Once-daily, oral levofloxacin monotherapy for low-risk neutropenic fever in cancer patients: a pilot study in China

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This pilot study assesses the safety and efficacy of once-daily, oral levofloxacin monotherapy in Chinese patients with low-risk febrile neutropenia. In this prospective, single-arm, open-label, multicenter clinical trial, 46 adult Chinese patients with solid tumors and low-risk febrile neutropenia were included. Patients received oral levofloxacin monotherapy (500 mg orally/day) until day 12, followed by 7 days of follow-up (day 19). Body temperature was measured three times per day. On days 2, 3, 5–7, 9, 12, and 19, disease symptoms and vital signs were recorded, adverse drug reactions were assessed, and blood samples were collected to determine the whole-blood cell count and the absolute neutrophil count. Blood cultures and chest radiographs were performed simultaneously until negative results were found. Oral levofloxacin was effective and well tolerated in 97.6% of patients irrespective of the cancer type and cause of fever. Body temperature began to decline in 24.4, 68.3, and 90.2% of patients, respectively, at 12, 24, and 48 h after initiating levofloxacin therapy. On days 5 and 7, 95.1 and 97.6% of the patients had complete defervescence, respectively. The median time for absolute neutrophil count recovery to at least 1500/mm³ after initiation of treatment was 3 days. Only one patient reported mild diarrhea. This pilot study showed that oral levofloxacin quickly and effectively reduced fever, initiated neutrophil recovery, and was well tolerated in Chinese low-risk febrile neutropenic patients with solid tumors. Further study is needed to compare patient data of levofloxacin with the standard amoxicillin/ciprofloxacin protocol in this population for both safety and efficacy. *Anti-Cancer Drugs* 26:359–362 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction
Patients with chemotherapy-induced neutropenia often develop fever of unknown origin and some may be at risk for serious infections [1–3]. A subset of patients with febrile neutropenia can be identified as being at a low risk for the development of serious clinical complications and subsequent hospitalization [4,5]. Outpatient management for adult cancer patients with low-risk febrile neutropenia includes the administration of oral antimicrobial agents, which is shown to be safe and effective in reducing fever and to compare favorably with hospital treatment [4,6,7]. Fluoroquinolone antibacterial agents are important clinical tools used for the prevention and management of infections in cancer patients with neutropenia [2,3,8,9]. Levofloxacin is a broad-spectrum antimicrobial agent of the fluoroquinolone drug class that has shown excellent tissue penetration [10]. Compared with other fluoroquinolones (e.g. ciprofloxacin), levofloxacin has shown greater activity against Gram-positive bacteria and less activity against Gram-negative bacteria [10]. Levofloxacin reduces the incidence of fever and different types of infections in cancer patients with neutropenia when compared with placebo [11–14]. However, differences have been shown between the microbiological spectrum in febrile neutropenic patients in Asia compared with that in western countries [15]. In addition, quinolone-resistant bacteria are prevalent in China [16–18]. Therefore, it is clinically important to understand the safety and efficacy of fluoroquinolone antibiotics such as levofloxacin within a Chinese population of cancer patients at low risk for infection. Accordingly, our goal was to carry out an initial prospective study to observe the ability of levofloxacin to treat infection and reduce fever in Chinese cancer patients with febrile neutropenia. This pilot study aimed to evaluate the safety and efficacy of once-daily, oral levofloxacin in the treatment of low-risk neutropenic fever in Chinese cancer patients.

Patients and methods
This pilot study was designed as a prospective, single-arm, open-label, multicenter clinical trial. The study was approved by the Ethics Committees of Zhongshan Hospital of Fudan University, Fudan, China, and the Respiratory Hospital of Tongji University (Shanghai, China). All enrolled patients provided signed informed consent. Eligible patients were more than 18 years of age. All patients had pathologically diagnosed cancer with solid tumors, were receiving chemotherapy, and had a

body temperature of more than 38°C but less than 40°C when taken orally. Low risk was defined as patients having an oral temperature of at least 38.5°C twice within 24 h and less than or equal to 7 days of fever, as described previously [19]. The low-risk patients had an absolute neutrophil count (ANC) less than 1500/mm^3, serum creatinine levels less than 2 mg/dl, serum aminotransferase levels four times the upper limit of normal, and a Multinational Association for Supportive Care in Cancer risk index score of at least 21 [8]. Patients with evidence of active infection, including mycobacteria, fungi, viruses, protozoa, or HIV, or those who had been treated with antibiotics less than 4 days before the start of the study, had used study drugs within 30 days before enrollment, were allergic to quinolones, or had cancer-related or unrelated fever before receiving chemotherapy were excluded. A total of 46 patients were enrolled, but the efficacy population was based on 41 patients per protocol. Patients were treated with oral levofloxacin (Daiichi Sankyo Co., Ltd, Japan) 500 mg once daily (750 mg levofloxacin is not commercially available in China) at the same time every day (immediately after breakfast) for 12 days. No other antibiotics were administered during the study period. Use of antifungal and antiviral drugs was also prohibited. Granulocyte colony-stimulating factor, blood transfusions, and intravenous infusions were administered as needed. Levofloxacin treatment was discontinued after 12 days (day 12). Patients were then followed for an additional 7-day period (day 19) without treatment. Body temperature was measured three times per day. On days 1–3, 5, 7, 9, 12, and 19, disease symptoms and vital signs were evaluated and recorded. Adverse drug reactions were assessed simultaneously. Blood samples were collected on the same day for whole-blood cell count, and ANC was counted simultaneously. Blood cultures and chest radiographs were performed at the same time until negative results were found. Urine and sputum cultures were obtained when signs of infection were clinically indicated to identify the site of infection. Some patients who responded well and quickly to levofloxacin treatment were permitted to discontinue treatment earlier than day 12, but these patients were still followed for an additional 7 days without treatment. Patients were withdrawn if their fever persisted or worsened, if ANC remained high, or if a levofloxacin-associated adverse reaction occurred. The primary endpoints were the effectiveness of levofloxacin as evaluated by the proportion of patients with fever defervescence on days 5 and 7, the median time to starting defervescence, and the median time to complete defervescence. Defervescence was defined as a body temperature of less than or equal to 37°C or returning to the baseline value. Other primary endpoints included the proportion of patients who did not respond and were treated in the intensive care unit, received other antibiotics, and deaths. The secondary endpoints included neutrophil recovery indicated by time for ANC returning to at least 1500/mm^3

and for white blood cell (WBC) counts to return to at least 3000/mm^3 or at least 5000/mm^3. No resistance data were collected. Safety endpoints included the incidence of adverse drug reactions and the proportion of patients who were withdrawn from the study because of adverse drug reactions. Continuous data were summarized by medians and ranges, and categorical data were expressed by frequencies and percentages. The response rates were described as the proportion of patients who responded and reported with a 95% confidence interval. All statistical analyses were carried out using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Results
Most patients (30/41; 73.2%) had been diagnosed with primary lung cancer. Other cancer types were mammary cancer ($n = 5$), gastric cancer ($n = 3$), gallbladder cancer ($n = 1$), thyroid carcinoma ($n = 1$), and renal carcinoma ($n = 1$). The median Multinational Association for Supportive Care in Cancer risk index score was 23 (range: 21–26). Before levofloxacin therapy, the median ANC was 590/mm^3 and the median WBC count was 1410/mm^3. The median body temperature was 38.7°C and the median duration of levofloxacin therapy was 10 days. Among 41 patients in the effectiveness population, the median time of starting defervescence was 24 h and the median time to complete fever reduction was 3 days (Table 1). The proportions of patients who showed a reduction in fever within 12, 24, and 48 h were 24.4, 68.3, and 90.2%, respectively, and the percentages with complete defervescence within 5 and 7 days were 95.1 and 97.6%, respectively (Table 1). Forty patients in the efficacy population responded to levofloxacin therapy, indicating a response rate of 97.6% (95% confidence interval: 87.4–99.6%, Table 2). The median time for improvement in ANC to at least 1500/mm^3 was 3 days, and that for recovery of WBC counts to at least 3000/mm^3 and at least 5000/mm^3 were 3 and 4 days, respectively, after initiation of treatment. Only one patient required administration of granulocyte colony-stimulating factor. Overall, 37 patients were diagnosed to have fever of

Table 1 Time to defervescence after receiving oral levofloxacin therapy

Time to defervescence	$N = 41$
Starting defervescence [n (%)] (h)	
≤12	10 (24.4)
≤24	28 (68.3)
≤48	37 (90.2)
Time to starting defervescence (h)	
Median (range)	24 (0–72)
Complete defervescence [n (%)]	
≤12 h	2 (4.9)
≤1 day	10 (24.4)
≤2 days	17 (41.5)
≤5 days	39 (95.1)
≤7 days	40 (97.6)
Time to complete defervescence (days)	
Median (range)	3 (0–14)

Table 2 Response to therapy on the basis of the nature of febrile episode and type of infection

Type of infection	Number of patients	Number of response (%)
Unexplained fever	37	37
Clinically diagnosed infection by chest radiograph		
Pneumonia	2	1
Confirmation of microbial infection		
Escherichia coli (urine culture)	1	1
Klebsiella pneumoniae (sputum culture)	1	1
Total	41	40 (97.6%)

unknown origin; two patients had confirmed infection, including one with *Klebsiella pneumoniae* found by sputum culture and one with *Escherichia coli* found by urine culture; two patients were clinically diagnosed to have infection on the basis of chest radiograph (Table 2). None of the 40 patients who responded to treatment experienced a new infection at day 7 of the follow-up period. Of the 46 patients in the safety population, only one patient reported an adverse event, which was drug-related diarrhea, but the symptoms were mild and the patient remained in the study.

Discussion and conclusion

The present study showed that once-daily, oral levofloxacin effectively treated infection and quickly reduced fever among Chinese patients with low-risk febrile neutropenia. Defervescence started at a median of 24 h, with complete fever reduction in median 3 days. Among 41 patients in the effectiveness group, 95.1 and 97.6% had complete defervescence within 5 and 7 days, respectively. Neutrophil recovery was indicated by a 3-day median time for improvement in ANC to at least $1500/mm^3$ and WBC counts returning to at least $3000/mm^3$ and at least $5000/mm^3$ in 3 and 4 days, respectively. These results in a Chinese population are especially important because of the prevalence of quinolone-resistant bacteria in China [16–18].

Recent studies measured antimicrobial resistance of Gram-positive isolates from 18 hospitals to commonly used antimicrobial agents according to the Clinical Laboratory Standards Institute guidelines, showing that nationwide resistance rates in China ranged from 45 to 81% for MRSA and MRSE, respectively, and were lower for vancomycin and linezolid resistance [16]. Macrolide resistance was more serious than that reported for Western countries [16]. In another Chinese study, a high proportion of extended-spectrum β-lactamase and/or plasmid-mediated *AmpC*-producing Enterobacteriaceae such as *Klebsiella* spp. were shown to carry the quinolone-resistance gene (*qnr*) [18].

Our results are also important when considering mono-therapy versus combined therapy for addressing neu-tropenic fever. Both the IDSA and the NCCN recommend applying antibiotic combination therapy for the treatment of low-risk febrile neutropenia, namely, ciprofloxacin in combination with amoxicillin/clavulanate, which shows anti-Gram-positive activity [19,20]. However, in our experience, combined therapies potentially increase side effects, resulting in lower treatment compliance and increased medical costs. Levofloxacin has a broad anti-bacterial spectrum, potent anti-Gram-positive activity, a long half-life, and is usually well tolerated [21]. The bio-availability of levofloxacin is as high as 99%, and once-daily oral levofloxacin is shown to be effective in treating febrile neutropenia [14,22]. Oral levofloxacin administered as monotherapy has also been used to successfully treat other diseases such as community-acquired pneumonia, chronic bronchitis, and enteric fever [21,23]. Good results have also been achieved with oral administration of the standard amoxicillin/ciprofloxacin combination. Results of first-day step-down administration of oral amoxicillin/ciprofloxacin on an outpatient basis for children with low-risk chemotherapy-induced neutropenia showed that out-comes were noninferior to the usual emergent hospitaliza-tion and intravenous antimicrobial therapy [24]. A comparison between monotherapy with once-daily oral moxifloxacin and twice-daily ciprofloxacin plus amoxicillin/clavulanic acid showed that oral moxifloxacin was safe and efficacious in low-risk febrile neutropenic patients who were discharged early and treated as outpatients; effec-tiveness and survival were similar in the oral monotherapy group and the combination therapy group [25]. However, the limited number of studies that compare levoflxacin monotherapy with standard intravenous therapies indicates the need for additional studies to evaluate the efficacy and safety of levofloxacin monotherapy compared with other treatments. In addition, the differences between the microbiological spectrum in febrile neutropenic patients in Asia and those in Western countries [15] as well as the prevalence of quinolone-resistant bacteria in China [18] make it important to examine the ability of levofloxacin monotherapy to treat infection and reduce fever in Chinese cancer patients with low-risk febrile neutropenia. The results of the present study have shown that levofloxacin is safe and effective in treating Chinese low-risk febrile neutropenic patients. Theoretically, the presence of infec-tion is related to the neutropenia. For example, an ANC of less than $1000/mm^3$ predicts risk for infection; an ANC of less than $500/mm^3$ predicts increased susceptibility to infection; and an ANC of $100/mm^3$ indicates severe infec-tion or bacteremia, but the infection may not be related to the types and sites of cancer [26]. Although our inclusion criteria used ANC less than $1500/mm^3$, other studies had different inclusion criteria, including ANC less than $500/mm^3$ or less than $1000/mm^3$ with a predicted decrease to $500/mm^3$ within the subsequent 48 h [8,26]. These differ-ences may help to explain the differences between our results and those of other studies. As low-risk neutropenic patients with ANC less than $1500/mm^3$ were selected for the present pilot study, this may, in fact, contribute toward the rapid antibiotic response and better recovery of ANC.

The results of this pilot study are limited because we did not include a comparator treatment arm without determining whether neutrophil recovery or defervescence with levofloxacin was better than that achieved with the standard amoxicillin/ciprofloxacin regimen. We also did not consider the effects of different chemotherapy regimens and may not have had a sufficient sample size to fully support our conclusion.

In conclusion, oral levofloxacin quickly and effectively reduced fever and was well tolerated in Chinese low-risk febrile neutropenic patients with solid tumors. Although this pilot study showed the safety and efficacy of oral levofloxacin in Chinese cancer patients with febrile neutropenia, additional prospective, multicenter, large-cohort studies are needed to compare the patient data of levofloxacin treatment with those of amoxicillin/ciprofloxacin in this population, investigating both neutrophil recovery and defervescence as indicators of effective treatment for low-risk febrile neutropenia.

Conflicts of interest
There are no conflicts of interest.

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