristics of study patients ($n = 361$)

Variables	N (%)
Demographic information	
Age > 60 years	38 (10.5)
Male sex	204 (56.5)
Underlying malignancies	
Acute myeloid leukemia	200 (55.4)
Acute lymphoblastic leukemia	124 (34.3)
Lymphoma	23 (6.4)
Other malignancies	14 (3.9)
Disease status	
Remission	109 (30.2)
Relapsed or uncontrolled	252 (69.8)
Risk factors	
Charlson Comorbidity Index > 3	45 (12.5)
Pitt bacteremia score ≥ 4	103 (28.5)
Neutropenia	
Profound neutropenia	339 (93.9)
Prolonged neutropenia	110 (30.5)
Previous chemotherapeutics	320 (88.6)
Receipt of corticosteroids	112 (31.0)
Dysfunctional organ systems	
Use of vasopressors	78 (21.6)
Acute respiratory failure	50 (13.9)
Causal microbial species	
Enterobacter spp.	187 (51.8)
Klebsiella spp.	72 (19.9)
Pseudomonas aeruginosa	51 (14.1)
Enterobacter cloacae	17 (4.7)
Acinetobacter baumannii	15 (4.2)
Stenotrophomonas maltophilia	9 (2.5)
Nonfermenting	75 (20.8)
Antibiotic therapy	
Prior antimicrobial exposure	228 (63.2)
Nosocomial bacteremia	309 (85.6)
MDR bacteremia	265 (73.4)
72-h IIAT	77 (21.3)
Laboratory parameters	
Hemoglobin < 70 g/dL	231 (64.0)
Platelet < 10 × 103 mm^{-3}	165 (45.7)
Albumin < 30 g/L	156 (43.2)
AST > 120 U/L	17 (4.7)
TBil > 34.2 μmol/L	41 (11.4)
PT > 14 s	150 (41.6)
7-Day mortality	45 (12.5)

MDR, multi-drug resistant; AST, aspartate aminotransferase; TBil, total bilirubin; PT, prothrombin time

antibiotics within 72 h of BSI onset, and 45 patients (12.5%) died within 7 days.

IIAT effect on early mortality

To determine whether IIAT affected the prognosis of the patients, we compared the mortality patients who were initially treated with sensitive antibiotics and those who were treated with resistant antibiotics (Fig. 2). Statistically significant increased mortality rates with IIAT was seen as early as 24 h (7.8% vs 18.7%) and the difference escalated with time at 72 h (7.7% vs. 29.9%).

In multi-variable analysis, IIAT remained an independent risk factor for 7-day mortality (Table 2, $p = 0.013$). Other patient characteristics contributing to the worse outcome included elderly age, presence of acute respiratory failure, disease state, platelet count, and Pitt score (supplementary Table 1, for reviewers' information only). These results suggest that IIAT significantly affects the mortality of HM patients with bloodstream infection.

Risk factors of IIAT

The preceding results showed that IIAT was an independent risk factor for early mortality. To find out what contributed to IIAT in our sample, we compared the clinical condition and therapeutic history of IIAT patients with non-IIAT patients (Table 3). In univariate analysis (supplementary Table 2, for reviewers' information only), the risk of IIAT increased in patients with ALL, previous antibiotic exposure, prolonged neutropenia, and respiratory failure. IIAT was not associated with age, gender or disease status ($p > 0.05$). In multivariate analysis, MDR bacterial infection, prolonged neutropenia and ALL remained independent risk factors for IIAT ($p < 0.05$).
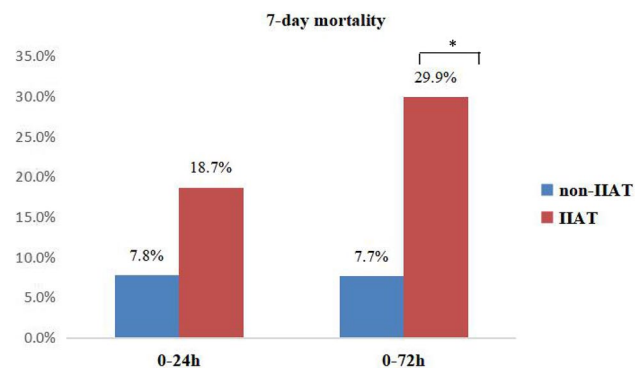
Table 2 Multivariate analysis of variables associated with 7-day mortality ($n = 361$)

Variables	OR (95% CI)	p
Age > 60 years	5.258 (1.263–21.887)	0.023
Acute respiratory failure	7.513 (2.196–25.699)	0.001
Disease relapsed or uncontrolled	102.236 (3.253–3213.591)	0.009
PLT $< 10 \times 10^3$ mm^{-3}	3.412 (1.194–9.751)	0.022
Pitt score ≥ 4	7.178 (1.987–25.929)	0.003
72-h IIAT	4.860 (1.541–15.323)	0.013

Antibiotic sensitivity in HM patients with GN-BSI

Table 4 lists the antibiotic susceptibility test results of different pathogens isolated from our sample population. Across all species, resistance to cephalosporins was high, up to 37.3%. Resistance to fluoroquinolones was also high at 45.9%. On the other hand, resistance to carbapenems, BLBLI (piperacillin–tazobactam and cefoperazone–sulbactam) and amikacin was relatively low at around 10%. MDR bacteria accounted for 73.4% of the resistance species. Nearly half (48.7%) of MDR bacteria were resistant to cephalosporins, and the resistance rates to BLBLI, carbapenems, and amikacin were relatively low, at 18.4%, 8.2% and 12.8%, respectively. Our results confirm high proportion of drug-resistant bacteria in HM patients with HM complicated by GN-BSI. The overall resistance rates of GN-bacteria were the lowest to carbapenems and aminoglycosides (such as amikacin), followed by BLBLI.

Appropriate antibiotics recommendation based on drug sensitivity and prior antibiotics exposure

As seen above, our patients often received IIAT when they were treated with fourth-generation cephalosporins recommended by established guidelines [11]. Therefore, we attempted to generate a recommendation for the combination of antibiotics according to the results of in vitro drug sensitivity of pathogens (Table 5). The sensitivity rate to carbapenem and cefoperazone–tazobactam monotherapy was nearly 90.0%. The results also indicated that only adding

Fig. 2 Initial antibiotic therapy and 7-day mortality of 361 isolates (*$p < 0.05$)

Table 3 Multivariate analysis of variables associated with IIAT ($n = 361$)

Variables	OR (95% CI)	p value
Acute lymphoblastic leukemia	1.977 (1.090–3.585)	0.025
Prolonged neutropenia	1.867 (1.069–3.261)	0.028
Acute respiratory failure	2.062 (1.043–4.076)	0.037
Prior antimicrobial exposure	2.692 (1.360–5.330)	0.004
MDR bacteremia	2.571 (1.182–5.595)	0.017

amikacin significantly improved appropriateness to cephalosporins and BLBLI, making antibiotics combinations more than 95% sensitive in vitro, which were significantly higher than those of monotherapies. Thus, carbapenem and cefoperazone–tazobactam monotherapy or combination of antibiotics selected based on antibiogram can reduce IIAT rate to less than 15%.

Our previous results showed that prior antimicrobial exposure was an independent factor in affecting IIAT, which can be explained by the previous utilization of antibiotics may lead to increased resistance of bacteria to subsequent antibiotics. To further explain this phenomenon we performed a statistical analysis on the effect of prior antimicrobial exposure (see Table 6). Our results showed that prior antimicrobial exposure may lead to a significant decrease in multiple antibiotic susceptibility except cefoperazone–tazobactam and carbapenems (imipenem or meropenem). For example, the sensitivity of cefepime for whom had received prior antimicrobial exposure decreased from 76.5 to 49.7% ($p < 0.001$), while the sensitivity of cefoperazone–sulbactam for whom had received prior antimicrobial exposure remain stable ($p = 0.761$). In addition, for patients who had not received prior antimicrobial exposure, the antibiotic sensitivity of cefepime, fluoroquinolones, aminoglycosides, piperacillin–tazobactam remain unsusceptible to most antibiotics (susceptibility rate was less than 85%), for

Table 4 Antimicrobial resistance for Gram-negative bacterial isolates

Gram-negative bacterium	Total no. of isolates (%)	No. of isolates (%) resistance to						
		Cefepime	Amikacin	Ciprofloxacin	Gentamicin	Imipenem or meropenem	Piperacillin–tazobactam	Cefoperazone–sulbactam
Total GN-bacteria	321 (100)	37.3	9.5	45.9	37.1	10	16.1	10.5
Escherichia coli	167 (46.3)	60	8	78.7	55.9	1.1	9.2	8.8
Klebsiella spp.	72 (19.9)	21.2	5.3	19.2	29.1	4.1	19.5	15.6
P. aeruginosa	51 (14.1)	4.3	1.7	5.2	1.7	5.4	8.6	7.1
Acinetobacter baumannii	15 (4.2)	84.6	63.6	80	80	87.5	86.7	37.5
Nonfermenting Gram-negative rods	75 (20.8)	24.6	16.9	21.4	21.9	29.7	26.4	11.8
MDR bacteria	265 (73.4)	48.7	12.8	60.2	47.6	8.2	18.4	14.5

Table 5 Appropriateness of various antibiotic combinations against Gram-negative pathogens in the study cohort

Antibiotic	Susceptible to at least one antibiotic plus								
	None	Ciprofloxacin	*p*	Amikacin	*p*	Gentamicin	*p*	Levofloxacin	*p*
Cefepime	62.7	70.7	0.076	93.7	<0.001	78.8	<0.001	66.3	0.014
Piperacillin–tazobactam	83.9	90.5	0.005	95.5	<0.001	91.6	0.001	85.1	0.486
Cefoperazone–sulbactam	89.5	89.9	0.854	95.6	0.034	92.5	0.330	90.5	0.709
Imipenem or meropenem	90.0	93.6	0.026	95.5	0.007	94.0	0.017	93.1	0.039

Table 6 Antimicrobial resistance with and without prior antimicrobial exposure

	Non-antimicrobial exposure			Prior antimicrobial exposure			*p*
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant	
Cefepime	76.5	1.7	21.7	49.7	3.6	46.7	<0.001
Amikacin	98.4	0	1.6	85.9	1.0	13.2	0.001
Ciprofloxacin	67.2	0.8	32.0	40.6	1.9	57.5	<0.001
Levofloxacin	69.3	6.3	24.4	46.8	1.8	51.4	<0.001
Gentamicin	78.3	0	21.7	51.2	0.5	48.4	<0.001
Piperacillin–tazobactam	89.3	3.3	7.4	73.6	5.8	20.7	0.002
Cefoperazone–sulbactam	85.1	8.4	9.5	86.8	2.9	10.3	0.761
Imipenem or meropenem	93.7	1.6	4.8	86.8	2.8	10.4	0.139

example, the sensitivities of cefepime was 76.5%. The sensitivities of carbapenems, BLBLI (cefoperazone–sulbactam and piperacillin–tazobactam)and amikacin were above 85%.

Discussion

This study examined issues related to IIAT in HM patients presenting with neutropenic fever caused by GN-BSI. The rate of IIAT was 21.3% among our patients. IIAT was associated with significant increase in mortality, by as much as sixfold in 7 days. IIAT remained an independent risk factor for early mortality in these patients after accounting for other demographic and clinical characteristics in our multivariate analysis.

It is generally believed that early use of appropriate antibiotics can improve prognosis, but controversy exists on the definitions of "early". Most studies suggest within 24–72 h of BSI onset [23, 24]. Our previous results demonstrated that the absence of appropriate antibiotics within 72 h, rather than 24 h, had a more significant impact on mortality rate. Therefore, in the current study, we adopted the 72-h time frame to assess the usage of sensitive antibiotics and IIAT.

The incidence of IIAT varies according to the underlying diseases, pathogenic bacteria species, and the degree of drug resistance [25, 26]. However, published data on IIAT in HM patients has been limited. Here we reported IIAT rate of 21.3% in HM patients with GN-BSI. In a previous study of 760 ICU patients with severe sepsis from GN-BSI, IIAT rate was 31.3% [25]. Other study focused on P. aeruginosa bacteremia reported an IIAT rate of 34.3% [26]. A much higher IIAT rate of 65% was observed in patients suffering from *Acinetobacter baumannii* bacteremia, most of whom were also on mechanical ventilation and had high APACHE II scores [27]. In comparison, the IIAT rate seen in our study might appear relatively low. One reason could be that our patients often (65.1%) received carbapenems or other broad-spectrum antibiotics as part of the initial regimen, following treatment protocols for neutropenic fever (supplementary material 3, for reviewers' information only). However, increasing use of carbapenem and other broad-spectrum agents aggravates drug resistance, which may in turn translate into higher IIAT rates in the future. Moreover, despite the lower IIAT rate in our population, it still had a significant adverse effect on patient mortality, compelling clinicians to aim for a lower IIAT in practice. We propose an institutionalized protocol based on local antibiogram and drug resistance rates of common pathogenic organisms to tackle this challenge.

In treating HM patients presenting with neutropenic fever caused by GN-bacteremia, the initial antibacterial therapy should cover the common pathogenic bacteria in order to reduce the occurrence of IIAT. This approach would help reduce patient mortality. Based on the data at our hospitals, carbapenems monotherapy or amikacin with BLBLI would be able to reduce the rate of IIAT to < 10%. However, due to the frequent use of carbapenems in recent years, antibiotics resistance of carbapenems is on the rise [13]. Carbapenems resistance is especially prominent among GN-bacteria and *Enterobacter* species (CRE, carbapenems-resistant Enterobacteriaceae), increasing from 3 to 20.9% in the last 10 years [13]. How to reduce the occurrence of IIAT while avoiding selecting for carbapenems resistance is one of the urgent issues in current anti-infection treatment. In this study, in vitro drug sensitivity test results showed that the rates of resistance to carbapenems, amikacin, and BLBLI, were less than 10%. Resistance to other drugs such as cephalosporins and fluoroquinolones was high. Moreover, according to the result of Table 6, we believe that either carbapenems, BLBLI could be used when patients with HMs had no prior antimicrobial exposure. Although amikacin has a low drug resistance rate, it is prone to generating resistant strains and should not be used alone [31]. In our analysis (Tables 5, 6) that amikacin combined with BLBLI are effective against more than 95% of pathogenic bacteria, which might be a strategy to reduce IIAT. Therefore, in order to reduce the incidence of carbapenems resistance, we suggested that BLBLI monotherapy could be used as the priority choice when patients with HMs had no prior antimicrobial exposure. In those who had received prior antimicrobial exposure, BLBLI (especially piperacillin–tazobactam) combined with amikacin is recommended. On a cautionary note, amikacin's nephrotoxicity and ototoxicity would limit its utility to short term treatment. Renal function and blood concentration of vancomycin should be monitored in time to minimize the occurrence of nephrotoxicity when BLBLI and amikacin combination when used concomitantly with empirical vancomycin for neutropenic fever prior to blood culture results. The combined therapy of amikacin and BLBLI was reported to have excellent effect against sepsis due to GN-bacteria [25], but few studies have been conducted in HM patients. A Turkey analysis showed that combination therapy of sulbactam–cefoperazone plus amikacin and imipenem–cilastatin monotherapy were equally effective empiric therapy for febrile granulocytopenic cancer patients [28]. However, since this study were older and the epidemiology of pathogenic bacteria is constantly evolving, the clinical significance of its conclusion could be debated.

Infection is the major cause of neutropenic fever in HM patients. 13–60% of HSCT recipients develop bloodstream infection (BSI), which are associated with 12–42% mortality [11]. Due to limitations on the timing of blood collection and blood culture technology, the yield of pathogenic isolates is often low. Our previous data show that the positive rate of blood culture was only 11.3% [7]. In this study, we included only patients with documented positive blood

cultures in order to assess IIAT. When HM patients are admitted with neutropenic fever, they are often in urgent need of early antibiotic treatment, but etiological evidence cannot be obtained immediately, so they receive empirical antibiotics. We suggest that institution and geographic drug resistance analysis of known common pathogens be extended to the HM patient population and the collective information used to guide empirical antibiotic administration. In addition, the epidemiological data of GN-bacteria in HM patients in Central and Southern China appear similar to those in other regions of the country (Northeast China) [29]. We speculate that the results of this study may be also applied to patients with neutropenic fever in those epidemiologically similar regions.

In the last, we want to say, although the result of blood culture is the golden standard to guide clinical medication, but the blood culture often takes long time. The results of pathogenic microorganisms can be obtained in a few hours by rapid diagnostics, but the results of drug sensitivity cannot be obtained [30]. Therefore, rapid diagnostics combined with existing bacterial susceptibility may allow patients with HMs to use appropriate antibiotics within 72 h.

This study has several limitations. First, as a retrospective study, we could not control the timing of antibiotic administration or blood culture collection. Delays in appropriate treatment caused by provider or organizational factors such as drug shortage could not be accounted. Second, the therapeutic regimen recommended in this paper was based strictly on in vitro drug sensitivity test. Amikacin combined with BLBLI is rarely used in actual clinical practice, and its specific efficacy remains to be confirmed by future prospective studies.

In summary, we showed that inappropriate initial antimicrobial therapy (IIAT) was one of the critical factors contributing to the mortality of HM patients with neutropenic fever from GN-bacteria bloodstream infections. In order to reduce the rate of carbapenems resistance, BLBLI monotherapy could be used as the priority choice when patients with HMs had no prior antimicrobial exposure. In those who had received prior antimicrobial exposure, BLBLI (especially piperacillin–tazobactam) combined with amikacin is recommended, thus could reduce the IIAT rate while preventing increase in carbapenem resistance.

Compliance with ethical standards

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