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# Randomized controlled trial comparing ciprofloxacin and cefepime in febrile neutropenic patients with hematological malignancies

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SUMMARY

*Background:* Ciprofloxacin (CPFX) is a potential alternative in patients with febrile neutropenia (FN) because of its activity against Gram-negative organisms. We conducted a non-inferiority, open-label, randomized controlled trial comparing intravenous CPFX and cefepime (CFPM) for FN patients with hematological malignancies.

*Methods:* Patients aged from 15 to 79 years with an absolute neutrophil count of $<0.500 \times 10^{9}$/l were eligible, and were randomized to receive 300 mg of CPFX or 2 g of CFPM every 12 h. Initial treatment efficacy, overall response, and early toxicity were evaluated.

*Results:* Fifty-one episodes were included in this trial, and 49 episodes (CPFX vs. CFPM: 24 vs. 25) were evaluated. Treatment efficacy at day 7 was significantly higher in the CFPM group (successful clinical response: nine with CPFX and 19 with CFPM; $p = 0.007$). The response was better in high-risk patients with neutrophil counts of $\leq 0.100 \times 10^{9}$/l ($p = 0.003$). The overall response during the study period was similar between the CPFX and CFPM groups ($p = 0.64$). Adverse events were minimal, and all patients could continue the treatment.

*Conclusions:* We could not prove the non-inferiority of CPFX in comparison with CFPM for the initial treatment of FN. CFPM remains the standard treatment of choice for FN.



## 1. Introduction

The goal of initial empiric antibiotic therapy for febrile neutropenia (FN) with hematologic malignancies is to prevent serious morbidity and mortality due to bacterial pathogens, until the results of blood cultures are available to guide more precise antibiotic choices. Although Gram-positive bacteria have increased as pathogens in FN during the past 20 years, Gram-negative bacteria are associated with a greater mortality.[1] In particular, *Pseudomonas aeruginosa* infection is associated with a higher mortality,[2] and coverage of this organism remains an essential component of the initial empiric antibiotic regimen. A commonly used therapy for FN is a combination of β-lactam antibiotic and aminoglycoside, which offers a broad spectrum of initial coverage, including *P. aeruginosa*.[3,4]

Although combination therapy with a β-lactam antibiotic and an aminoglycoside has been reported to be highly effective for neutropenic patients,[3,4] aminoglycosides have some serious adverse effects such as renal dysfunction and ototoxicity. Antibiotics as monotherapy are generally less toxic, less costly, and more convenient to administer to patients than combination therapy,[5] so monotherapy with a fourth-generation cephem or carbapenem has been applied and compared to combination therapy in randomized controlled trials; these did not show diminished effectiveness of monotherapy.[6–9] Monotherapy is now also recommended as standard therapy in the Infectious Diseases Society of America (IDSA) guidelines 2010.[10]

However, the incidence of drug-resistant bacterial species in the institute should be taken into consideration when using monotherapy, because resistant bacteria would tend to result in

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treatment failure in the case of monotherapy compared with combination therapy.[5] In fact, extended-spectrum β-lactamase (ESBL)- and metallo-β-lactamase-producing Gram-negative bacteria are emerging at an increasing rate, and these cause significant mortality.[11–13] In this context, alternative effective regimens other than β-lactams are warranted for neutropenic patients to overcome the resistant bacteria.

Ciprofloxacin (CPFX) is an attractive drug that has wide coverage against Gram-negative organisms including *P. aeruginosa*, good pharmacokinetic characteristics, and an absence of the need for drug level monitoring.[14,15] A number of studies have demonstrated that CPFX combined with a β-lactam is effective for neutropenic patients.[16–18] Furthermore, CPFX inhibits DNA gyrase of prokaryotic organisms,[14] and the drug mechanism is completely different from that of β-lactams. Therefore, CPFX may be active for some organisms resistant to β-lactams and it would be acceptable for those who are allergic to β-lactams.[19] In this context, CPFX is a potential alternative for the empiric treatment of patients with FN. However, monotherapy with CPFX has been less well reported and is not well established in the treatment of FN patients.

To assess the possibility of increasing the choice of initial treatment for FN, we designed a randomized controlled trial of intravenous CPFX vs. cefepime (CFPM) in FN patients. This trial aimed to prove its non-inferiority compared to CFPM, a standard therapy for FN.

## 2. Materials and methods

From January 2005 to December 2009, a non-inferiority, open-label, randomized, multicenter trial was conducted to evaluate the efficacy of intravenous CPFX for FN. The study was approved by both the protocol committee and the institutional review board of each institution. Informed consent was obtained from all patients before registration in this study. The study was registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR number: UMIN C000000083) and at ClinicalTrials.gov (identifier: NCT00137787). Randomization was performed automatically, stratified by primary disease and balanced in each institute, at the time of enrollment, on a website operated by the Center for Supporting Hematology-Oncology Trials (C-SHOT) data center.

## 3. Definitions

Fever was defined as an axillary temperature of not less than 38 °C, or of 37.5–38 °C sustained for more than 1 h. Resolution of fever was defined as a maximum temperature of less than 37.5 °C sustained for three successive days, and the first day was defined as the date the fever disappeared. Fever was considered to be worse when at least one of the following criteria was met: more than 1 °C elevation in maximum body temperature, change from remittent fever to continued fever, emergence of new infectious foci, blood culture positivity after administration of antibiotics, more than 10% fall in arterial $O_2$ pressure or oxygen saturation, and a decline of performance status.

Episodes of fever were classified as microbiologically documented infection, clinically documented infection, or fever of unknown origin (FUO). Microbiologically documented infection was defined as the isolation of microorganisms. Clinically documented infection was considered when there were foci of infection on physical examination or clinical data, without microbiological documentation. FUO was considered when there was no clinical or microbiological evidence of infection in a febrile episode.

Neutropenia was defined as an absolute neutrophil count (ANC) of $<0.500 \times 10^9$/l or that from $0.500 \times 10^9$/l to $0.100 \times 10^9$/l showing a decline compared with the level at the last examination. Recovery of neutropenia was defined as an ANC of $\geq 0.500 \times 10^9$/l sustained for 24 h after ANC had dropped to $<0.500 \times 10^9$/l. The first day was considered to be the recovery date.

### 3.1. Patients

Patients had to meet all of the following criteria for inclusion in the study: age 15–79 years, at least one episode of fever, neutropenia within 72 h, total bilirubin of 2.0 times the upper limit of normal (ULN) or less, creatinine of 1.5 times ULN or less, and giving informed consent. Patients were excluded if they had a history of allergic reaction to antibiotics, HIV infection, were pregnant or lactating, had a family history of deafness, had received antibiotics in the last 14 days, had received an antifungal or antiviral agent, ketoprofen, or sodium valproate, were infected with bacteria resistant to agents used in this study, were in septic shock, or other inappropriate cases as judged by a physician. If the ANC did not recover to $\geq 1.000 \times 10^9$/l after the last episode of fever, the patient was also ineligible for this study.

### 3.2. Treatment

Patients received 300 mg of CPFX or 2 g of CFPM intravenously every 12 h immediately upon the development of FN. Treatment was continued until patients met the criteria for treatment discontinuation as follows: fever absent for more than 48 h (ANC of $\geq 0.500 \times 10^9$/l) or for more than 5 days (ANC from $0.100 \times 10^9$/l to $0.500 \times 10^9$/l) without any symptoms. If the associated symptoms worsened or were sustained during the study period, the treatment was modified according to the study protocol (Figure 1). From 72 h to 120 h after the study started, an aminoglycoside was added to the treatment if fever symptoms worsened. From 120 h to 168 h, the initial antibiotic was discontinued and the combination therapy of carbapenem (meropenem or imipenem), aminoglycoside, and antifungal agents was started. After 168 h, patients were allowed to receive any treatment as required if fever persisted. Patients could receive granulocyte colony-stimulating factor, if required, at any time.

### 3.3. Clinical and laboratory evaluations

Clinical symptoms were monitored daily. Blood cell counts were obtained at least twice a week, and biochemical parameters were measured at least once a week. Blood culture, serum endotoxin, β-D-glucan, and chest radiographs were obtained before starting antibacterial therapy and in the case of a sustained or worsened pattern of fever.

### 3.4. Response criteria

The primary endpoint of this study was the rate of the initial treatment success at day 7. Response to treatment at day 7 was divided into four groups as follows: very effective: fever disappeared with a temperature below 37.5 °C within 4 days and an afebrile state remained for more than 3 days; effective: maximum temperature decreased 1 °C or more within 4 days and an afebrile (below 37.5 °C) state persisted for 7 days; partial response: maximum temperature decreased 1 °C or more within 7 days accompanied by the improvement of clinical symptoms; not effective: maximum temperature did not decrease by 1 °C or more within 7 days and/or no improvement of febrile symptoms. The response to treatment was categorized as a success if patients were