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A Prospective Observational Study of Antibiotic Therapy in Febrile Neutropenia Patients with Hematological Malignances from Multiple centers in Northeast China

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ABSTRACT

Objectives: Febrile neutropenia (FN) is a common but lethal complication of chemotherapy in hematological malignance. The aim of this study was to identify the prognostic risk factors for antibiotic treatment outcome in PN patients, and provide the optimal choice for the initial empirical antibiotic treatment.

Methods: 227 consecutive FN hematologic malignancies from four hospitals in Northeast China were enrolled. The outcome of antibiotic therapy was investigated until 14 days after the onset of FN. The factors affecting antibiotic therapy outcome were evaluated using Univariate analysis and Multivariate logistic regression analysis.

Results: Among all patients, 27 patients did not achieve favorable outcome either clinically or bacteriologically. It was shown that the risk factors for poor FN therapy outcome were associated with prolonged duration of neutropenia over 9 days during FN (P=0.019), slow neutrophil recovery (P=0.039), respiratory infection (P=0.005), and that initial monotherapy with drugs recommended by the guidelines indicated better outcome (P=0.009). Additionally, patients with multi-bacterial infection, as well as further ANC decrease after fever, had a poor prognosis.

Conclusions: Our results indicate that early application of antibiotics and prevention of respiratory infection as well as good clinical care are able to improve clinical outcomes from empirical antibiotic treatment in FN patients with hematological malignances.

1. Introduction

Febrile neutropenia (FN) represents a common but potentially lethal complication of chemotherapy in patients with hematological malignances[1–3]. Several studies have been performed in order to identify the potential risks which provide valuable information to select better intervention for clinical practice. Some previous studies have demonstrated that prolonged neutropenia correlates with worse outcome in FN[4,5]; however, inconsistent results regarding the effect of different durations of neutropenia on the outcome of FN still exist. In addition, because the symptoms and signs of inflammation are typically attenuated or even absent in a significant majority of FN patients, whether the documented clinical infection site can be considered as one of the prognostic risk factors was still controversial[6,7].

As the majority of infections in FN are predominantly Gram-negative, third generation cephalosporin, carbapenems or cephalosporin with anhydrase inhibitors have been recommended as the optimal initial choice for empirical therapy[8,9]. Although rapid and accurate antibiotic regimens in the first line could ensure better outcome in FN patients, increasing incidence of antibiotic

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resistances and changes of pathogen epidemiology require improved treatment strategies in FN patients, especially for the initial empirical approach. While monotherapy has become the standard regimen in the empirical approach[10,11], it is still unclear whether combination therapy should be used to prevent the development of multiple drug resistance (MDR)[12,13].

In this multicenter prospective observational study, 227 cases of FN with hematological malignances in Northeast China have been analyzed in order to determine the predictors of outcome of FN after antibiotic treatment as well as the optimal initial antibiotics therapy regimen.

2. Methods

2.1. Patient enrollment

This prospective observational study was conducted in multiple centers in Northeast China including 4 tertiary hospitals: Institute of Hematology and Blood Diseases Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College, the first center hospital of Tianjin, the Qilu affiliated hospital of Shandong medical school and the second affiliated hospital of Hebei medical university, which were abbreviated to X, Y, Q, and H respectively. All patients were diagnosed with hematologic malignances, including acute or chronic leukemia, Hodgkin or non-Hodgkin lymphoma, myelodysplastic syndrome, multiple myeloma, and others from April 2013 to August 2013. No fluoroquinolone prophylaxis was used for neutropenic patients. This study was approved through the ethics review process by the Institutional Review Board. Written informed consent was obtained from all registered patients before the study protocol was implemented.

2.2. Diagnostic definition

The febrile neutropenia was diagnosed with both parameters of fever and neutropenia as follows: (1) a single axillary temperature $\geq$ 38.3 °C or a temperature $\geq$37.8 °C sustained over a 1-h period, and (2) an absolute neutrophil count (ANC) $\leq$ 500 cells/mm^3 or an ANC that was expected to decrease to 500 cells/mm^3 during the following 48 h. Preindex characteristics (age and sex), and selected risk factors such as primary hematology disease, infectious history within a month before enrollment, especially the neutropenia duration including the whole phase of neutropenia, neutropenia before fever, as well as febrile neutropenia duration were evaluated. Complete blood count, blood urea nitrogen (BUN), creatinine, AST, ALT, bilirubin and albumin were examined before chemotherapy and on the initial day of FN. If a fever developed, at least two blood cultures, and, if appropriate, cultures from other suspected body sites were carried out. Additional blood cultures were performed if the patient's fever was sustained. The lowest leukocyte count and its change trend were recorded. For all strains isolated, the antibiograms were primarily determined with the disk diffusion method standardized according to the Swedish Reference Group for Antibiotics (SRGA). Pathogen isolates were classified either as susceptible (S), intermediate (I), or resistant (R), according to the SRGA breakpoints.

2.3. Therapeutic effect assessment

Three antibiotic treatment regimens were used in this study: Monotherapy with drugs recommended by the Guideline including Cefepime, Ceftazidime, Piperacillin/Tazobactam, Sulbactam/Cefoperazone, Meropenem and Imipenem (reference), Monotherapy with non-recommended drugs and combination therapy with Guideline recommended drugs plus others such as Teicoplanin or Linezolid. The therapeutic outcome with antibiotics was followed-up for 14 days after the onset of fever in the neutropenic patients. Patient data were collected, including baseline information, and a standardized case report form was used to evaluate antibiotic therapeutic outcome by researchers who were not involved in the study. Treatment effect was evaluated by clinical manifestation and microbiological results. The success of antibiotic therapy, labeled "a favorable outcome", was defined as defervescence at least for 3 days without any sign of persistent infection, and no pathogen growth or fungus in culture of different samples. If the outcome did not meet the described criteria, it was diagnosed as failure of antibiotic therapy or poor/unfavorable outcome.

2.4. Statistical analysis

Univariate analysis was performed for each episode variable, with poor outcome as the dependent variable. Multivariate logistic regression analysis was performed in order to identify independent predictors of poor outcome. We used the SAS program to confirm model reliability and validity by multi-collinearity analysis. A tolerance (TOL) below 0.1 was considered as having multi-collinearity. The SAS 9.2 software was used for all the statistical analysis. All the tests were two-tailed, and a P value below 0.05 was considered statistical significance.

3. Results

3.1. Patient characteristics

Two hundred and twenty seven FN patients with hematologic malignances were enrolled. Baseline characteristics were summarized in Table 1. The median patient age was 38 years (18-78), and the male to female ratio was 1.29:1. Diseases presented were acute leukemia, myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML), multiple myeloma (MM) and other hematological malignances. Most patients received standard or high dose of chemotherapy; 5.7% of patients had maintenance therapy. Seventy three patients had co-morbidity diseases. The most common co-morbidity was respiratory system disease (9.25%), followed by cardiovascular disorders. The majority of FN occurred after chemotherapy in hospitals; 15.4% of patients contracted FN outside the hospitals. 162 patients had central venous catheters and 46.7% of patients had infection history within one month.

3.2. Overall outcome evaluation

The overall failure rate from antibiotic treatment was 11.9% (27 cases) and the mortality rate was 0.8% (2 patients) in this study. Among those patients, 12 were clinically diagnosed as probable invasive fungal infection. After antibiotic treatment, the outcome was no different with respect to gender, fever onset out of the hospitals, indwelling time of central venous catheter, disease status, MASCC risk, chemotherapy regimen for hematological malignances, or pre-infection history (Table 2 and Table 3). Although 12.6% of patients (26 cases) at age less than 60 had a higher unfavorable outcome than patients (n=1, 4.8%) over 60 years old, no statistical significance was reached (Tables 2 and 3, $p > 0.3$).

3.3. The effect of antibiotic treatment regimens on outcome

For antibiotic treatment, three regimens were applied in this study: monotherapy with drugs recommended by the Guideline, monotherapy with drugs beyond the Guideline and combination therapy. 8.4% (n=13) and 14.8% (n=4) of patients had poor results after treatment with monotherapy with drugs recommended by the Guideline and combination therapy, respectively ($p > 0.1$, Tables 1–3). Significantly higher incidence of favorable outcome

Table 1
Characteristics of FN patients with hematology malignances.

	Favorable outcome(n)	Unfavorable outcome(n)	Total(n)
Center			
X	114	23	137
H	26	1	27
Q	22	2	24
Y	38	1	39
Sex			
Male	110	18	128
Female	90	9	99
Fever onset			
Outside the hospital	30	5	35
Nosocomial infection	170	22	192
Central-venous catheter			
Yes	145	17	162
No	55	10	65
Diagnosis			
AML	141	21	162
ALL	45	3	48
MDS	5	3	8
MM	1	0	1
CML	5	0	5
Co-morbidity disease			
No	135	19	154
Cardio-vascular system	8	1	9
Respiratory system	19	2	21
Digestive or urinary system	6	1	7
others	19	3	22
missing	13	1	14
MASCC score			
High risk	59	11	70
Low risk	141	16	157
Disease Status			
Controlled	123	13	136
Uncontrolled	77	14	91
Chemotherapy			
Standard dose	141	21	162
High dose	42	4	46
Maintenance	17	2	19
Infectious history			
Yes	91	15	106
No	109	12	121

Abbreviations: X, Institute of Hematology and Blood Diseases Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College; Y, the first center hospital of Tianjin; Q, affiliated Qilu hospital of Shandong medical school; H, the second affiliated hospital of Hebei medical university; MASCC score, Multinational Association for Supportive Care in Cancer; AML, acute myelogenous leukemia; ALL, acute lymphocte leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; CML, chronic myelogenous leukemia.

was observed in patients treated with Guideline recommended monotherapy drugs (OR=0.124, p=0.009, Tables 2 and 3).

3.4. The effect of neutropenia on outcome of antibiotics treatment

It is well known that the severity and duration of neutropenia impact the therapeutic outcome of antibiotics. In this study, the median neutropenia duration was 11 days (1-69 days, Table 2). To predict the effect of neutropenia on antibiotics treatment, we studied three aspects: the durations of neutropenia before and after fever occurrence, as well as the trend of neutropenia after fever. It was shown that neutropenia duration before fever and the whole duration of neutropenia were not associated with the treatment response in FN patients. Patients with longer duration of neutropenia after fever (more than 9 days) had poor antibiotic treatment outcome ($p \leq 0.005$, Tables 2 and 3). After chemotherapy, the kinetics of ANC recovery also played a role in achieving favorable outcome. The ANC increase during day 10-14 after chemotherapy was observed in 185 patients with favorable outcome (92.5%), however, only 17 patients (63%) with unfavorable outcome had ANC increase during this period (p=0.039, Tables 2 and 3). Although multivariant analysis did not reveal the relationship between ANC decrease after fever with antibiotic treatment outcome, the patients with further ANC decrease after fever had unfavorable outcomes with univariate analysis (p=0.0308, Tables 2 and 3).

Table 2
The results of antibiotics treatment.

	Favorable outcome (%)	Unfavorable outcome (%)	Total(n)
Sex			
Male	110(85.9)	18(14.1)	128
Female	90(90.1)	9(9.9)	99
Fever onset			
Outside the hospital	30(85.7)	5(14.3)	35
Nosocomial infection	170(88.5)	22(11.5)	192
Central-venous catheter			
Yes	145(89.5)	17(10.5)	162
No	55(84.6)	10(15.4)	65
Age			
≤ 60	180(87.4)	26(12.6)	206
>60	20(95.2)	1(4.8)	21
Co-morbidity disease			
No	135(87.7)	19(12.3)	154
Cardio-vascular system	8(88.9)	1(11.1)	9
Respiratory system	19(90.4)	2(9.6)	21
Digestive or urinary system	6(85.7)	1(14.3)	7
others	19(86.4)	3(13.6)	22
missing	13(92.6)	1(7.4)	14
MASCC score			
High risk	59(84.3)	11(15.7)	70
Low risk	141(89.8)	16(10.2)	157
Disease Status			
Controlled	123(90.4)	13(9.6)	136
Uncontrolled	77(84.6)	14(15.4)	91
Chemotherapy			
Standard dose	141(87.0)	21(13.0)	162
High dose	42(91.3)	4(8.7)	46
Maintenance	17(89.5)	2(10.5)	19
infectious history			
Yes	91(85.8)	15(14.2)	106
No	109(90.1)	12(9.9)	121
ANC decline*			
Yes	81(82.7)	17(17.3)	98
No	119(92.2)	10(7.8)	129
ANC recovery*			
Increase*	185 (91.5)	17 (8.5)	202
Decline	15 (60)	10 (40)	25
Neutropenia pre-fever			
>2d	107(87.7)	15(12.3)	122
≤2d	92(89.3)	11(10.7)	103
Missing	1(50.0)	1(50.0)	2
FN duration*			
>9d	62(78.5)	17(21.5)	79
≤9d	134(93.7)	9(6.3)	143
Missing	4(80.0)	1(20.0)	5
Bacterium*			
G-	41(91.1)	4(8.9)	45
G+	11(78.6)	3(21.4)	14
Multi-bacterial*	25(75.8)	8(24.2)	33
Unidentified	123(91.1)	12(8.9)	135
Infection site*			
Not respiratory	69(95.8)	3(4.2)	72
Respiratory*	92(80.7)	22(19.3)	114
Unidentified	39(95.1)	2(4.9)	41
Antibiotics*			
Combination	23(85.2)	4(14.8)	27
Recommended Mono-*	141(91.6)	13(8.4)	154
Not recommended Mono-	36(78.3)	10(21.7)	46
Anti-coccus			
Yes	81(83.5)	16(16.5)	97
No	119(91.5)	11(8.5)	130

Abbreviations: MASCC score, Multinational Association for Supportive Care in Cancer; ANC decline, ANC continue to decline after fever; ANC Recovery: ANC during the day 10∼14 after chemotherapy when compared to the lowest count of ANC during therapy.
* indicates the statistical significance for the factors (refer to Table 3).

Table 3
Univariant and multivariant analyses of FN outcome

Item	Univariant analysis				Multivaiant analysis			
	OR	P	95%	CI	OR	P	95%	CI
Sex								
Female	0.611	0.254	0.262	1.426	0.336	0.127	0.083	1.365
Male	Reference	-	-	-	Reference	-	-	-
Age								
<=60y	0.346	0.310	0.045	2.689	153.804	0.577	<0.001	>999.99
>60y	Reference	-	-	-	Reference	-	-	-
Infection Onset place								
Nosocomial	0.776	0.635	0.273	2.20	0.799	0.820	0.115	5.543
Outside hospital	Reference	-	-	-	Reference	-	-	-
Disease Status								
Uncontrolled	1.72	0.187	0.768	3.855	0.985	0.983	0.234	4.140
Controlled	Reference	-	-	-	Reference	-	-	-
Chemotherapy								
High-dose	0.639	0.435	0.208	1.966	1.931	0.471	0.322	11.572
Maintenance	0.79	0.763	0.17	3.667	1.979	0.578	0.178	21.963
Standard dose	Reference	-	-	-	Reference	-	-	-
MASCC score								
Low risk	0.609	0.238	0.267	1.39	0.453	0.266	0.112	1.831
High risk	Reference	-	-	-	Reference	-	-	-
Pre-infection history								
No	0.681	0.352	0.304	1.529	1.023	0.973	0.264	3.961
Yes	Reference	-	-	-	Reference	-	-	-
ANC decline trend at the beginning	2.498	0.030	1.088	5.731	1.357	0.682	0.315	5.852
ANC recovery	0.138	<.0001	0.054	0.353	0.167	0.039	0.030	0.920
Duration of neutropenia before fever								
>2d	1.021	0.151	0.992	1.051	1.102	0.449	0.856	1.419
<=2d	Reference	-	-	-	Reference	-	-	-
Duration of FN								
>9d	4.082	0.001	1.724	9.669	5.456	0.019	1.315	22.638
<=9d	Reference	-	-	-	Reference	-	-	-
Pathogenic bacterium								
G-	1	1	0.306	3.272	1.774	0.542	0.280	11.228
G+	2.796	0.152	0.684	11.422	1.508	0.745	0.126	18.116
Multi-bacteria	3.28	0.019	1.216	8.851	3.675	0.107	0.752	17.950
No documented	Reference	-	-	-	Reference	-	-	-
Infection site								
Not respiratory infection	0.848	0.859	0.136	5.295	1.230	0.878	0.087	17.443
Respiratory infection	4.663	0.043	1.045	20.798	30.181	0.005	2.801	325.217
Unknown of origin	Reference	-	-	-	Reference	-	-	-
Initial antibiotic therapy								
Combination	1.886	0.301	0.566	6.289	1.264	0.850	0.111	14.359
Not recommended	Reference	-	-	-	Reference	-	-	-
Mono-drug	0.332	0.016	0.135	0.818	0.124	0.009	0.026	0.606
Anti-coccus	0.626	0.740	0.175	2.234	0.914	0.898	0.230	3.639

Abbreviations: MASCC score, Multinational Association for Supportive Care in Cancer; ANC decline, ANC continue to decline after fever; ANC Recovery: ANC during the day 10~14 after chemotherapy when compared to the lowest count of ANC during therapy; Mono-drug, mono-drug recommended by the Guideline, including Cefepime, Ceftazidime, Piperacillin/Tazobactam, Sulbactam/Cefopcrazone, Meropenem and Imipenem.

3.5. Infection sites impact antibiotic treatment result

Of the 227 patients, no infection sites were found in 39 (16.74%) patients (Table 2). The most common infection site was the respiratory tract (114 patients, 50%, Table 2), followed by multi-site infections. No difference was shown for antibiotic treatment outcome between patients with documented infection sites and those without clear infection ($p>0.05$, Table 3). However, in patients with respiratory infections, 22 patients (19.3%) had unfavorable outcomes, whereas a poor outcome was only found in 4.2% (n=3) and 4.9% (n=2) of patients with non-respiratory infection or no documented infection, respectively ($p<0.05$, Tables 2 and 3).

In our study, all 12 cases with BSI achieved favorable outcomes (Table 4). One BSI patient did not have a central venous catheter. No catheter infection was diagnosed in the other 11 patients. The low rates of catheter infection may be attributed to valid and strict nursing procedure. Seven of the 12 BSI patients had a previous infection before enrollment. The median neutropenia duration for BSI patients was 7 days, similar to the total group. One BSI patients received meropenem plus linezolid because of the previous G+ bacterium infection, and others received monotherapy of drugs recommended by the guidelines.

3.6. Pathogen survey and drug resistance result

We have carried out 492 episodes of bacterium culture in 227 patients; the pathogens were isolated from 169 episodes (Table 5). Gram-negative bacteria were isolated in 116 episodes (68.64%) from 45 patients, with Escherichia being the most common (Table 5). 14 patients had Gram-positive bacterial infection, which accounted for 31.36% of pathogen positive episodes; *Staphylococcus epi.*, *E. faecalis* and *Enterococcus faeium* were the most common G+ bacteria (Table 5). The outcome from antibiotic treatment was comparable in patients with G- bacterium infection and those without isolated bacterium (8.9% for both); however, a poor result was observed in patients with multiple bacterial infections (24.2%,, $p<0.05$ when compared to patients with no bacterium infection, Table 3). Among isolated G- bacteria, all except pseudomonas and stenotrophomonas maltrophilia were

Table 4
Patients with BSI

No	center	sex	age	Central-venous catheter	MASCC score	Duration of neutropenia(day)	Pathogens isolated
1	X	Male	31	Yes	High-risk	13	*Escherchia coli.*
2	X	Male	74	Yes	Low-risk	14	*Escherchia coli.*
3	X	Male	20	Yes	High-risk	3	*Klebsiella.*
4	X	Male	29	Yes	Low-risk	6	*Escherchia coli.*
5	X	Male	47	No	Low-risk	14	*Enterobacter.*
6	X	Male	45	Yes	Low-risk	4	*Enterobacter.*
7	X	Male	20	Yes	High-risk	6	*Staphylococcus. epidermidis*
8	X	Male	30	Yes	Low-risk	5	*Klebsiella.*
9	X	Male	25	Yes	High-risk	9	*Escherchia coli.*
10	X	Male	39	Yes	High-risk	7	*Klebsiella.*
11	X	Female	33	Yes	Low-risk	7	*Klebsiella.*
12	Y	Female	20	Yes	Low-risk	10	*Escherchia coli.*

Abbreviations: X, Institute of Hematology and Blood Diseases Hospital of Chinese Academy of Medical Sciences and Peking Union Medical College; Y, the first center hospital of Tianjin; Q, affiliated Qilu hospital of Shandong medical school; H, the second affiliated hospital of Hebei medical university; MASCC score, Multinational Association for Supportive Care in Cancer.

Table 5
Isolated bacterium from 492 episodes in 227 patients with documented infection sites

Isolated bacterium	No.	%
G-	116	68.64
Escherchia coli.	39	23.08
Klebsiella.	25	14.79
Enterobacter.	9	5.33
Pseudomonas.	15	8.88
Stenotrophomonas maltrophilia	5	2.96
Acinetobacter.	13	7.69
Proteus.	3	1.78
Morganella.	1	0.59
Serratia marcescens	3	1.78
Areomonas.	3	1.78
G+	53	31.36
Staphylococcus aureus	4	2.37
Staphylococcus epidermidis.	16	9.47
Enterococcus faeium	8	4.73
Enterococcus faecalis	12	7.10
Enterococcus avium	1	0.59
Hemolytic strepcocci	9	5.33
Staphylococcus hominis	2	1.18
Leukonoid	1	0.59

susceptive to imipenem and meropenem. It was demonstrated that all strains of G- bacteria isolated from some patients were ceftazidime resistant (Table 6). All G+ bacteria were sensitive to vancomycin, teicoplanin, linezolid and tigecycline. Some G+ bacteria were resistant to ciprofloxacin (Table 6).

4. Discussion

In this study, we demonstrated that a favorable outcome with empirical antibiotic treatment was obtained in FN patients with hematological malignancies from four centers in Northeast China when patients had short periods of neutropenia without documented respiratory infection after chemotherapy for primary diseases. The continuous decline of ANC after fever and slow neutrophil recovery as well as the presence multi-bacterial infection significantly impact antibiotic treatment outcome.

Although both degree and duration of neutropenia have been considered as vital factors influencing antibiotic therapy effects in neutropenia patients, some other studies have shown different results. Rosa, et al. found that several other factors, including relapsed underlying disease status, were independently associated with mortality within 28 days, but not the duration of neutropenia[14]. Similar results were obtained by Yong Park and colleagues[15]. In our study, we separated the duration of neutropenia into two stages based on the onset of fever: neutropenia before FN and neutropenia duration after fever. In univariate analysis, neither the whole duration of neutropenia nor neutropenia duration before FN was associated with the patient's outcome. However, prolonged neutropenia after fever lasting more than 9 days was identified as one of the risk factors for poor outcome. Additionally, it is worth noting that the kinetics of ANC recovery also impact FN patients' outcome: it holds true that early ANC recovery leads to better outcome. Furthermore, an unfavorable outcome was observed when ANC continued to decline after fever in univariate analysis (OR=2.498, P=0.030), although this

Table 6
Resistance of Gram-negative and Gram-positive bacteria

Species						
Gram-negative	**ciprofloxacin**	**TZP**	**ceftazidime**	**Cefepime**	**imipenem**	**meropenem**
Escherchia coli.	15(40.54%)	2(5.1%)	5(27.8%)	2(5%)	0	0
Klebsiella.	3(12%)	1(4.2%)	2(25%)	2(8%)	1(4%)	1(4%)
Pseudomons.	0	1(7.1%)	1(7.1%)	1(6.7%)	2(13.3%)	2(13.3%)
Acinetobacter.	0	0	2(18.2%)	0	0	0
Enterobacter.	3(37.5%)	0	2(22.2%)	2(22.2%)	0	0
Stenotrophomonas maltrophilia	-	-	1(25%)	1(25%)	4(100%)	1(100%)
Gram-positive bacteria	**ciprofloxacin**	**vancomycin**	**teicoplanin**	**linezolid**	**Tigecycline**	
Staphylococcus aureus	2(50%)	0	0	0	0	
Staphylococcus epidermidis.	2(12.5%)	0	0	0	0	
Enterococcus faeium	6(100%)	0	0	0	0	
Enterococcus faecalis	2(18.2%)	0	0	0	0	
Hemolytic strepcocci	7(77.8%)	0	0	0	0	

Abbreviations: TZP, Piperacillin -Tazobactam.

relationship was not found by multivariate analysis (OR=1.357, P=0.682). As the tendency of ANC to decline is observed in the very early stages of FN, it would be a promising prognostic factor to predict antibiotic treatment responses.

In spite of reduced absolute neutrophil count (ANC), lack of signs or symptoms and the low positive rates of bacterium isolation make it hard to find the clear infection site in FN patients. No documented infection sites usually have better prognostics after antibiotics treatment. Klastersky, et al. reported that mortality was 13% in FN patients without a clinical site of infection and 23% with documented infection sites[16]. In contrast to the above observation, no difference was obtained for antibiotic treatment results regardless of clear infection site or not, which may be attributed to effective and early antibiotics application in our study. It is interesting to note that patients with respiratory infection had worse outcomes than those with no infection site identified during FN in this study (OR=31.181, P=0.005). The same observation was demonstrated in other studies[17].

Bloodstream infection (BSI) has been considered as a risk factor of FN unfavorable outcome[18–21]. Surprisingly, all 12 cases with BSI achieved favorable results in our research. The most common bloodstream isolate was *Escherichia coli*, followed by *Klebsiella pneumonia*, and *Staphylococcus. epi*., which is in good agreement with the study conducted by Ali. N and collegues[22]. Similar results were also observed in another retrospective research study[23]; *E.coli* was more common in the neutropenic group when compared to the non-neutropenic one (22.7% vs 2.5%.p<0.001). It is well-accepted that the translocation of gut organisms is the major cause for E.coli BSI. In this study, no BSI case was identified in catheter-related episodes even though *staphylococcus epi* was isolated in one patient. This result implicates that timely checking and strict care reduce catheter related infection.

Empirical therapy with antimicrobials is always used in patients with FN, even without clear microbiological evidence. Previous meta-analysis has suggested that empirical monotherapy of third generation cephalosporins and carbapenems was as effective, or even more effective, than combination therapy[12,13]. The Guideline of antibiotics drugs for FN patients has recommended sulbactam/cefopcrazone, piperacillin/tazobactam, cefepime, ceftazidime or carbapenem including meropenem and imipenem as the first choice for the initial treatment[4,11,13]. However, many clinicians would rather choose a combination regimen for FN patients comparable with a low-risk one based on availability, costs, ease of administration and local antibiogram. For example, in a prospective research study that involved 2092 bacteraemias in neutropenic patients, empirical therapy with amikacin was reported to be associated with lower mortality (OR 0.50, p=0.016)[24]. In this study, we compared antibiotic treatment outcome from 3 regimens: monotherapy with antibiotics recommended from the Guideline, combination therapy, and the monotherapy with fluoroquinolone, amikacin and other third generation cephalosporins. Multivariate analysis showed that monotherapy with antibiotics recommended by the Guideline as initial therapy could benefit FN patients by reducing the risk of treatment failure, compared with the regimen of antibiotics beyond the recommendation. Additionally, the combination regimen had no advantages over monotherapy with recommended antibiotics. Based on the results from the bacterial etiology and antibiogram, no drug resistant bacterium was isolated after treatment with our regimens. These results suggest that the monodrug regimen with cefepime, ceftazidime, carbapenem, sulbactam/cefopcrazone or piperacillin/tazobactam is the optimal initial approach in empirical treatment. Although there was no significant difference for achieving a favorable outcome between patients with G+ isolates and patients without documented infection sites, due to limited number of patients with G+ bacterium, we did not perform further analysis to evaluate the role of monotherapy. However, based on the sensitivity of G+ isolates to antibiotics, the combination therapy should be recommended if a Gram-positive infection exists. Vancomycin and other anti-coccus drugs should not be routinely used as part of initial empirical therapy, but would achieve a favorable outcome when pathogen is isolated[25].

In conclusion, the outcome of antibiotic treatment in FN patients with hematological malignancies after chemotherapy was closely related to the duration of neutropenia, the kinetics of neutrophil recovery, respiratory infection and utilization of empirical therapy with drugs recommended by the Guideline. Good clinical practice with optimization of the inpatient environment and strict patient care decreases the risk of unfavorable outcomes from antibiotic treatment. Early application of empirical drugs and effective prophylaxis of respiratory infection will improve overall clinical results.

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