



A Prospective Observational Study of Antibiotic Therapy in Febrile Neutropenia Patients with Hematological Malignancies 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 malignancy. The aim of this study was to identify the prognostic risk factors for antibiotic treatment outcome in FN 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 malignancies.

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1. Introduction

Febrile neutropenia (FN) represents a common but potentially lethal complication of chemotherapy in patients with hematological malignancies^{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 anhydase 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 malignancies 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 malignancies, 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 ≥ 38.3 °C or a temperature ≥ 37.8 °C sustained over a 1-h period, and (2) an absolute neutrophil count (ANC) ≤ 500 cells/mm³ or an ANC that was expected to decrease to 500 cells/mm³ 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/Cefoprazone, 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 malignancies 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 malignancies. 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 malignancies, 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

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